Sleep Disorders Associated With Traumatic Brain Injury

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Objectives: To investigate the frequency of sleep disorders in traumatic brain injury (TBI) patients with hypersomnia and to discern the relationship between posttraumatic sleep disorders and pretraumatic sleep symptoms.

Design: Prospective cohort study using the criterion standard to diagnose sleep disorders in a consecutive sample of TBI patients.

Setting: Academic medical center with level I trauma center, rehabilitative medicine services, and accredited sleep disorders center.

Patients: Ten TBI patients with subjective excessive sleepiness.

Intervention: Nocturnal polysomnography followed by Multiple Sleep Latency Test. Subjects who had overt sleep apnea on the first nocturnal polysomnography had a second nocturnal polysomnography with titration of nasal continuous positive airway pressure.

Main Outcome Measures: Diagnosis of sleep-disordered breathing, narcolepsy, and posttraumatic hypersomnia.

Results: A diagnosis of treatable sleep disorder was made in all 10 subjects. Sleep-disordered breathing was found in 7 subjects: overt obstructive sleep apnea (OSA) was diagnosed in 5 subjects, rapid eye movement–related OSA in 1, and upper airway resistance syndrome (UARS) in 1. Narcolepsy was diagnosed in 2 subjects, and the diagnosis of posttraumatic hypersomnia was made in 1 subject. Three subjects had symptoms of hypersomnia before their injury (1 each with narcolepsy, OSA, UARS), and 2 of these were driving a car at the time of injury.

Conclusion: Treatable sleep disorders appear to be common in the sleepy TBI population, but may be largely undiagnosed and untreated.

Key Words: Craniocerebral trauma; Hypersomnia; Rehabilitation; Sleep apnea, obstructive; Sleep-disordered breathing.

THE RELATIONSHIP BETWEEN sleepiness and traumatic brain injury (TBI) is complex but important. Hypersomnolence after TBI may result from a preexisting sleep disorder or from the effects of the brain injury itself. In either situation, post-TBI care and recovery might be altered considerably if a sleep disorder were known to exist. Sleepiness is a major cause of highway fatalities (36%) and collisions (42%–54%),[1] which may result in traumatic injury. Sleepiness can result from insufficient sleep or from sleep disorders such as sleep apnea and narcolepsy. Motor vehicle crashes[2-4] and unintentional injuries at work and home[4] are much more likely to occur in people with sleep apnea. It has been estimated that 90% of men and 98% of women with obstructive sleep apnea (OSA) remain undiagnosed,[5] yet the prevalence of OSA is 2% of women and 4% of men in the middle-aged working population.[6]

TBI may result in hypersomnia[7,8] and has well-known effects on physical, cognitive, and psychosocial functioning. In the United States, more than 80,000 people incur permanent disability from TBI each year as a result of vehicular incidents, falls, acts of violence, and sports incidents.[9] TBI affects people of all ages and is the leading cause of long-term disability among young adults. The cost related to work loss and disability is estimated to be 54% of total cost of brain injury or $48.3 billion per year.[10] Presently, 2% of the US population, or 5.3 million people in the United States, are living with disability secondary to head trauma.[11] Poor occupational outcome and dependency for activities of daily living (ADLs) may derive from daytime hypersomnolence attributable to sleep disorders in traumatic injury patients.[8] Patients who have sustained significant head trauma may be at risk for various sleep disorders, including posttraumatic hypersomnia, narcolepsy, central sleep apnea (CSA), OSA, nocturnal seizures, and insomnia. The present prospective pilot study was designed to determine further the prevalence of various treatable sleep disorders in TBI patients by using nocturnal polysomnography and the Multiple Sleep Latency Test (MSLT).

Polysomnography is the standard tool of the sleep laboratory and includes measurements of breathing, respiratory muscle effort, muscle tone, and the division of sleep into 5 stages: rapid eye movement (REM) sleep and 4 stages of non-REM (NREM) sleep. REM sleep is physiologically different from wakefulness and NREM sleep. It is the stage during which normal dreaming occurs, and during which muscle paralysis occurs, with active brain metabolism. The muscle paralysis prevents acting out dreams, but the reduced muscle tone also facilitates relaxation of the muscles in the upper airway that must keep air passages open. REM sleep is the highest risk period for OSA and for hypoxemia, the latter because of the altered hypoxic arousal threshold that occurs during REM sleep. OSA is the cessation of breathing (apnea) with continued effort to breathe. It is caused by collapse of the upper airway between the pharynx and glottis, a passageway that is without bone or cartilage support and hence held open only by muscle activity. Upper airway resistance syndrome (UARS) is hypersomnia that occurs when sleep is disrupted by an increased effort to breathe through a narrowed airway without measurable cessation of breathing (apnea) or reduction in breathing (hypopnea). CSA is the cessation of breathing with no effort to breathe, caused by an abnormal respiratory drive. Narcolepsy is a disorder of REM sleep with hypersomnia, sleep attacks, early REM onset, and the intrusion of REM sleep physiology into wakefulness (cataplexy, sleep paralysis, hypnogogic hallucinations).

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The many factors recorded during nocturnal polysomnography facilitate diagnosis of sleep disorders such as sleep-disordered breathing (OSA, UARS, CSA), nocturnal seizures, and periodic limb movements, which are characterized by sleep disruption that causes nonrefreshing sleep. Diagnosis of narcolepsy and posttraumatic hypersomnia requires a MSLT after a relatively normal night's sleep, documented by nocturnal polysomnography. The MSLT is the objective measurement of daytime sleepiness expressed as the mean sleep latency of 5 naps (20min each) taken at 2-hour intervals from 8:00 AM to 4:00 PM. The diagnosis of narcolepsy is based on a MSLT score of less than 5 minutes with REM sleep on at least 2 of the naps. Posttraumatic hypersomnia is excessive daytime sleepiness with onset after TBI. The diagnosis is based on history, the exclusion of other sleep disorders, and objective sleepiness based on a MSLT score of less than 10 minutes without sleep-onset REM periods after a relatively normal nocturnal polysomnography.

METHODS

Ten adult patients with TBI and daytime sleepiness were enrolled in the present study. Informed consent was obtained according to the criteria of the Committee for the Protection of Human Subjects of the University of Texas–Houston Health Science Center. TBI was defined as blunt trauma to the head secondary to an external force with initial loss of consciousness or an abnormal initial head computed tomography (CT) scan. Patients had to be at least 72 hours postinjury, alert, and oriented to person. All subjects had to be age 18 years or older and noncombative. Patients were excluded from the study if they were taking medications known to cause hypersomnolence such as barbiturates, benzodiazepines, or opiates. Patients were excluded if they were pregnant, had unstable or decompensated cardiopulmonary disease including recent myocardial infarction, or recent abdominal or thoracic surgeries or tracheotomy. Each patient underwent a clinical interview and physical examination by a physician. Each patient responded to the Epworth Sleepiness Scale[12] (ESS), a self-administered 8-item questionnaire to assess subjective daytime sleepiness in which the subject rates from 0 to 3 the likelihood of dozing in specific situations (appendix). Subjects who score 10 or more on the ESS are considered to have excessive daytime sleepiness. Each patient underwent a standard nocturnal polysomnography and MSLT, unless the nocturnal polysomnography showed significant OSA, in which case the MSLT was cancelled. These procedures were performed in a sleep disorders center, accredited by the American Academy of Sleep Medicine. Nocturnal polysomnography monitoring included electroencephalogram (EEG), electrooculogram, chin, intercostal and anterior tibialis electromyogram, electrocardiogram, oral and nasal airflow by thermistor, thoracic and abdominal movements by piezocrystals, breath sounds, and oxygen saturation by pulse oximeter. If patients were diagnosed with OSA or UARS, a second night of nocturnal polysomnography with continuous positive airway pressure (CPAP) was performed to eliminate snoring, apneas, and hypopneas. Standard sleep stages were scored according to Rechtschaffen and Kales,[13] and the MSLT was performed according to the guidelines established by the American Sleep Disorders Association's Task Force on Daytime Sleepiness.[14] Urine drug testing was performed on all subjects undergoing the MSLT. All nocturnal polysomnographies and MSLTs were scored by a registered polysomnographic technologist and interpreted by a physician who was certified by the American Board of Sleep Medicine. Obstructive apnea was defined by cessation of breathing longer than 10 seconds with $\geq$ 4% fall in oxygen saturation with continuous respiratory effort and/or EEG arousal. Central apnea was defined by cessation of breathing longer than 10 seconds with $\geq$ 4% fall in oxygen saturation without respiratory effort and/or EEG arousal. Hypopnea was defined as a greater than 50% decrease in airflow for more than 10 seconds $\geq$ 4% oxygen desaturation and/or EEG arousal. The diagnosis of OSA was made with $\geq$ 5 apneas/hr of sleep and $\geq$ 10 apneas + hypopneas/hr of sleep. REM-related OSA (REM-OSA) was defined as $\geq$ 5 apneas/hr of REM sleep and $\geq$ 10 apneas + hypopneas/hr of REM sleep with fewer than 5 apneas/hr of total sleep and fewer than 10 apneas + hypopneas/hr of total sleep. UARS was diagnosed in patients with excessive daytime sleepiness defined as an ESS score $\geq$ 10 and MSLT $\leq$ 10 minutes without significant sleep apnea or periodic limb movement activity on nocturnal polysomnography, but with $\geq$ 10 spontaneous arousals/hr and a greater than 50% reduction in arousals with relief of excessive daytime sleepiness by application of CPAP. Narcolepsy was defined as a MSLT score (average sleep latency) shorter than 5 minutes with $\geq$ 2 sleep-onset REM periods after an unremarkable nocturnal polysomnography with adequate total sleep and REM sleep and negative urine drug screen. Posttraumatic hypersomnia was defined as a MSLT score $\leq$ 10 minutes with fewer than 2 sleep-onset REM periods after an unremarkable nocturnal polysomnography.

RESULTS

Ten patients (6 women, 4 men; age range, 31–86yr; mean $\pm$ standard deviation, 56.3 $\pm$ 5.3yr) were enrolled in the study. Three subjects sustained TBI from a motor vehicle crash (MVC), 3 from a work-related injury, and 4 from falls or altercations with others. The mean time between the date of the collision and the sleep study was 110 $\pm$ 191 months (range, 1mo–46yr). Six of 10 subjects sustained severe head injury and 4 had mild head injury according to the initial Glasgow Coma Scale (GCS) score. All subjects with severe head injury showed abnormality in their initial head CT scan and all subjects with severe TBI required neurosurgical intervention except for 1 subject, who was treated conservatively. Two of the 4 subjects who sustained mild head injury had negative initial head CT scan results.

The mean ESS score was 15.2 $\pm$ 5.3 (range, 6–24). All subjects complained of excessive daytime sleepiness and all but 1 subject scored greater than 10 on the ESS. That patient had an ESS of 6, but had a MSLT score of 9.4 minutes without sleep-onset REM periods and had moderate OSA with 19 apneas/hr of sleep. The mean daytime sleep latency on the MSLT was 6.2 $\pm$ 3.4 minutes. This finding is an objective confirmation of hypersomnia. The subjects had a low sleep efficiency (total sleep time/time in bed) with a mean of 74.7% $\pm$ 18.5% (range, 46%–92%).

All 10 subjects tested had abnormal sleep studies (table 1). Sleep-disordered breathing was found in 7 subjects: overt OSA was diagnosed in 5 patients, REM-related OSA in 1, and UARS in 1. Narcolepsy was diagnosed in 2 subjects, and the diagnosis of posttraumatic hypersomnia was made in 1 subject. One of those with OSA also had CSA (22.5 central apneas/hr, 36.4 obstructive apneas/hr). No subject had significant periodic limb movements or seizure activity during sleep. The 2 subjects diagnosed with narcolepsy both had 5 sleep-onset REM periods on the MSLT. The patient with REM-OSA had 8.3 apneas + hypopneas/hr of total sleep and 34.3 apneas + hypopneas/hr of REM sleep. Four patients with OSA had severe head injury whereas the other 2 had mild head injuries. One of the latter had posttraumatic vocal cord paralysis and dysphagia. This case was the only instance in which the location of neurologic deficit appeared to be related to the type of

Table 1: TBI Circumstances and Sleep Disorder Diagnosis

Age (yr)	Gender	ESS Score	Injury (mo)	Sx PTI	MVC dr	Dx	GCS Injury	CT Scan	LOC	Surg
51	F	24	348	Y	Y	UARS	Severe	+	+	+
31	M	20	1	Y	Y	NARC	Mild	−	+	−
35	M	18	13	N	N	NARC	Severe	+	+	+
36	M	6	156	N	N	OSA	Severe	+	+	+
66	F	*	1	N	N	OSA	Mild	+	−	−
86	F	14	7	N	N	OSA/CSA	Severe	+	+	+
85	F	18	1	Y	N	OSA	Mild	+	+	−
43	F	12	21	N	N	PTH	Mild	−	+	−
70	F	12	2	N	N	REM/OSA	Severe	+	+	−
60	M	13	552	N	N	OSA	Severe	+	+	+

Abbreviations: Injury, time between injury and sleep studies; Sx PTI, symptoms of sleepiness before TBI; MVC dr, driver of car at time of TBI; Dx, diagnosis from polysomnography and the MSLT; LOC, loss of consciousness; Surg, neurosurgical intervention; F, female; M, male; +, yes; −, no; NARC, narcolepsy; PTH, posttraumatic hypersomnia.
* Not applicable.

sleep disorder found. Three subjects had complaints of daytime hypersomnia before the head injury (1 each with UARS, narcolepsy, OSA). Of these 3 subjects, 2 subjects (those with UARS and narcolepsy) sustained head injury from a MVC while driving and may have fallen asleep at the wheel.

DISCUSSION

Posttraumatic hypersomnia was reported as early as 1941,[15] and posttraumatic narcolepsy has been documented in case reports.[16,17] However, the prevalence of daytime hypersomnia secondary to TBI is not known. Guilleminault et al[8] found a MSLT score less than 10 (ie, hypersomnia) in 82.6% and sleep-disordered breathing (OSA, UARS) in 32% of patients with head or neck trauma referred to their sleep disorders center, but this included patients with whiplash. Our present findings of sleep-disordered breathing in 7 of 10 TBI subjects and narcolepsy in 2 are all the more remarkable because our prospective study design enrolled subjects who would not otherwise have been referred to a sleep disorders center. Had they not participated in the study, these 10 patients would not have been diagnosed and treated for a sleep disorder. It was therefore somewhat surprising that all 10 subjects had treatable sleep disorders that may have contributed to their daytime hypersomnia. Three of the 10 patients had symptoms before their TBI and at least 2 of them may have had untreated sleep disorders that resulted in the motor vehicle injury that lead to their head trauma.

The effects of daytime hypersomnia on patients' rehabilitation recovery, cognitive improvement, ADLs mood, and long-term disability is yet to be identified. It is possible that undiagnosed hypersomnia in this context may impair the rehabilitative process. Excessive sleepiness of any cause may be an obstacle to learning, but OSA has been associated with cognitive deficits and impaired vigilance that may be related to hypoxemia rather than just sleep disruption.[18-22] Further studies to determine the prevalence of excessive daytime sleepiness in the TBI population, to identify the treatable causes of hypersomnia, and to determine if treatment of sleep disorders in patients with TBI improves quality of life (QOL) and cognitive function are needed. In all but 1 of the present subjects treatment of the sleep disorder with either CPAP (for sleep-disordered breathing) or modafinil (for narcolepsy and posttraumatic hypersomnia) resulted in subjectively improved QOL. One patient with OSA refused treatment with CPAP and was lost to follow-up because she lived a great distance away.

Our present study design and small sample size preclude any definitive conclusions about prevalence of sleep disorders after TBI or the effects of treatment on recovery. Nor can we draw conclusions about whether sleep disorders are predominantly a result of TBI or existed before injury. Persons with OSA are 6 to 7 times more likely to be involved in MVCs,[2,3] 11 times more likely if they consume alcoholic beverages,[3] and 25% of narcoleptics have had sleep-related MVCs.[1] They also have higher accident rates at home, at work, and while driving,[4] and so it is not unreasonable to expect a high prevalence of sleep disorders in a TBI population. However, others have not been able to document preinjury symptoms of OSA and hypersomnia in TBI patients with OSA.[8] Treatment of these sleep disorders usually leads to a substantial improvement in daytime function, as happened in our subjects. Identifying and treating persons with sleep disorders may prove to be a rewarding endeavor, but the effect of treatment must still be evaluated in a larger outcome-based study.

CONCLUSION

Sleep disorders (especially sleep-disordered breathing) in TBI patients may be greatly underdiagnosed and largely untreated. This oversight could have far-reaching implications for the care of many TBI patients whose lethargy and intellectual impairment may be from an easily treated sleep disorder.

APPENDIX: EPWORTH SLEEP SCALE

NAME:_____ TODAY'S DATE:_____
AGE:_____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

Situation	Chance of dozing Using scale above (0–3)
Sitting and reading	_____
Watching TV	_____

APPENDIX: EPWORTH SLEEP SCALE (Cont'd)

Situation	Chance of dozing Using scale above (0–3)
Sitting, inactive in a public place (eg, meetings or a theater)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

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Article

Head Injury as Risk Factor for Psychiatric Disorders: A Nationwide Register-Based Follow-Up Study of 113,906 Persons With Head Injury

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Objective: Studies investigating the relationship between head injury and subsequent psychiatric disorders often suffer from methodological weaknesses and show conflicting results. The authors investigated the incidence of severe psychiatric disorders following hospital contact for head injury.

Method: The authors used linkable Danish nationwide population-based registers to investigate the incidence of schizophrenia spectrum disorders, unipolar depression, bipolar disorder, and organic mental disorders in 113,906 persons who had suffered head injuries. Data were analyzed by survival analysis and adjusted for gender, age, calendar year, presence of a psychiatric family history, epilepsy, infections, autoimmune diseases, and fractures not involving the skull or spine.

Results: Head injury was associated with a higher risk of schizophrenia (incidence rate ratio [IRR]=1.65, 95% CI=1.55–1.75), depression (IRR=1.59 95% CI=1.53–1.65), bipolar disorder (IRR=1.28, 95% CI=1.10–1.48), and organic mental disorders (IRR=4.39, 95% CI=3.86–4.99). This effect was larger than that of fractures not involving the skull or spine for schizophrenia, depression, and organic mental disorders, which suggests that the results were not merely due to accident proneness. Head injury between ages 11 and 15 years was the strongest predictor for subsequent development of schizophrenia, depression, and bipolar disorder. The added risk of mental illness following head injury did not differ between individuals with and without a psychiatric family history.

Conclusions: This is the largest study to date investigating head injury and subsequent mental illness. The authors demonstrated an increase in risk for all psychiatric outcomes after head injury. The effect did not seem to be solely due to accident proneness, and the added risk was not more pronounced in persons with a psychiatric family history.

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The possible development of psychiatric disorders as a consequence of head injury has been investigated for decades with greatly varying results. A recent meta-analysis (1) suggested that onset of schizophrenia appears more frequently following head injury; however, the included studies showed significant heterogeneity. Two of the most robust studies based on the Scandinavian registers did not seem to find an overall increased risk of schizophrenia (2, 3) but found only a small increase in risk among male patients with schizophrenia (3) and in nonaffective nonschizophrenia psychosis (2). Depression seems to be the most common psychiatric disorder following head injury (4). However, although one study (5) found the risk of depression to be highly increased when a head-injury group was compared with a noninjured control group, another study (6), comparing a head-injury group with persons who had other injuries, did not find a significantly increased risk. Bipolar disorder has been suggested to be the most uncommon mood disorder following head injury (7). Nonetheless, the largest study found a moderately increased risk of postinjury bipolar disorder (8), while others did not observe a significantly increased risk (5). Several hypotheses have been proposed about the association between mental illness and head injury, addressing aspects such as the location of the injury, postinjury changes in the brain (4, 9–12), and the ability of the brain to recover through neuroplasticity (13). The potentially harmful inflammatory response in the CNS after a head injury (14, 15) may also have an impact on the subsequent risk of mental illness.

Use of the Danish registers to investigate the link between head injury and mental illness offers advantages in overcoming many limitations of previous studies: elimination of recall bias, comparison of the head-injury cohort with the background population, and adjustment for various confounders. To consider the possibility of greater accident proneness among persons who received psychiatric diagnoses after head injury, we additionally controlled for non-CNS-related fractures, a factor included in few other studies (3, 8). In line with recent immunological hypotheses, we investigated the possible interaction between head injury and infections or autoimmune diseases.

This article is featured in this month's AJP Audio and is the subject of a CME course (p. 475)

TABLE 1. Risk of Psychiatric Disorders Associated With Hospital Contact for Head Injury[a]

	Schizophrenia Spectrum Disorders					Unipolar Depression	
Head Injury Contact and Severity	N	IRR	95% CI	IRR[b]	95% CI[b]	N	IRR
No hospital contact for head injury (reference)	9,303	1.00		1.00		21,793	1.00
Hospital contact for head injury	1,304	1.65	1.55–1.75	1.48	1.40–1.57	2,812	1.59
Mild head injury	1,156	1.64	1.54–1.74	1.47	1.38–1.56	2,539	1.59
Skull fracture	52	1.28	0.96–1.66	1.15	0.86–1.49	107	1.27
Severe head injury	96	2.16	1.75–2.62	1.83	1.49–2.23	166	1.77

[a] IRR=incidence rate ratio; adjusted for gender, age, and calendar year.
[b] Further adjusted for fractures not involving the skull or spine, a family history of psychiatric disorders, epilepsy, and infections.
[c] Because of low case numbers, IRRs were adjusted only in the basic model.

To our knowledge, this is the largest study to date to investigate the association between head injury and psychiatric disorders.

Method

The Registers

The Danish Civil Registration System (16), established in 1968, contains demographic data and allows identification of parents. It assigns all Danish residents a unique identification number that permits linkage between the national registers. Inpatient psychiatric contacts are registered in the Danish Psychiatric Central Register (17), which was computerized in 1969. In 1995, outpatient psychiatric and emergency department contacts were also included. The Danish National Hospital Register (18) has contained information on somatic inpatient hospital contacts since 1977 and outpatient and emergency department contacts since 1995. All registered diagnoses are defined according to ICD codes; ICD-8 was used until 1993 and ICD-10 from 1994 onward.

Study Population

The national registers enabled us to create a cohort of individuals born in Denmark between January 1, 1977, and December 31, 2000. These individuals were identified by their identification number and followed until death, emigration, or December 31, 2010. All individuals were followed in the Danish National Hospital Register for diagnoses of head injury and linked to the Danish Psychiatric Central Register for the included psychiatric outcomes. We used the first-time psychiatric diagnoses of each outcome after the 10th birthday during the period 1987–2010. Persons who had psychiatric diagnoses before injury, including substance use disorders, were excluded.

Data Collection

We acquired data on four general outcomes from the Danish Psychiatric Central Register: schizophrenia spectrum disorders, unipolar depression, bipolar disorder, and organic mental disorders (diagnostic codes are listed in the data supplement that accompanies the online edition of this article). The organic mental disorders are characterized by a known physical etiology to the psychiatric symptoms. Some of the organic disorders included diagnoses that imply a previous head injury diagnosis. Hence, we performed subanalyses with the definition restricted to diagnoses that do not necessarily presuppose head injury and with symptoms similar to those in the schizophrenia and mood disorder spectrum. We collected the parental history of psychiatric disorders (including substance use disorders) identified in the Danish Psychiatric Central Register and the Danish National Hospital Register. The Danish National Hospital Register provided the exposure diagnoses of head injury, which were categorized according to a three-level hierarchy (19): mild head injury, skull fracture, and severe head injury. The occurrence of more than one head injury diagnosis for the same patient within 14 days was considered a coding error and thus recorded as the same event according to this hierarchy. The definition of mild brain injury used in Denmark is that of the American Congress of Rehabilitation Medicine (19) and involves a direct trauma to the head resulting in a change of brain function. Any loss of consciousness cannot exceed 30 minutes, and any posttraumatic amnesia cannot exceed 24 hours; after 30 minutes, the Glasgow Coma Scale score cannot be <14. If these criteria are exceeded, the brain injury is defined as severe. Skull fracture can be present alone or combined with other types of head injury. In the present study, a total of 6,452 persons had hospital contacts for skull fracture; of these, 2,749 individuals (43%) also had a mild head injury and 1,501 individuals (23%) also had a severe head injury. From the Danish National Hospital Register, we obtained diagnoses of fractures not involving the skull or spine. These were included as an indicator of accident proneness prior to the head injury potentially due to an undiagnosed psychiatric disorder. Individuals diagnosed with both head injury and such fractures entered the study as part of the head-injury cohort. We collected diagnoses of autoimmune disease and infections leading to hospital contact in order to investigate the possible added risk of mental disorders in persons with concomitant head injury. Our definition of infections excluded diagnoses of AIDS/HIV and ICD-8 diagnoses with the modification code "suspected" or "not found" and similar codes in ICD-10. We also obtained the first-time diagnoses of epilepsy.

The Danish Data Protection Agency approved the study.

Statistical Analysis

Survival analysis was performed in SAS, version 9.2 (SAS Institute, Cary, N.C.), and the incidence rate ratios (IRRs) were estimated by log-linear Poisson regression. All analyses were adjusted for gender, age, and calendar year in the basic model. In the fully adjusted model, we included non-CNS-related fractures, psychiatric family history, epilepsy, and infections. We investigated for multiplicative interaction between head injury and psychiatric family history, infections, and autoimmune disease. The risk of mental illness following head injury was evaluated in different age groups divided into 5-year intervals and estimated according to time since head injury. All variables except gender were treated as time dependent.

Results

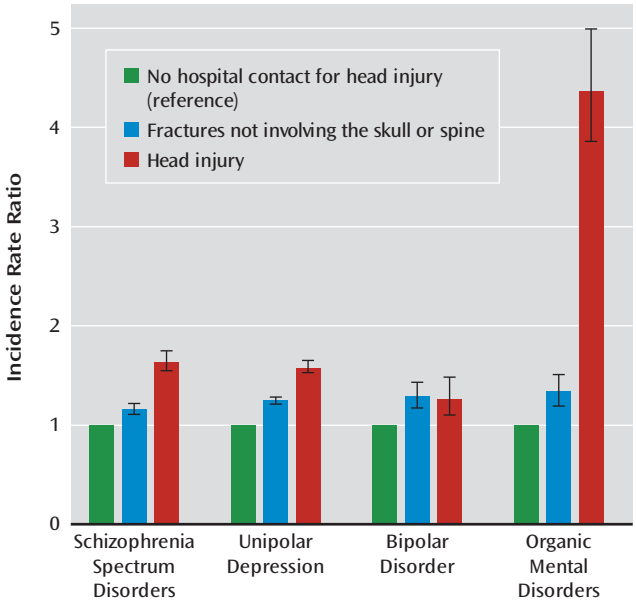
During the period 1977–2000, a total of 1,438,339 individuals were born in Denmark, of whom 113,906 had a hospital contact for head injury between 1977 and 2010. All individuals with a hospital contact for head injury were followed for

Unipolar Depression			Bipolar Disorder[c]			Organic Mental Disorders[c]		
95% CI	IRR[b]	95% CI[b]	N	IRR	95% CI	N	IRR	95% CI
	1.00		1,668	1.00		877	1.00	
1.53–1.65	1.46	1.40–1.51	191	1.28	1.10–1.48	322	4.39	3.86–4.99
1.53–1.66	1.46	1.40–1.52	180	1.35	1.16–1.57	155	2.38	2.00–2.82
1.04–1.52	1.16	0.95–1.39	5	0.67	0.24–1.43	22	5.63	3.58–8.38
1.51–2.05	1.56	1.33–1.81	6	0.72	0.29–1.47	145	36.22	30.23–43.09

the included psychiatric outcomes from their 10th birthday in the period 1987–2010. During this period, 38,270 individuals were diagnosed with any of the included psychiatric disorders, amounting to 16,269,924 person-years of follow-up. Out of these, a total of 10,607 persons had a diagnosis of schizophrenia, of whom 1,304 (12%) had previously been exposed to head injury; 24,605 persons had a depression diagnosis, of whom 2,812 (11%) had a previous head injury; 1,859 persons had a bipolar disorder, of whom 191 (10%) had a previous head injury; and 1,199 persons had an organic mental disorder, of whom 322 (27%) had a previous head injury. Of all persons with head injury, a total of 4,629 (4%) were subsequently diagnosed with one of the included severe psychiatric disorders.

A hospital contact for head injury was associated with an increased risk of schizophrenia, depression, bipolar disorder, and organic mental disorders (IRRs, 1.65, 1.59, 1.28, and 4.39, respectively) (Table 1). The risks of schizophrenia and depression were still significantly elevated in the full model (IRRs, 1.48 and 1.46), which adjusted for several confounders, including epilepsy. For schizophrenia, depression, and organic mental disorders, the risk was highest after exposure to severe head injury (IRRs, 2.16, 1.77, and 36.22). A trend in the hierarchy of head injury severity was present only in relation to the organic disorders (p=0.51) but not to schizophrenia (p=0.01) or depression (p=0.006). Trend analyses could not be performed for bipolar disorder because of low case numbers. There was no interaction between gender and risk of schizophrenia, depression, bipolar disorder, or organic mental disorders. Non-CNS-related fractures increased the risk of all outcomes (schizophrenia: IRR=1.16, 95% CI=1.11–1.22; depression: IRR=1.25, 95% CI=1.21–1.28; bipolar disorder: IRR=1.29, 95% CI=1.17–1.43; and organic mental disorders: IRR=1.34, 95% CI=1.19–1.51) (Figure 1). However, the effect of head injury was significantly greater than the effect of these fractures with respect to schizophrenia, depression, and organic mental disorders (p values <0.001) but not with respect to bipolar disorder. When the analyses of organic mental disorders were restricted to diagnoses with symptoms included in the schizophrenia and mood disorder spectrum (394 persons, of whom 88 had hospital contacts for head injury), the risk after exposure to head injury was still significantly increased (IRR=3.26, 95% CI=2.54–4.13).

FIGURE 1. Risk of Psychiatric Disorders Associated With Hospital Contact for Head Injury and Fractures Not Involving the Skull or Spine[a]



[a] Adjusted for gender, age, and calendar year. Error bars indicate 95% confidence interval.

There was significant interaction between head injury and time since head injury for organic mental disorders, schizophrenia, and depression (p values <0.001) but not for bipolar disorder.

The risk increased with temporal proximity to the head injury, with the highest risk found during the first year after injury for organic mental disorders, schizophrenia, and depression (IRRs, 9.47, 2.26, and 1.95) (Table 2). Among all age groups, head injury between 11 and 15 years of age was the strongest predictor of the subsequent development of schizophrenia, depression, and bipolar disorder (IRRs, 1.86, 1.60, and 1.30) (Table 3). The risk of schizophrenia and depression in this age group was significantly larger than the risk found in the group of persons 6–10 years of age (p<0.001 and p=0.002) and in the group of persons older than 15 years of age (p values <0.001).

Individuals with a psychiatric family history might be expected to be more accident prone than others; however,

TABLE 2. Risk of Psychiatric Disorders, by Time Since Hospital Contact for Head Injury[a]

Time Since Hospital Contact for Head Injury	Schizophrenia Spectrum Disorders			Unipolar Depression			Bipolar Disorder			Organic Mental Disorders		
	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI
No hospital contact for head injury (reference)	9,303	1.00		21,793	1.00		1,668	1.00		877	1.00	
<1 year	89	2.26	1.82–2.76	151	1.95	1.66–2.28	6	1.09	0.43–2.21	35	9.47	6.63–13.08
1–5 years	319	1.87	1.67–2.08	650	1.87	1.73–2.02	39	1.48	1.06–2.01	84	5.31	4.21–6.60
6–10 years	356	1.72	1.54–1.91	733	1.60	1.48–1.72	56	1.51	1.15–1.95	90	4.58	3.66–5.66
11–15 years	285	1.53	1.36–1.72	647	1.52	1.41–1.65	42	1.21	0.88–1.62	59	3.56	2.70–4.59
>15 years	255	1.35	1.19–1.53	631	1.36	1.26–1.47	48	1.05	0.78–1.39	54	3.02	2.26–3.96

[a] IRR=incidence rate ratio; adjusted for gender, age, and calendar year.

TABLE 3. Risk of Psychiatric Disorders, by Age at Hospital Contact for Head Injury[a]

Age at Hospital Contact for Head Injury	Schizophrenia Spectrum Disorders			Unipolar Depression			Bipolar Disorder			Organic Mental Disorders		
	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI
No hospital contact for head injury (reference)	9,303	1.00		21,793	1.00		1,668	1.00		877	1.00	
0–5 years	226	1.35	1.18–1.54	511	1.36	1.24–1.48	27	0.95	0.63–1.36	56	3.51	2.65–4.56
6–10 years	242	1.33	1.16–1.50	522	1.34	1.23–1.46	27	0.88	0.59–1.26	52	3.00	2.24–3.93
11–15 years	334	1.86	1.66–2.07	637	1.60	1.48–1.74	40	1.30	0.93–1.75	55	3.28	2.47–4.27
>15 years	502	1.14	1.04–1.25	1,142	1.26	1.19–1.34	97	1.23	0.99–1.50	159	3.67	3.08–4.34

[a] IRR=incidence rate ratio; adjusted for gender, age, and calendar year.

as shown in Table 4, head injury actually added significantly more to the risk of schizophrenia, bipolar disorder, and organic mental disorders in persons without a psychiatric family history. The risk of depression after head injury was the same regardless of psychiatric family history. Infections and autoimmune disease have previously been shown to act as independent risk factors for psychiatric disorders (20, 21), and they could interact with the effect of head injury. Nonetheless, head injury contributed significantly more to the risk of organic mental disorders in individuals without infections compared with individuals with infections (p=0.008). This was not the case for the risk of schizophrenia, depression, or bipolar disorder. In persons with and without autoimmune disease, head injury did not add significantly more to the risk of schizophrenia, depression, bipolar disorder, or organic mental disorders.

Discussion

In the largest population-based study to date, we found an increased risk of schizophrenia, depression, bipolar disorder, and organic mental disorders following head injury. The findings regarding schizophrenia, depression, and organic mental disorders could not altogether be attributed to accident proneness, since the effect of head injury exceeded the effect of non-CNS-related fractures. The risk seemed to be largest after exposure to severe head injury, even though the expected dose-response relationship of head injury severity was present only for organic mental disorders. The added risk did not differ in those with and without a psychiatric family history.

Our results demonstrated a 65% increase in the risk of schizophrenia following head injury, which is in line with results of a recent meta-analysis (1) and several previous studies (1, 22–24), although several other studies did not find a strong association (2, 3, 25, 26). In a Taiwanese follow-up study (22), the risk of schizophrenia was found to be doubled after traumatic brain injury, but the authors could not rule out preinjury mental illness. A smaller Danish register study (3) found only a slight increase in the risk of schizophrenia among men when accident proneness was taken into account. The incidence of nonaffective nonschizophrenia psychoses, but not of schizophrenia, was increased in a Swedish register study (2) after adjustment for birth-related data and socioeconomic status.

In this study, we found the risk of depression to be increased by 59% after a head injury. This is supported by some previous studies (5, 23, 27) but not by others (6, 28). A study relying on retrospective self-report (27) among U.S. soldiers found exposure to mild head injury to increase the risk of depression more than threefold compared with exposure to other types of injury. Another study (28), however, compared 437 persons exposed to mild head injury to otherwise injured controls and did not find the prevalence of depression to be significantly increased.

We found the risk of bipolar disorder following head injury to be increased by 28%, while previous prevalence rates ranged widely from 2% to 17% (29). A Danish register study (8) found the risk of bipolar disorder to be approximately

TABLE 4. Risk of Psychiatric Disorders Associated With Head Injury in Persons With and Without a Family History of Psychiatric Disorders, a Hospital Contact for Infection, and Autoimmune Disease[a]

	Schizophrenia Spectrum Disorders			Unipolar Depression			Bipolar Disorder			Organic Mental Disorders		
Variable	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI
No psychiatric family history												
No head injury (reference)	6,596	1.00		16,298	1.00		1,124	1.00		627	1.00	
Head injury	873	1.65	1.53–1.77	1,939	1.55	1.47–1.62	130	1.37	1.14–1.63	235	4.76	4.09–5.53
Psychiatric family history[b]												
No head injury (reference)	2,707	1.00		5,495	1.00		544	1.00		250	1.00	
Head injury	431	1.41	1.27–1.56	873	1.49	1.39–1.60	61	0.96	0.73–1.24	87	3.10	2.41–3.93
No hospital contact for infection												
No head injury (reference)	5,670	1.00		13,307	1.00		1,010	1.00		438	1.00	
Head injury	690	1.66	1.53–1.79	1,441	1.56	1.47–1.64	100	1.30	1.05–1.58	155	4.93	4.08–5.92
Hospital contact for infection[b]												
No head injury (reference)	3,633	1.00		8,486	1.00		658	1.00		439	1.00	
Head injury	614	1.52	1.39–1.65	1,371	1.51	1.42–1.60	91	1.19	0.95–1.47	167	3.48	2.89–4.16
No hospital contact for any autoimmune disease												
No head injury (reference)	9,100	1.00		21,165	1.00		1,626	1.00		847	1.00	
Head injury	1,259	1.63	1.54–1.73	2,720	1.59	1.53–1.66	185	1.28	1.10–1.48	313	4.45	3.89–5.06
Hospital contact for any autoimmune disease[b]												
No head injury (reference)	203	1.00		628	1.00		42	1.00		30	1.00	
Head injury	45	2.17	1.55–2.97	92	1.46	1.17–1.81	6	1.31	0.50–2.86	9	2.93	1.31–5.92

[a] IRR=incidence rate ratio; adjusted for gender, age, and calendar year.
[b] The main effect of a psychiatric family history, infections, and autoimmune disease is not included.

40% higher after head injury when adjusting for other fractures, while another study (5) did not find an increased risk.

Gender did not seem to interact in our study with the risk of psychiatric illness after head injury. This is in line with several previous findings (2, 9, 30), whereas other studies found an effect of both male (3) and female gender (8, 23). The incidence of schizophrenia and depression in our study was highest the first year after injury and continued to be significantly elevated throughout the following 15 years and beyond, which makes detection bias a somewhat unlikely explanation for these findings. The risk of schizophrenia has previously been shown to be significantly increased the first years (3, 23) and even 30 years (29) after head injury. The latter result was also found for depression (29), suggesting that depression is not merely a transient psychological reaction following head injury, as indicated by previous results (31). The late increase in risk of bipolar disorder in our study contrasts with previous findings (8) and could reflect the fact that many patients with bipolar disorder are initially diagnosed with other psychiatric disorders. Persons exposed to head injury between ages 11 and 15 had the highest risk of a later diagnosis of schizophrenia or depression. A fivefold higher risk of depression was previously found for individuals who suffered traumatic brain injury at 12–14 years of age compared with traumatic brain injury before age 9 (30). A meta-analysis (1) did not find childhood or adolescent head injury to be more strongly associated with schizophrenia. Interestingly, it has been theorized that essential neurodevelopment occurs from 11 to 15 years of age, when deterioration in development can possibly lead to psychosis (32).

The more than fourfold higher risk of organic mental disorders following head injury and 36-fold following severe head injury strongly suggests that some individuals do experience psychiatric symptoms after a head injury. The risk was still more than three times higher for the restricted definition of organic mental disorders, including diagnoses with symptoms similar to those in the schizophrenia and mood disorder spectrum. The inclusion of the organic mental disorders that presuppose a previous head injury served primarily as validation of the expected dose-response relationship of head injury severity, which was presented only for the organic disorders. Only a few studies have observed a dose-response relationship (11, 33), while the majority did not (1, 6, 9, 10, 22, 24, 29, 31). This might be due to fundamental limitations in the assessment of head injury severity (34, 35). Furthermore, the boundaries between the head injury subgroups are most probably subject to diagnostic overlap (19). Also, in our study, not all patients with skull fracture were concomitantly diagnosed with mild (43%) or severe head injury (23%). For the remaining patients, either only the main head injury diagnosis was noted in the medical record or the patients actually experienced less severe cognitive symptoms than the other groups.

Persons with psychiatric disorders that are not yet diagnosed might be more prone to accidents (23, 36). However, the observed increased risk of schizophrenia,

depression, and organic mental disorders associated with non-CNS-related fractures was significantly exceeded by the effect of head injury. Nevertheless, accident proneness has been suggested to be associated with prodromal symptoms of psychosis (2, 3) and with decreased attention in patients with depression (36) and even in unaffected individuals predisposed to schizophrenia (24). In line with previous studies (2, 9, 10), we found that head injury did not add more to the risk of mental illness in persons with a psychiatric family history. The finding that persons without a psychiatric family history or infections experienced a greater effect of head injury with regard to some psychiatric outcomes could be due to undiagnosed illness or less severe illness treated outside the hospital. We also used psychiatric family history as a proxy for lower socioeconomic status (4) and lower education levels (6), both of which have been suggested to increase the risk of postinjury psychiatric disorders. Psychiatric family history might also be an indicator of dysfunctional family dynamics, which has been suggested to complicate postinjury recovery and contribute to mental illness (2, 4, 22). Individuals with preinjury psychiatric and substance use disorders were excluded. Physical abuse might also have confounded our results. However, besides adjusting for psychiatric family history, the adjustment for other fractures probably also removed some of this possible effect. Furthermore, individuals with epilepsy might have an increased risk of head injury (37), schizophrenia (38), and bipolar disorder (33), and epilepsy occurs more frequently following head injury (19). Nonetheless, after adjustment in the full model, which included epilepsy, the risks for schizophrenia and depression remained significantly elevated.

Head injury has been shown to increase the permeability of the blood-brain barrier (39) and possibly activate microglia within the brain (14). This might allow immune components from the peripheral blood access to the brain (14), possibly leading to neural dysfunction (39). Additionally, it has been suggested that after injury, brain tissue can be released into the peripheral blood with a possible synthesis of CNS-reactive antibodies (15). Such antibodies might reach the brain during subsequent periods of increased permeability of the blood-brain barrier, in line with the mechanisms by which autoimmune diseases and infections have previously been suggested to increase the risk of schizophrenia and depression (20, 21, 39). Although we did not find significant interaction between head injury and infections or autoimmune disease, they still acted as independent risk factors associated with mental illness, as has been shown previously (20, 21).

However, the most prominent hypotheses of the possible detrimental effect of head injury have been nonimmunological. Studies have found psychosis and mania after head injury to be associated with the anatomical location of the injury (10–12), and postinjury depression has been associated with reduced volumes of certain brain regions (4, 9). Moreover, it has been suggested that diffuse axonal injury disrupts neurotransmitter systems involved in psychosis and mood regulation (35). The outcome after head injury may also depend on the ability of the brain to recover through processes of neuroplasticity, and this ability may depend on age at injury (13), as reflected in the age effect observed in our study. The subsequent mental illness could also be a psychological reaction to the traumatic nature of the accident (2) or to the functional deficits that some individuals experience following a head injury (23, 34).

The large national cohort and the 34-year follow-up period are major strengths of the study. Restricting the cohort to individuals born on or after January 1, 1977, provided complete data on hospital contacts of the persons included, and the prospective design eliminated recall bias, as the outcomes were registered independently of all exposure diagnoses. A validation study (40) examined selected ICD-8 head injury diagnoses from the Danish National Hospital Register in the matched medical records and found correct diagnoses in 88% of the cases. A limitation of our study is that because the oldest cohort members were 33 years old, we may have underestimated the effect of head injury, as some individuals were probably not yet diagnosed with psychiatric disorders. Since our study included severe illness that led to hospital contact, our results are probably not referable to milder illness treated outside hospital settings. Furthermore, it was not possible to adjust for physical abuse as a confounder or to include posttraumatic stress disorder as an outcome.

In summary, we found that head injury increased the risk of all psychiatric outcomes. For schizophrenia, depression, and organic mental disorders, this effect did not seem to be ascribable merely to accident proneness or a psychiatric family history. The risk appeared to be greatest the first year following injury, and for schizophrenia and depression, those in the 11- to 15-year age group were shown to be especially vulnerable to exposure to head injury. This age effect could indicate a particularly sensitive period in neurodevelopment when the impact of a head injury can possibly lead to the development of mental illness.

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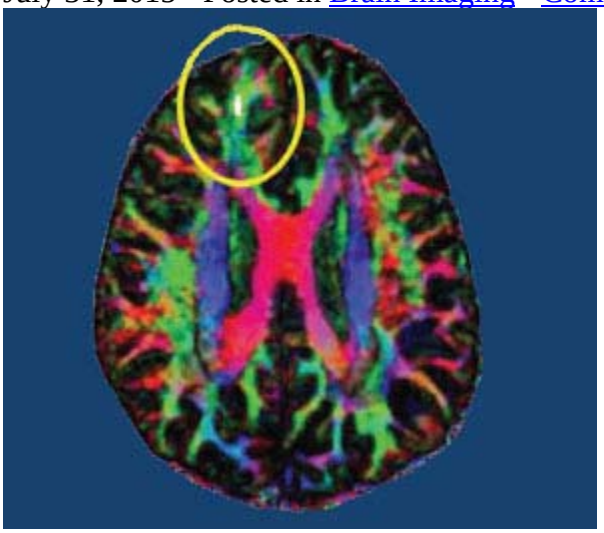
From BipolarNetwork.org

Neuropsychological Deficits After Concussion Are Correlated with White Matter Abnormalities

July 31, 2015 · Posted in Brain Imaging · Comment



DTI brain scan can show damage to white matter following a concussion.

Many people suffer problems with mental functioning after an apparent concussion (otherwise known as mild traumatic brain injury, or mTBI) that does not show abnormalities on traditional brain imaging measures such as the MRI. New technology called diffusion tensor imaging (DTI) shows that the integrity of white matter tracts may be disturbed by concussions. White matter comprises parts of the brain where myelin wraps around axons, as opposed to grey matter, which reflects the presence of neuronal cell bodies.

In a longitudinal study published in the *Journal of Neurotrauma,* Vigneswaran Veeramuthu and colleagues compared 61 people with an mTBI to 19 healthy controls. The mTBI participants had their neuropsychological faculties assessed an average of 4.35 hours after their trauma, and participated in DTI scans an average of 10 hours after the trauma. Both the neuropsychological assessment and the DTI scan were repeated six months later. When the acute and follow-up assessments were compared to the same assessments in control participants, the two groups showed differences in numerous white matter tracts at the six-month mark. There was also an association between the degree of abnormality observed on the DTI scans and decrements in performance on the tests of neuropsychological functioning both immediately after the trauma and six months later.

The researchers concluded that their results "provide new evidence for the use of DTI as an imaging biomarker and indicator of [white matter] damage occurring in the context of mTBI, and [the results] underscore the dynamic nature of brain injury and possible biological basis of chronic neurocognitive alterations."

Editor's Note: People should be aware of these findings, which confirm earlier studies, and begin rehabilitative treatment as soon as possible after a concussion. New research should target white matter tract changes, with the goal of secondary prevention, i.e. limiting damage to the brain after a traumatic injury has occurred. There are several promising drugs that can prevent damage if administered immediately after an mTBI, including the antioxidant supplement N-acetylcysteine (NAC), which has shown promise in preliminary clinical and laboratory studies, and many others, including lithium and valproate, as reported by De-Maw Chuang and this editor Robert M. Post in a 2015 article in the Journal of Neurology and Stroke *titled "Preventing the Sequelae of Concussions and Traumatic Brain Injury."*

POST-TRAUMATIC VERTIGO

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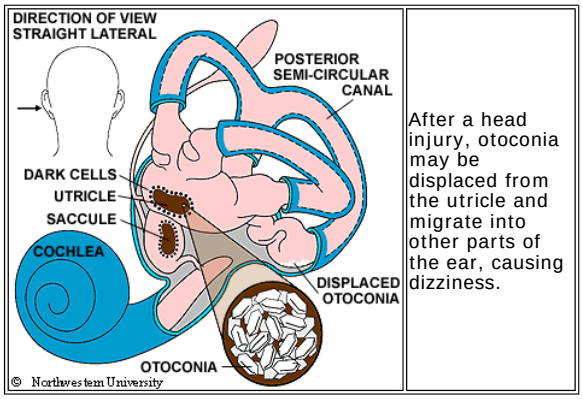
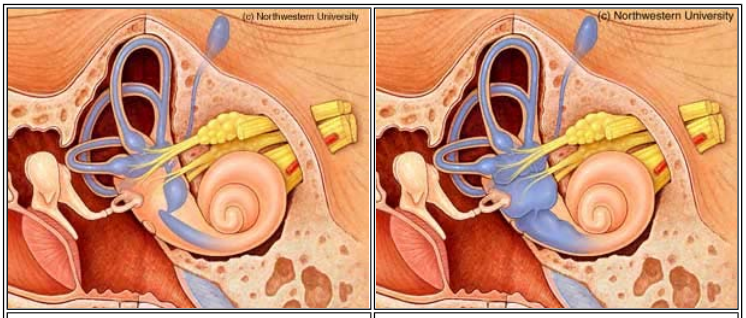
Head injuries are sustained by 5% of the population annually. Post-traumatic vertigo refers to dizziness that follows a neck or head injury -- while injuries to other parts of the body might in theory be associated with dizziness, in practice this is almost never the case. Patients with head or neck injury may also have loud and disturbing tinnitus (Folmer and Griest, 2003). The literature suggests that recovery occurs in from 3-9 months in most individuals, but that symptoms persist for more than 1 year in 10 to 15%.

Because of the high incidence of litigation associated with post-traumatic vertigo, most clinicians are extremely cautious in making this diagnosis. There are many potential causes of post-traumatic vertigo. A recent study performed in an otolaryngology setting suggested the following distribution of "primary" disorders: labyrinthine concussion (18), rupture of the round window membrane -- fistula (6), and cervicogenic vertigo (12). The secondary disorders included otolith disorders (5), delayed endolymphatic hydrops (12), and canalolithiasis (9)(BPPV). (Ernst et al , 2005). Another recent study (Hoffer et al, 2004) grouped patients into "positional vertigo", migraine-associated dizziness, and "Spatial Disorientation" (a wastebasket category). It seems likely that the distribution differs according to the practice setting (e.g. neurology, otolaryngology, general medicine).



After a head injury, otoconia may be displaced from the utricle and migrate into other parts of the ear, causing dizziness.

1. **Positional Vertigo**, and particularly Benign Paroxysmal Positional Vertigo or BPPV , is the most common type of severe dizziness, and it is also common after head injury, occuring in about 28% of persons with post-traumatic vertigo (Hoffer et al, 2004). It is easily recognized by the pattern of dizziness that is brought only when the head is placed in certain positions. There are several good treatments for BPPV and the prognosis for this syndrome, in the proper hands, is excellent. It is also possible to have rarer causes of positional vertigo including mainly utricular injury, vestibular atelectasis, and various forms of central vertigo caused by cerebellar or brainstem disturbances.



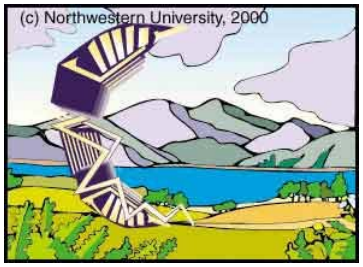
Normal membranous labyrinth

Dilated membranous labyrinth in Meniere's disease. After a head injury, scarring of the drainage pathways may cause fluid to build up.

2. **Post-traumatic Meniere's syndrome** --Also sometimes called "hydrops". Episodes of dizziness accompanied by noises in the ear, fullness, or hearing changes. Mechanism thought to be bleeding into inner ear, followed by disturbance of fluid transport. Onset of symptoms may vary from immediate to as long as one year later. There are frequently legal implications to this diagnosis. The probability of Menieres being reasonably attributed to post-traumatic mechanisms is a function of the severity of injury (severe makes more likely),

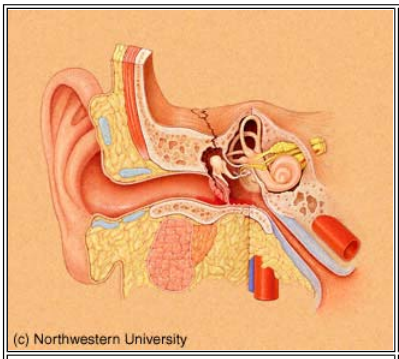
the latency from the injury (longer is less likely), the presence of a pre-existing condition, and the presence of secondary gain. Persons with the Large Vestibular Aqueduct syndrome are felt to be more likely to develop these symptoms (Berettini et al, 2000).

3. Labyrinthine "concussion". Defined as a non-persistent hearing or labyrinthine disturbance which follows a head injury, not caused by another mechanism. A hearing loss or a nystagmus must be present to make this diagnosis with a reasonable degree of medical certainty. While the name implicates an inner ear disturbance, this symptom complex may be impossible to differentiate from other entities. For example, it might be difficult to differentiate a labyrinthine "concussion" from an eighth nerve stretch injury, although newer testing modalities may help (e.g. VEMP).

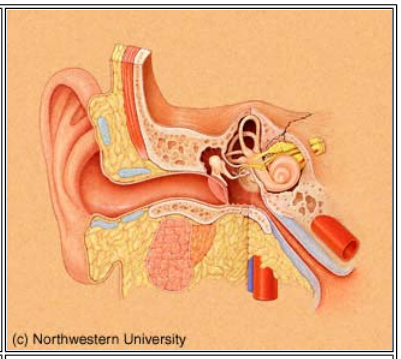


4. **Post-traumatic migraine**. Dizziness combined with migraine headaches. Migraine has been reported as common as 41% in persons with posttraumatic vertigo (Hoffer et al, 2004) Headaches and vertigo are common after head injuries. The main difficulty in this situation is to determine whether they are related or coincidental. It may also be difficult to distinguish post-traumatic headaches (which are very common), from migraine. The lack of a "litmus test" for Migraine, other than perhaps response to triptan medication, makes this diagnosis tenuous.

5. **Cervical Vertigo.** Imbalance following a severe neck injury. While nearly all dizziness specialists agree that cervical vertigo does exist, there is controversy regarding the frequency with which it occurs (Brandt T, 1996). Several theories exist as to the mechanism, the main ones being: 1). Vascular compression 2). Alteration of sensory input to the vestibular system. See later section on Whiplash.

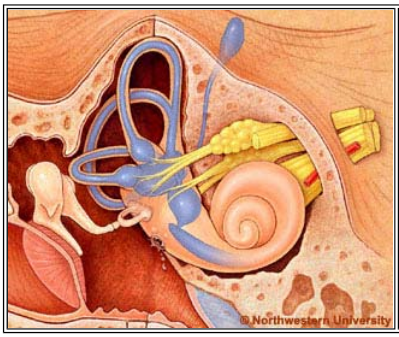


Longitudinal temporal bone fracture



Oblique temporal bone fracture

6. **Temporal bone fracture**. Severe dizziness after the injury, with skull or temporal bone CT scan indicating a fracture. Often accompanied by hearing loss or peripheral facial weakness (Bell's Palsy). Temporal bone fractures, especially the oblique variety (see above), may impair hearing and cause dizziness. There often is blood seen behind the ear-drum (hemotympanum). Either a conductive or sensorineural hearing loss may be present. Vestibular deficits are also common, especially in the oblique variety. Bilateral vestibular problems are exceedingly rare. Treatment is conservative. Prophylactic antibiotics are given, usually for 4 weeks. Myringotomy and insertion of a ventilating tube may be indicated, especially for serious otititis that persists after one month (Pulek and Deguine, 2001).



Round window fistula. A membrane "blows out" between the inner and middle ear, causing dizziness and possibly also hearing loss.

7. **Perilymph fistula**. Usually symptoms of imbalance and dizziness provoked by straining or blowing the nose. People with fistula may also get dizzy with loud noises (called Tullio's phenomenon). The frequency to which this syndrome occurs is controversial, but general opinion holds that it is rare.

7. Psychogenic vertigo. There are many possibilities. Factitious vertigo is complaints of vertigo related to psychological causes such as depression, anxiety, or an attempt to obtain compensation (also known as "malingering"). Anxiety and depression may result from traumatic brain injury that creates a self-perpetuating psychological reaction (Alexander, 1998). Post-traumatic stress disorder (PTSD) can result in reexperiencing and hyperarousal symptoms (King et al, 1998; Stein, 2002).

8. Epileptic vertigo. Vertigo due to brain injury, typically the part of the temporal lobe that processes vestibular signals. Loss of consciousness usually occurs at the time of injury and vertigo is generally accompanied by altered consciousness (Tusa et al, 1990). The typical symptom is "quick spins", although this symptom has other potential causes (BPPV, vestibular neuritis). Treatment is with anticonvulsants. Topirimate is a particularly good medication for this condition as it is also useful in Migraine.

9. Diffuse axonal injury (DAI). Pure decelleration forces can produce diffuse axonal injury (Gennarelli et al, 1982). In some individuals who come to autopsy after a twisting type injury of the head on neck, small areas of bleeding (petechial hemorrhage), and interruption of neuronal circuits (axonal damage) can be found.Complaints of dizziness attributed to brainstem injuries which cannot be imaged with a good MRI. This is an autopsy diagnosis -- it cannot be made with certainty prior to death. Historically, significant DAI is not felt to occur in awake humans who do not report loss of consciousness. A thirty minute loss seems likely to be needed for a significant DAI (Alexander, 1998).

10. Postconcussion syndrome. This is basically a combination of headache, dizziness, and mental disturbance which follows a head injury, without an identifiable etiology. It is a "wastebasket" syndrome, meaning that the diagnosis is made mainly by excluding other diagnoses. If an etiology can be determined for symptoms, a more specific diagnosis should be used. Post conconcussion syndrome is often attributed to "Traumatic Brain Injury", or TBI, which is simply a general term for a head injury affecting the brain. While dizziness and nausea symptoms usually resolve over 6 weeks, cognitive symptoms and headaches may be persist longer. Hoffer et al (2004) suggested that symptoms persisted an average of 39 weeks -- about 9 months, and that return to work usually occured at about 16 weeks. Occasionally symptoms are permanent. As noted above, in many cases, chronic symptoms are psychological in origin. Balance symptoms after concussion generally resolve by 10 days (Peterson et al, 2003)

11. Whiplash injury syndrome. The term "whiplash" is generally used to describe neck injuries that follow a rear-end collisions. Vertigo in this situation is usually attributed to "Cervical vertigo", but there are other potential causes (see below). Whiplash is classically attributed to soft tissue injury caused by hyperextension of the neck (Carroll et al, 1985). Injuries may include rupture of the anterior logitudinal ligament, muscle hemmorhage and tear, disk rupture, and occasionally, brain injury. Visual disturbances as well as inner ear disturbances are classically attributed to vertebrobasilar artery injury (Carroll et al, 1985). The vertebral arteries might be injured by movement of the vertebrae, or elongation of the vertebral arteries (Panjabi et al, 1998: Eck et al, 2001). In the latter situation, one would not expect to find any abnormalities of vertebral motion on imaging.

Whiplash clinically is similar to postconcussion syndrome, but with the addition of neck complaints. It is possibly related to cervical vertigo. Dizziness occurs in 20-60%. It can persist for years but fortunately about 75% of patients are recovered by 1 year (Radanov et al, 1994). Long term studies show that aches and pains may persist in 20 to 45% of patients with significant whiplash. Degenerative problems develop after injury in about 40% of patients. They are more common in persons with more severe collisions.

Vibert and associates (2003) reported three cases of peripheral ear type vertigo (1 BPPV, 2 vestibular nerve injury) after whiplash. They suggested that dizziness associated with whiplash may be more often due to vestibular injury rather than neck or brain trauma.

Whiplash may be increased by use of seat-belts. Seat-belts limit body injury, but can paradoxically increase cervical injuries as they restrict movement of the trunk. Testing for this condition may include X-rays of the neck. Active flexion and extension lateral views can be helpful in documenting dynamic stability. A CT scan of the cervical spine may help in better defining bony injuries. An MRI and MRA scan of the neck may be helpful with disks, vascular syndromes, and other soft tissue injuries.

Diagnosis of post-traumatic vertigo

First the doctor will want to know exactly when and how the head or neck was injured, and the character of the dizziness (i.e. spinning ? unsteadiness ? confusion ?). He/she will want to know if you were unconcious and the duration of time. Did the airbag deploy ? There is a significant incidence of vertigo and hearing disturbance after airbag deployment (Yaremchuck and Dobie RA. 2000). All available records from the emergency room or hospital where you were seen after the injury should be obtained and shown to your doctor. This is especially important when there is litigation as much may depend on small details.

Next, a specialized examination for dizziness will be performed. Balance will be measured, often with moving platform posturography. A search for "nystagmus" will be made, related to head and/or neck position or to vibration of the neck. You may be checked for pressure sensitivity with the fistula test.

Laboratory tests will be ordered. In most instances these will include an audiogram, ENG, possibly an MRI scan or CT scan of the inner ear (temporal bone CT scan). If available, a VEMP may be useful. An EEG may be obtained for persons with paroxysmal cognitive symptoms suggestive of epilepsy. In patients with hearing disturbance, an "ECOG" may be done. Moving platform posturography is helpful to quantify balance deficits.

Psychological testing is sometimes done in persons who have entirely normal test results. They can document interactions between symptoms and personality as well as cognitive difficulties. Such testing is often useful in sorting out the situation when patients are in litigation and could benefit from an appearence of ill health.

Treatment of post-traumatic vertigo

Treatment is individualized to the diagnosis. Treatment usually includes a combination of medication, changes in life style, and possibly physical therapy. Occasionally, surgery may be recommended.

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ACUTE PERIPHERAL VESTIBULAR DEFICITS AFTER WHIPLASH INJURIES

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We report 3 patients who had acute peripheral vestibular dysfunction minutes to hours after a car collision with whiplash injury without head trauma. The accident was a frontal collision in 1 case, a rear impact in the second, and lateral in the third. All patients complained immediately of cervicalgia, headache, acute vertigo with a sensation of erroneous body movements, and slipping of image with head movements. A sudden sensation of tilting of the environment when driving, tinnitus, and hyperacusis were also described. The otoneurologic findings showed bilateral canalolithiasis in 1 patient and an acute peripheral vestibular deficit in 2 patients. Tilt of the subjective visual vertical was measured in all patients. Cerebral magnetic resonance imaging yielded normal findings. As angular and linear accelerometers, the vestibular organs are directly exposed to high forces generated by whiplash mechanisms. Vertigo generated by peripheral vestibular lesions is probably underestimated in whiplash injuries and may often be incorrectly attributed to cervical or cerebral lesions.

KEY WORDS — otolith organ, semicircular canal, subjective visual vertical, vertigo, whiplash injury.

INTRODUCTION

Biomechanically, whiplash is a dynamic and inertial event that is not caused by a direct blow to the neck or head.[1] It corresponds to an acceleration-deceleration mechanism of energy transfer to the neck. The most common causes are car accidents such as rear-end, frontal, or lateral collisions. Such impact might generate bony and/or soft tissue injuries of the head and neck ("whiplash injuries"), which in turn may lead to a variety of clinical manifestations ("whiplash-associated disorders").[2] The symptomatology is often polymorphous. The most common complaints are cervicodynia, headache, and scapulodynia. Dizziness and vertigo are reported in 25% to 50% of cases, depending upon the study.[3,4] Auditory disorders such as tinnitus and hearing impairment are described in 14% and 5% of cases, respectively.[4] More complex complaints are reported: memory disorders, concentration disorders, and visual disturbances in 31%, 34%, and 24%, respectively.[4] Otoneurologic findings of 3 patients with an acute peripheral vestibular deficit beginning some minutes to hours after a car accident with whiplash injury are reported and discussed.

PATIENTS AND METHODS

All patients underwent a complete otoneurologic examination including history, clinical vestibular examination, pure tone audiogram, brain stem auditory evoked potentials (BAEPs), electronystagmography (ENG), and measurements of subjective visual vertical (SVV) by the monocular method of modified Maddox glasses as described previously.[5]

Electronystagmography consisted of recording spontaneous nystagmus with (light) and without (darkness) visual fixation; positional nystagmus with the head in hyperextension, then turned to the right and to the left (positions of Rose); and optokinetic nystagmus at speeds of 25°/s, 50°/s, and 75°/s (rotation to left and right) with whole retinal field stimulation. This was followed by an examination of smooth pursuit, a rotatory pendular test (undamped rotation of 360° in 20 seconds; sinusoidal frequency of 0.05 Hz with a peak velocity of 60°/s) with (light) and without (darkness) visual fixation suppression, and a bithermic caloric test with recordings of nystagmus duration after irrigation of each ear for 20 seconds with 20 cm^3 of water at 44°C and 30°C and with ice water if needed. The corneoretinal potentials were recorded for all examinations simultaneously on both eyes with horizontal and vertical leads. Criteria of abnormality were defined as follows: presence in darkness of horizontal (≥1 Hz) spontaneous nystagmus, and rotatory, vertical positional nystagmus; irregular smooth pursuit, irregularity, and gain of <50% of the optokinetic nystagmus (normal value, 100%); and asymmetry of nystagmic responses (side difference ≥ 25%) to caloric and rotatory pendular testing.

Case 1. A 57-year-old man was the seat-belted driver of an automobile during a frontal collision that occurred at a speed of approximately 100 km/h. Im-

mediately after the impact, he complained of cervicodynia and positional transient vertigo on head rotation toward the left. During the following days, he described a feeling of erroneous movements on driving the car, particularly when executing short curves, as well as an episode of subjective vertical tilt of the environment toward the left during a rear maneuver with his car. During the following weeks and months after the accident, he suffered from repeated episodes of vertigo with dizziness, nausea, vomiting, and sensations of images slipping during head and body movements, as well as sensations of erroneous movements. He also reported difficulties of concentration at his workplace, as well as disturbances of comprehension in discussions during meetings. These problems disappeared progressively after several weeks. Otoneurologic examination was performed 2 months after the accident.

Clinical vestibular examination showed transient geotropic rotatory nystagmus during the Hallpike maneuver to the left and transient upper vertical nystagmus with a geotropic rotatory component for the Hallpike maneuver to the right. The SVV was tilted 5° toward the left. The first ENG showed normal smooth pursuit, decreased gain (34%) of optokinetic nystagmus at 75°/s during rotation toward the left, a preponderance of the left nystagmus (44%) during rotatory pendular testing, and symmetric caloric responses at 44°C and 30°C (side difference, 11%). Audiological findings revealed a high-frequency sensorineural hearing loss on the left side, which had been known for several years, and normal hearing in the other ear. Brain stem auditory evoked potentials and findings on cerebral magnetic resonance imaging (MRI) were normal. No persistent cervical disorder was found on follow-up clinical examination. Eighteen months after the accident, the vertigo had disappeared and the follow-up ENG findings were normal.

Case 2. A 22-year-old woman was the seat-belted driver during a rear-end collision that occurred with an impact speed of about 60 km/h while her car was stopped at a red light. Three hours after the event, she complained of dizziness, slipping of images with head and body movements, and mild cervicodynia. Several hours later, during the night, she complained of acute vertigo with ataxia and vomiting, as well as hyperacusis and tinnitus on both sides. She also complained of concentration disturbances, especially on reading, for several weeks after the accident. During examination showed a spontaneous right second-degree nystagmus, a permanent positional right nystagmus during the Rose maneuvers, irregular smooth pursuit, decreased gain of optokinetic nystagmus to 30% and 10% at 50°/s and 75°/s, respectively, during rotation toward the right, a preponderance of right nystagmus (side difference, 42%) during rotatory pendular testing, and left areflexia during caloric testing at 44°C and 30°C (side difference, 100%; Fig 1A). The SVV was tilted 5° toward the left. The cerebral MRI findings were normal. No persistent cervical disorder was found on follow-up clinical examination.

The acute dizziness episodes decreased progressively and disappeared after several weeks. However, erroneous perception of movements such as a feeling of attraction toward the left remained, especially during quick changes of body positions. Five months after the accident, the follow-up ENG showed normal smooth pursuit, persistent decreased gain of optokinetic nystagmus of 44% and 15% at 50°/s and 75°/s, respectively, during rotation toward the right, and hyporeflexia of the caloric response in the left ear (side difference, 32%). The rotatory pendular test results were normal (side difference, 20%; Fig 1B).

Case 3. A 56-year-old woman was the seat-belted driver during a lateral collision that occurred at a speed of about 50 km/h while her car was stopped at a red light. Immediately after the impact, she complained of headache and cervicodynia. During the following days, she described an acute dizziness and a feeling of erroneous movements on walking. During the following months, she suffered from recurrent positional vertigo episodes with nausea, as well as a sensation of erroneous movements on walking. Since the accident, she has suffered from problems with concentration, difficulties with memory and ideation, and difficulty falling sleep.

Otoneurologic examination was performed 14 months after the accident. Clinical vestibular examination showed transient right nystagmus during the Hallpike maneuver to the left. The pure tone audiogram and BAEPs were normal. The ENG showed a permanent positional right nystagmus during the Rose maneuver to the right, an irregular smooth pursuit, a preponderance of right nystagmus during rotatory pendular testing (side difference, 30%) with a subtotal visual suppression of the per-rotatory nystagmus, and mild left hyporeflexia on caloric testing at 44°C and 30°C (side difference, 29%). The SVV was

diometry and BAEPs were normal. The first ENG

points of tenderness on the left side.

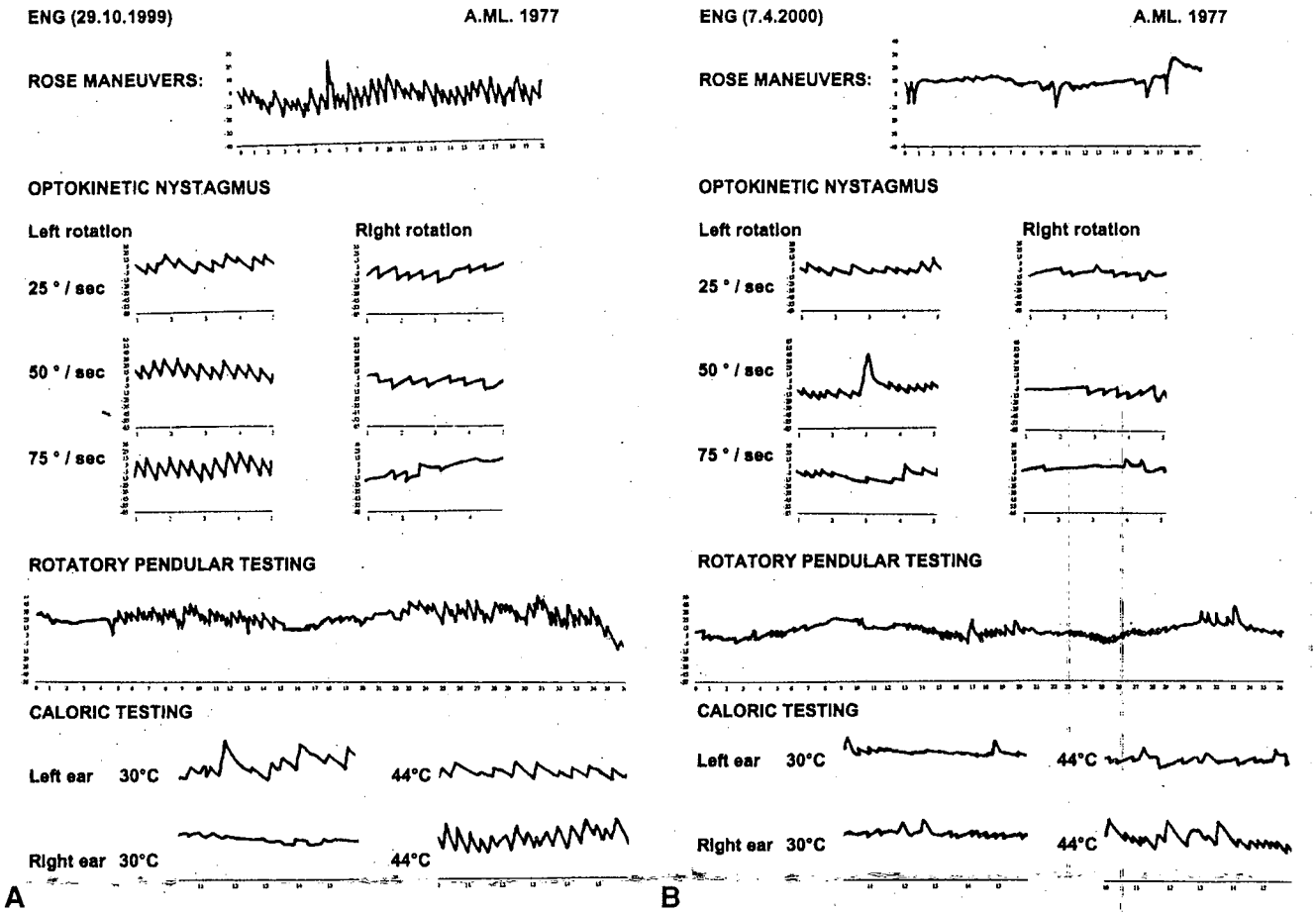

Fig 1. (Case 2) Electronystagmographic findings **A)** 2 days and **B)** 5 months after rear-end collision.

DISCUSSION

In 1995, the Québec Task Force on Whiplash-Associated Disorders proposed a classification of whiplash injuries into 4 grades depending on the neck's symptoms (see Table[6]). Grade I corresponds to complaints of neck pain without physical signs, and grade IV neck pain is associated with cervical bone fracture or dislocation. The 2 intermediate grades, II and III, correspond to neck complaints associated with musculoskeletal signs and neurologic signs, respectively. Auditory and vestibular symptoms such as hearing impairment, tinnitus, vertigo, and dizziness may be present in all grades of the classification.

CLINICAL CLASSIFICATION OF QUEBEC TASK FORCE FOR WHIPLASH-ASSOCIATED DISORDERS[6]

*Grade**	*Clinical Symptoms*
0	No complaint about neck; no physical sign(s)
I	Neck complaint of pain, stiffness, or tenderness only; no physical sign(s)
II	Neck complaint and musculoskeletal sign(s)

Neck pain is the most common symptom described after whiplash injury mechanisms and is reported in 88% to 100% of cases, depending on the study. Visual disturbance, auditory symptoms, and vertigo are described in 8% to 21%, 4% to 18%, and 17% to 25% of cases, respectively.[3]

From the otoneurologic point of view, Oosterveld et al[4] demonstrated that of 262 patients investigated 6 months to 5 years after a whiplash injury, 85% complained of persistent dizziness such as rotatory vertigo (50% of cases), and 35% complained of erroneous body sensations (floating sensations). Tinnitus was present in 14% of patients, and unilateral or bilateral hearing loss was reported in 5% of cases. Visual disturbances such as blurred vision and focusing impairment were described by 24% of patients. The ENG findings showed spontaneous, positional nystagmus, gaze nystagmus, and disturbances of smooth pursuit and of optokinetic nystagmus. Saccade impairments may be present more than 1 year after an accident.[7] Disturbances of the vestibulo-ocular reflex are also

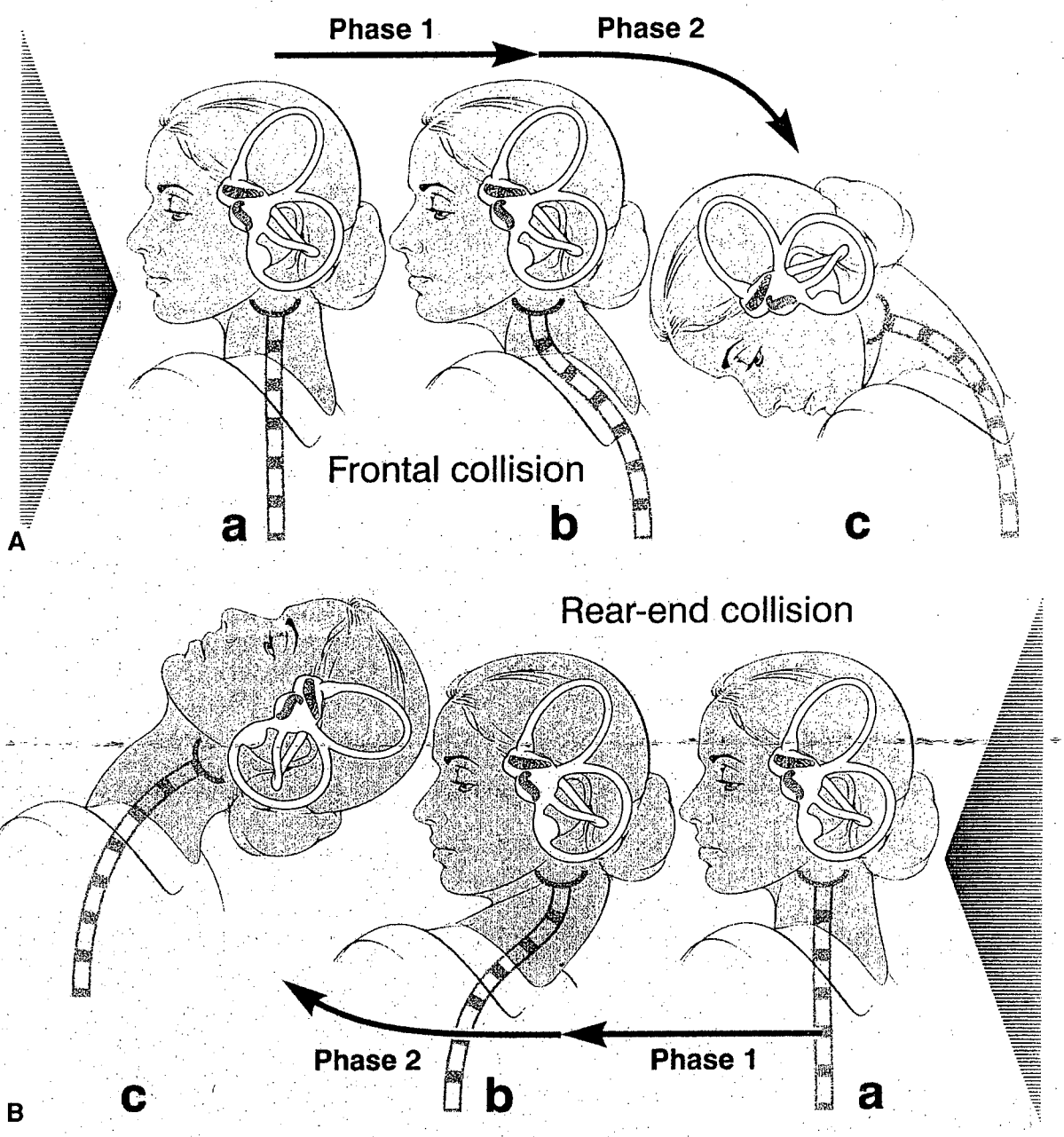

Fig 2. Positions of otolith organs during horizontal translational displacement of head in **A)** frontal collision and **B)** rear-end collision.

Otoneurologic findings in our patients included complaints of positional vertigo, sensations of erroneous movements and sudden tilting of the environment, and dizziness with ataxia that lasted for several days. These were consistent with a bilateral canalolithiasis (case 1) and an acute otolithic and horizontal semicircular canal deficit (cases 2 and 3) present

tibular deficit.[12,13] The progressive increased gain of the optokinetic response shown on the follow-up ENG might be interpreted as a sign of beginning central compensation for the peripheral vestibular deficit. In the literature, a directional preponderance of optokinetic nystagmus has also been described in cases of unilateral peripheral vestibular disorders such as

ous nystagmus generated by the left peripheral ves-

part of the ocular tilt reaction, which corresponds to

clinical signs of lesions attributed to the otolithic organs or graviceptive pathways. This is well documented as occurring after surgical vestibular deafferentation,[15-17] as well as after peripheral acute vestibular deficits such as unilateral sudden cochleovestibular loss and sudden idiopathic unilateral peripheral vestibular loss.[5,18-20] A tilt of the SVV after canalolithiasis is also measurable, but only in a small percentage of patients (17%) that is not statistically significant.[21]

Regarding case 3, it was interesting to note that the SVV remained tilted more than 1 year after the otolithic lesion. Such a finding was also observed in the long-term evolution of SVV after surgical peripheral vestibular deafferentation and interpreted as an incomplete otolithic compensation of the peripheral deficit.[22] Frontal and rear-end collisions generate a significant strain on neck and head structures. During this acceleration-deceleration event, the force acceleration might reach 5 to 30 g, depending on the speed of impact.[23] As angular and linear accelerometers, the vestibular organs directly encounter such acceleration-deceleration movements. During the initial phase, the head undergoes a horizontal translational displacement relative to the torso. This is called protraction in the case of a frontal collision and retraction in a rear-end collision (Fig 2). In both situations, the force of translation generated by the impact is recorded by the otolithic organs, especially the utriculus. Depending on the acceleration force, one can hypothesize that the "slipping" movement during the head translation generates otolith displacements or damage of the sensorineural cells, especially the hair cells. One can hypothesize that the acute or persistent dizziness and feeling of erroneous movements might be correlated to transient or permanent lesions of these structures, perhaps similar to the mechanism that has been described for the cochlear hair cells after noise exposure.

Lesions of the vestibular organs, particularly the otolithic organs, after whiplash injuries are probably underestimated by attributing dizziness and vertigo symptoms mainly to cervical damage and lesions of the central nervous system. Furthermore, the otolithic dysfunction seems not to be directly correlated to the severity of the whiplash injury. Indeed, patients 1 and 2 were classified as grade I and patient 3 as grade II on the Quebec Task Force classification system (see Table).

Various complaints such as lack of concentration, decreased efficiency, disturbance of intellectual faculties, and depression could also be manifestations of the peripheral vestibular dysfunction. Indeed, these symptoms are often clinically observed by patients after peripheral vestibular deficit that remains incompletely compensated.

A complete otoneurologic examination, including measurements of otolithic function, should be undertaken as soon as possible after the accident, that is, within the first days to weeks. The aims would be to demonstrate the presence of an acute peripheral vestibular lesion in order to have objective findings in case of possible future litigation and to treat the peripheral vestibular dysfunction appropriately and quickly by vestibular physiotherapeutic training.

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Vestibular Deficits after Whiplash Injuries

Synopsis by: William J. Owens, D.C., D.A.A.M.L.P.
Mark E. Studin, D.C., F.A.S.B.E. (C), D.A.A.P.M., D.A.A.M.L.P.

USE: When trauma patients present with tinnitus, dizziness or visual field deficits

CITATION: *Ann Otol Rhinol Laryngol 112:2003*

AUTHORS: Dominique Vibert, M.D. and Rudolf Hausler, M.D.
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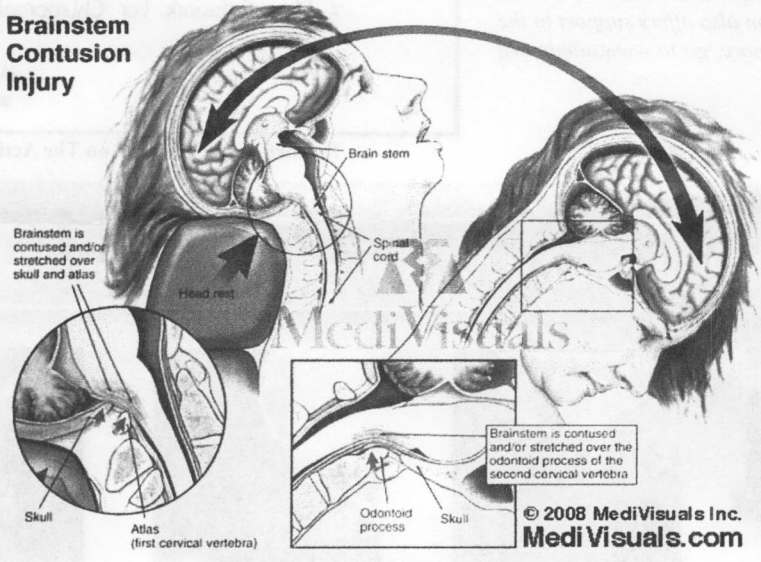
This manuscript addresses one of many important issues to keep in mind when evaluating patients that present with neck or head trauma. In the case of whiplash type injuries, it is the inertia of the trauma that causes the injury. The context of this paper was relative to whiplash injuries without direct head trauma; however, any type of acceleration/deceleration syndrome can produce symptoms of tinnitus, dizziness or visual field deficits (falls, fights, contact sports). It is reported that "dizziness and vertigo are reported in 25 percent-50 percent of [whiplash] cases."



When evaluating a patient that complains of the above symptoms, in what ways do you strive to objectify those subjective complaints? Determining the proper diagnostic test will assist you in a proper and timely medical specialty referral.

In this paper, the authors reviewed three individual cases where the patients had experienced acute peripheral vestibular dysfunction following car accidents. The following cases were discussed and, as you can see, the speed and collision type varies.

1: Case #1: "Fifty-seven-year-old male, frontal collision, speed approx 100km/hr."

2: Case #2: "Twenty-two-year-old female, rear-end collision, speed approx 60km/hr."

3: Case #3: "Fifty-six-year-old woman, lateral collision, speed approx 50km/hr."

Most importantly, "Lesions of the vestibular organs, particularly the otolithic organs after whiplash injuries, are probably underestimated by attributing dizziness and vertigo symptoms mainly to cervical damage and lesions of the central nervous system." They also stated in the article that "otolithic dysfunction seems not to be directly correlated to the severity of the whiplash injury".

It was determined that these types of symptoms can be found in all five categories of whiplash injury; therefore, it is most important to evaluate the patient properly to obtain an accurate diagnosis.

Two tests that are specific to these injuries and subjective complaints include:

1. Brainstem Auditory Evoked Potential (BAEP): This test, as the name implies, targets the brainstem area and is a recording of the electrical activity coming from the brain stem.

2: Electronystagmography (ENG): Electronystagmography is a test to look at voluntary and involuntary eye movements.

It evaluates the acoustic nerve, which aids with hearing and balance.

The paper also references that Oosterveld, et al., 1991, "demonstrated that of 262 patients investigated six months to five years after a whiplash injury, 85 percent complained of persistent dizziness such as rotary vertigo (50 percent of cases), and 35 percent complained of erroneous body sensations (floating sensations). Tinnitus was present in 14 percent of patients and unilateral or bilateral hearing loss was reported in 5 percent of cases.

Finally, it was stated that, "Lesions of the vestibular organs, particularly the otolithic organs after whiplash injuries, are probably underestimated by attributing dizziness and vertigo symptoms mainly to cervical damage and lesions of the central nervous system. A complete otoneurological examination should be undertaken as soon as possible after the accident, that is, within the first days to weeks.

Each issue, a clinical topic will be provided by Drs. Mark Studin & William J. Owens of the American Academy of Medical Legal Professionals (AAMLP), which is a national non-profit organization comprised of doctors and lawyers. The purpose of the organization is to provide its members with current research in trauma and spinal-related topics to keep the professional on the cutting edge of healthcare. Members may also sit for a Diplomate examination and be conferred a DAAMLP. The organization also offers support to the individual member's practice. To learn more, go to www.aamlp.org or call 1-716-228-3847.

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Topics in Diagnostic Imaging

Chiropractic Response to a Spontaneous Vertebral Artery Dissection

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Key indexing terms:
Vertebral artery dissection;
Manipulation, spinal;
Stroke;
Chiropractic;
Adverse effects

Abstract

Objective: The purpose of this case report is to describe a case in which early detection and proper follow-up of spontaneous vertebral artery dissection led to satisfactory outcomes.

Clinical Features: A 34-year old white woman reported to a chiropractic clinic with a constant burning pain at the right side of her neck and shoulder with a limited ability to turn her head from side to side, periods of blurred vision, and muffled hearing. Dizziness, visual and auditory disturbances, and balance difficulty abated within 1 hour of onset and were not present at the time of evaluation. A pain drawing indicated burning pain in the suboccipital area, neck, and upper shoulder on the right and a pins and needles sensation on the dorsal surface of both forearms. Turning her head from side-to-side aggravated the pain, and the application of heat brought temporary relief. The Neck Disability Index score of 44 placed the patient's pain in the most severe category.

Intervention and Outcome: The patient was not treated on the initial visit but was advised of the possibility of a vertebral artery or carotid artery dissection and was recommended to the emergency department for immediate evaluation. The patient declined but later was convinced by her chiropractor to present to the emergency department. A magnetic resonance angiogram of the neck and carotid arteries was performed showing that the left vertebral artery was hypoplastic and appeared to terminate at the left posterior inferior cerebellar artery. There was an abrupt moderately long segment of narrowing involving the right vertebral artery beginning near the junction of the V1 and V2 segments. The radiologist noted a concern regarding right vertebral artery dissection. Symptoms resolved and the patient was cleared of any medications but advised that if symptoms reoccurred she was to go for emergency care immediately.

Conclusion: Recognition and rapid response by the chiropractic physician provided the optimum outcome for this particular patient.

Introduction

Stroke was the fifth leading cause of death in the United States in 2013. [1] Most vascular diseases, including stroke, "share common risk factors (high blood pressure,

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diabetes, dyslipidemia, and obesity), which can be influenced by modifiable health behaviors such as unhealthy diet, smoking, lack of physical activity, and stress."[2] The disruption of blood flow to the brain is also affected by anatomical variations and anomalies, disruption of the arterial intimal lining in the carotid and/or vertebral arteries, and disease resulting in coagulation issues and/or the obstruction of normal hemodynamics. (See Figs. 1– 7.)

Not all patients who experience stroke symptoms face immediate death or disability. The traditional definition of a transient ischemic attack (TIA) is a time-defined temporary blockage of blood flow in the brain that causes brief stroke symptoms. A new definition is a tissue-defined TIA that exhibits an absence of evidence of fresh brain infarction on magnetic resonance imaging (MRI). Such tissue-defined TIAs are considered to be warning signs of more serious strokes in the future. Transient ischemic attack symptoms do not last long. Such symptoms may include weakness on one side of the body, dizziness, blurred vision, confusion, and speech problems.[3] As a vascular disease, TIAs share the same risk factors as stroke and can be influenced by modifiable health behaviors.[2]

Although there is no evidence to support causation, an association between manual cervical spine manipulation and the occurrence of stroke or stroke-like symptoms has been suggested in the medical literature[4–6] and occasionally mistakenly attributed to chiropractic manual manipulation.[7] Practitioners of manual manipulation of the cervical spine, including chiropractic physicians, osteopathic physicians, qualified medical physicians,

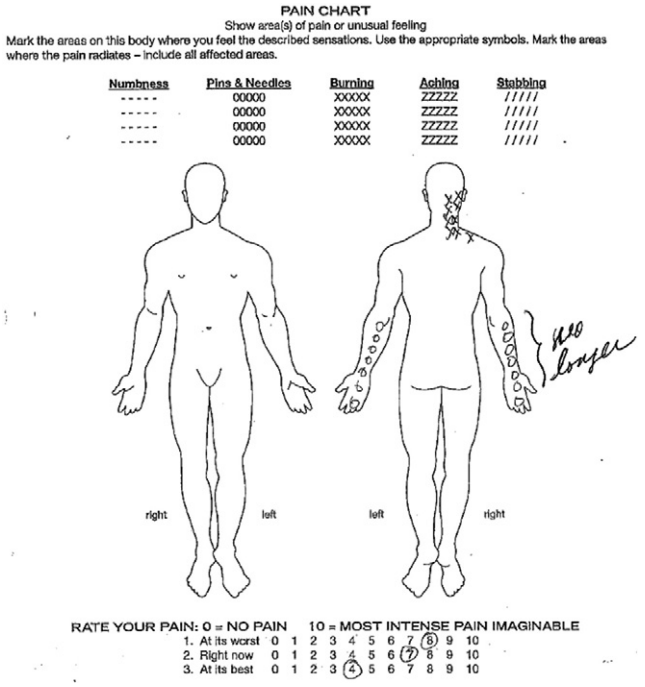

Fig. 1. Pain drawing indicating burning pain in the area of the right sub-occipital and cervical area and pins and needles sensation on the dorsal surface of both forearms.

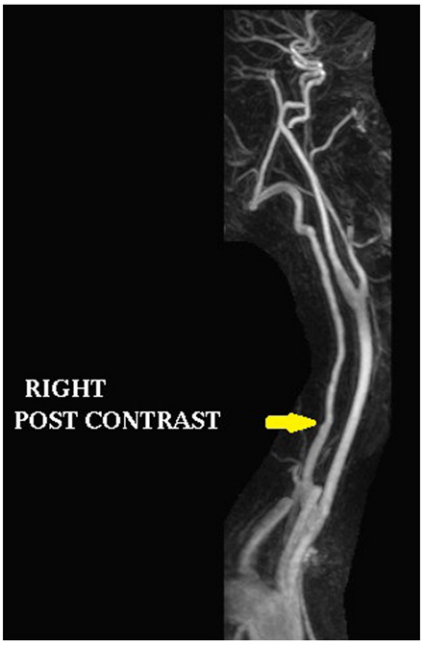

Fig. 2. MRA neck image. Three-dimensional dynamic time-resolved contrast-enhanced MRA of the neck reveals abrupt moderate long segment narrowing of the right vertebral artery involving the V2 and distal V1 segments. *(Color version of figure appears online.)*

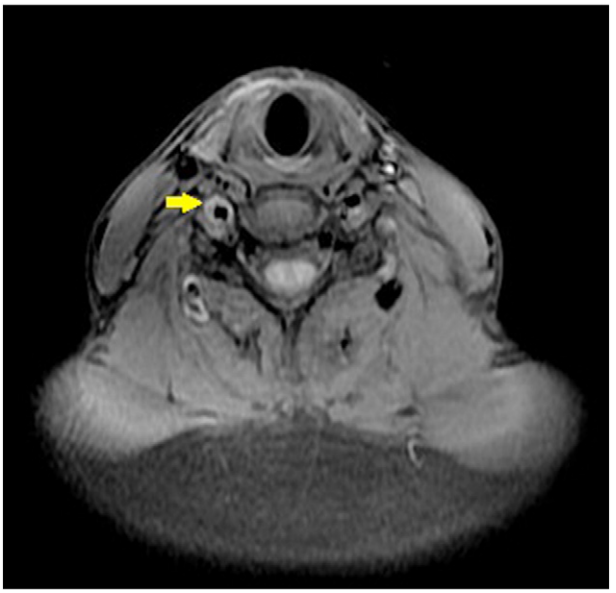

Fig. 3. MRA neck image. Fat suppressed axial T1 weighted imaging of the neck utilizing IDEAL technique (Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation) reveals high signal within the wall of the V2 segment of the right vertebral artery compatible with intramural hematoma. *(Color version of figure appears online.)*

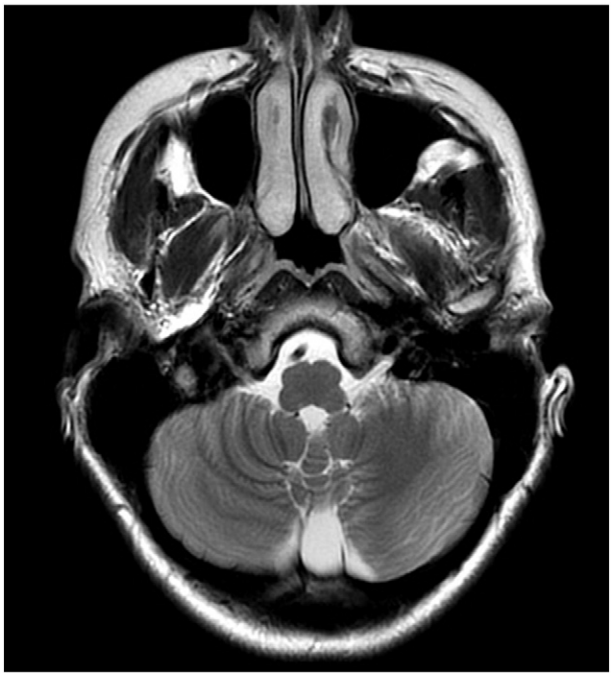

Fig. 4. MRI brain image. Axial MRI of the brain (including diffusion weighted imaging) through the posterior fossa and posterior cerebral artery distribution territory reveals no evidence of acute or subacute infarction.

physical therapists, and any other qualified practitioners must be vigilant for signs of stroke. The early detection, immediate appropriate care, patient education, and short- and long-term follow-ups are key factors in the prevention of undue consequences and potentially tragic outcomes.

The purpose of this case report was to provide an example of how early detection and proper follow-up led to satisfactory outcomes.

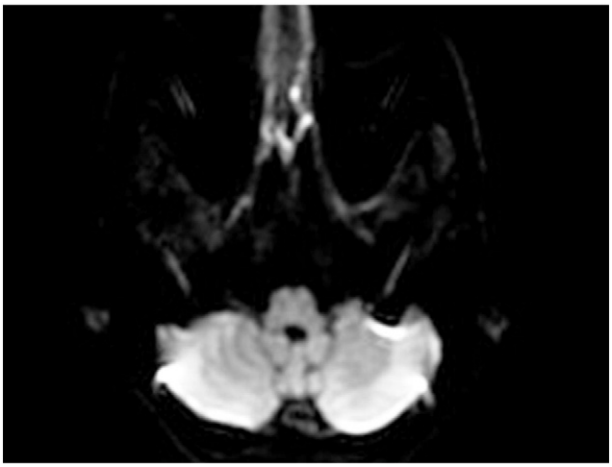

Fig. 5. MRI brain image. Axial MRI of the brain (including diffusion weighted imaging) through the posterior fossa and posterior cerebral artery distribution territory reveals no evidence of acute or subacute infarction. *(Color version of figure appears online.)*

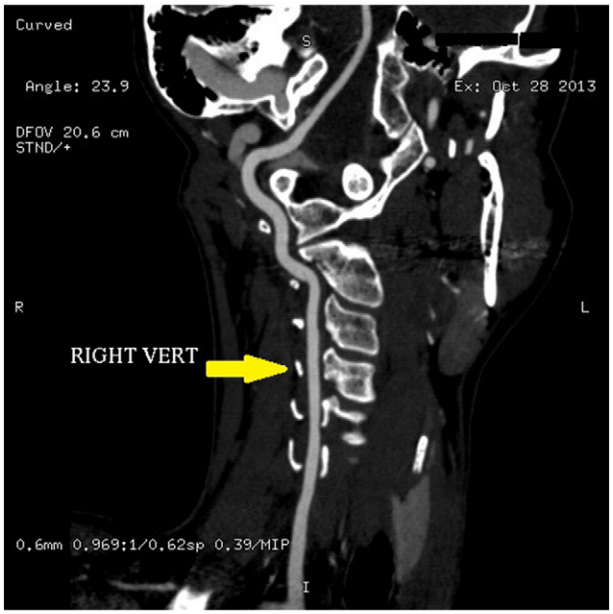

Fig. 6. CT angiography neck image. Curved planar reformatted imaging of the right vertebral artery from CT angiography of the neck performed 3 months after initial imaging reveal near complete resolution of the right vertebral artery narrowing related to arterial dissection.

Case Report

On July 22, 2013, a 34-year-old white woman reported to the office of a chiropractic physician in the

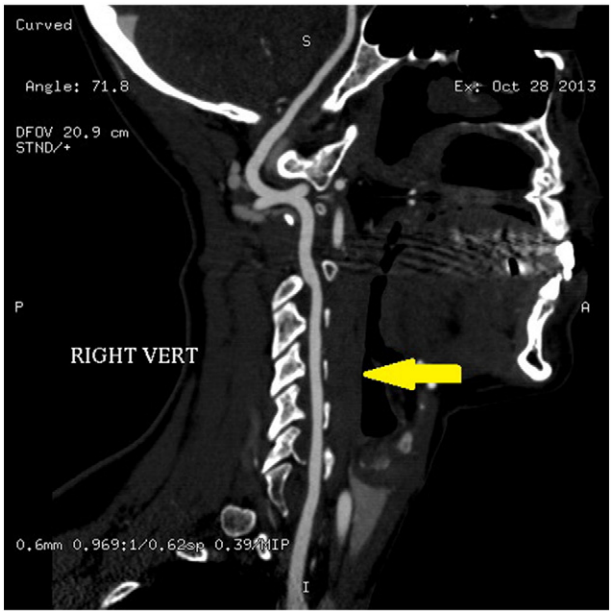

Fig. 7. CT angiography neck image. Curved planar reformatted imaging of the right vertebral artery from CT angiography of the neck performed three months after initial imaging reveal near complete resolution of the right vertebral artery narrowing related to arterial dissection. *(Color version of figure appears online.)*

Chiropractic Medicine division of the Lehigh Valley Hospital Network (LVHN). The patient worked as an operating room nurse in the same hospital system. The cardiothoracic surgeon whom the patient was working with directly referred her to the chiropractor.

Chief Complaint

The chiropractic physician initially saw the patient at 5 pm. The patient's chief complaint was a constant burning pain in the right side of her neck and shoulder with a limited ability to turn her head from side to side. She also experienced periods of blurred vision and muffled hearing since the onset of symptoms, which began at 9:30 AM on the same day. The immediate onset of symptoms started after she lifted a patient's legs onto the operating table. At the time onset, there was dizziness, spots in her field of vision, and a partial loss of balance that resulted in a walk that listed to the right. There were no nausea nor vomiting. She reported that her dizziness, visual and auditory disturbances, and balance difficulty abated within 1 hour of onset and were not present at the time of evaluation. The patient reported that she had "[taken] some ibuprofen and a little later some valium and left work early." The patient denied any prior symptoms of this nature.

History

There was no family history of any significant disease or condition. She had no known allergies and was taking ethinyl estradiol and levonorgestrel,[8] for birth control and diazepam[8] for pain. The patient had never been to a chiropractor prior to this event. The patient reported smoking 2 cigarettes per day, drinking 1 cup of coffee and tea per day and using alcohol "socially." The date of her last menstrual period was July 17 to July 21, 2013, and she stated that she was not pregnant. She had no history of cancer and no significant weight change over the last year. She presented with mild scoliosis in the lumbar and thoracic regions.

Initial Examination

The patient was 5' 10" in height, weighed 145 lb, and had a body mass index of 21, a blood pressure of 118/78, and a pulse rate of 70 beats per minute. Her walking was normal with no drifting or abnormal gait. Her cervical range of motion exhibited limitations in flexion (40/45), extension (10/30), right lateral flexion (20/40), left lateral flexion (30/40), right rotation (40/80), and left rotation (60/80). Her eyes, ears, nose, throat, and heart were normal.

A cervical compression test was negative for aggravation of the symptoms, cervical distraction decreased the pain, and Spurling test[9] reproduced the localized neck pain, particularly in the upper right cervical area, but no dizziness occurred. There was no nystagmus. The deep tendon reflexes, sensations, and muscle strengths of the upper extremities were normal. Cranial nerves 2 to 12 were normal. There were no long tract signs. Palpable tenderness, tension, and edema were noted in the upper right cervical region, and mild scoliosis was noted in the lumbar/thoracic region.

The patient had a prior history of mid and low back pain and arm/hand numbness. She reported that transient dizziness, loss of balance, ringing in ears, and blurred vision occurred earlier that day. At the time of the examination, she was still experiencing right-side neck and shoulder area pain, a headache, and neck tension.

On a pain drawing,[10] the patient indicated the presence of burning pain in the sub-occipital area, neck, and upper shoulder on the right and a pins and needles sensation on the dorsal surface of both forearms, although this sensation had subsided on the right. The intensity of the pain ranged from 8 (worse) to 4 (best) and averaged 7 at the time of the clinic visit. Turning the head from side-to-side aggravated the pain, and the application of heat brought temporary relief. The Neck Disability Index[11] score of 44 placed the patient's pain in the most severe category. A working diagnosis of *ICD-9* codec 723.1 (cervicalgia) and 737.3 (scoliosis) were entered into the patient's record. Based on the patient's age, sudden nontraumatic onset of severe upper neck pain and headache and transient neurological symptoms that included visual and auditory disturbances, dizziness, and mild ataxia, the index of suspicion was raised for the possibility of spontaneous vertebral or carotid artery dissection. These symptoms may also be observed in some patients with migraine headaches and viral infections.

Initial Management

The patient was not treated on the initial visit on the 22nd of July. The chiropractic physician advised her of the possibility that a vertebral artery or carotid artery

dissection caused reduced blood flow to the brain. The patient was provided a recommendation that she attend the Emergency Department (ED) for immediate evaluation. The patient declined, and said she decided to go home and rest. She was urged to go to the ED immediately if any of her neurological symptoms returned, and she was taken home by her husband. She was given a follow-up appointment on the following day for reassessment.

On the July 23, 2013, the patient returned feeling better with only minor right-side upper neck pain without recurrence of the neurologic symptoms. On examination, she exhibited mild tenderness of the right upper cervical area, and Spurling's test reproduced the mild right upper cervical pain. With both subjective and objective improvements, the initial symptoms were thought to have been due to vasovagal effect, and the continuing neck pain was likely mechanical/myofascial in nature. Treatment consisted of myofascial release and mild distraction and mobilization techniques, which provided some relief. Again, she was advised to go directly to the ED if any of her previous symptoms reoccurred. She was scheduled for another follow-up 2 days later.

On July 24, 2013, the chiropractic physician sent a report to the referring cardiothoracic surgeon and a copy to her primary care physician (PCP) that outlined his findings, diagnostic suspicions, and patient management plan.

The patient returned to the chiropractic physician on July 25, 2013. She continued to complain of pain of varying intensity in the right upper cervical area. She denied the return of dizziness, sensory problems, visual/auditory disturbances, or coordination difficulties but stated that she simply did not feel right. On renewed suspicion of vertebral or carotid artery dissection, the chiropractic physician ordered an MRI and magnetic resonance angiography (MRA) of the brain and MRA of the vertebral and carotid arteries at the hospital's Imaging Center, due to the acute onset of the right neck and head pain with transient dizziness and visual, auditory, and balance disturbances to rule out arterial dissection.

On July 25, 2013, at 8 PM, the patient reported to the LVHN Imaging Center. An MRA of the neck and carotid arteries was obtained using 3D time-of-flight and gadolinium-enhanced imaging. The common carotid and cervical internal carotid arteries were normal. The left vertebral artery was hypoplastic and appeared to terminate at the left posterior inferior cerebellar artery. There was an abrupt moderately long segment of narrowing involving the right vertebral artery beginning near the junction of the V1 and V2 segments. The radiologist noted a concern regarding right vertebral artery dissection.

Images of the brain using MR sagittal T1, axial T2, axial FLAIR, axial fiesta, axial T1, axial SWI, and axial diffusion and post-contrast axial SPRG resulted in the impression of a normal brain scan with no masses, intracranial hemorrhages, or acute infarcts. An MRA of the head also failed to exhibit any abnormal findings.

The radiologist called the chiropractic physician at approximately 11 PM to inform him of these findings. The patient was put on the phone, and the chiropractic physician instructed her to go immediately to the ED. The chiropractic physician phoned the ED in advance to advise the attending physician of her arrival.

At 11:26 PM on July 25, the patient went directly from the hospital imaging center to the emergency department and was admitted. The ED record noted the following: "Patient presented to the chiropractor with upper neck pain and some neurological symptoms… 3 days ago. The chiropractor advised her to go to the ED that day, but the patient declined (because she felt her symptoms were improving)." The record also noted that "on Monday afternoon, saw chiropractor, but did no manipulations." At 12:12 AM on July 26, she spoke with the neurologist on call who recommended a computed tomographic (CT) angiogram to confirm the vertebral artery dissection (VAD) and gave low-dose aspirin for blood thinning. At 3:10 AM on July 26, a CT angiogram was completed. A right VAD was confirmed. The patient was discharged from the hospital on July 26 to follow up with her PCP.

Post Imaging Follow-Up

The patient reported to her PCP on the August 1, 2013, for a follow-up visit after her release from the Emergency Department on July 26. The patient reported that the initial symptoms had subsided with the exceptions of the headache and neck pain. The remaining examinations and historical findings were not different from those entered into the record by the chiropractic physician on July 22, 2013, and are thus not repeated. A neurological consultation was scheduled for September 4, and daily aspirin was prescribed.

On August 15, 2013, the patient returned to the LVHN Family Practice Department for a routine follow-up visit. She reported significant improvement in all symptoms and no headaches. With her improved symptom picture, Percocet, and ibuprofen were

removed from her medication list. Future appointments were to be scheduled on an "as needed" basis.

The patient was seen on September 5, 2013, in the Neurology Department. The patient was reported to be stable with no brain infarct due to the VAD that seemed to occur with no clear cause. The daily use of 81 mg of aspirin was continued. A follow-up CT angiogram was scheduled for the October 28 at which time the right vertebral artery appeared normal with minimal residual circumferential narrowing at C5-C6 and in the distal V2 segment that was indicative of the previous dissection.

A final visit to the Neurology Department on November 11, 2013, revealed that all of the problems had resolved. The patient was taken off all medication with the exception of the continued daily use of aspirin and discharged with instructions to return if the symptoms reappeared. The patient provided consent for the publication of this case.

Discussion

The overall incidence of VAD is approximately 1 to 1.5 per 100 000.[12] Although some claim that there is an association of manipulation of the neck with VAD, a direct causal connection has not been established.[13,14] The estimates and literature relating vascular accidents and chiropractic manipulation have been questioned.[15] Evidence suggests that the majority of strokes related to vertebral or carotid artery dissection may be spontaneous in susceptible individuals.[7] The common initial symptoms of neck pain and headache entice patients to seek professional attention from health care providers, including medical doctors and chiropractic physicians.[16,17] Cassidy et al performed a study and found that patients who seek clinical care for neck pain and headache (chiropractic or medical) and subsequently experience stroke are likely experiencing an arterial dissection before any treatment is rendered.[18,19] Additional analysis of this study revealed that the patients who consulted a chiropractor in the year before their strokes tended to be older, had one cardiac risk factor or comorbidity, and that women were more commonly affected than men.[20]

Blood passing from the lumen of the artery into the layers of the arterial wall is considered a dissection. The accumulation of blood in the arterial wall can narrow the lumen and potentially occlude arterial blood flow to distal points.[21] While arterial dissections may spontaneously occur, the risk factors contributing to the dissection include hypertension, diabetes mellitus, smoking, hyperlipidemia, oral contraception, and connective tissue disorders.[22] An arterial occlusion may be transient (TIA) or progress to a stroke with attendant cardiac or cerebral manifestations. A person with a transient occlusion may present with neck pain or suboccipital headache[23] and upper limb radiculopathy.[24]

Prior to the case published by Maddox et al,[16] only 1 case of an undiagnosed arterial dissection presenting to a chiropractor had been published.[25] The present case is the third published VAD case involving a patient who presented to a chiropractic physician with symptoms of neck pain and headache. This particular case is unique in that the chiropractic physician, the patient, the referring physician, and the radiological and neurological consults were all employed in the same hospital system. Consequently, expedient access, the flow of patient information between the providers, and the successes of the consultations and follow-up care were well managed and contributed to the positive outcome experienced by the patient. Such collaborative care appears to serve the needs of patients in an effective and efficient manner.

Vascular deficiencies can and do occur spontaneously and are occasionally associated with neck movement and the application of external mechanical forces to the neck. Such deficiencies are not limited to any particular age group, gender, or race, although they are believed to be more common in females. Common risk factors include high blood pressure, smoking, diabetes, dyslipidemia, birth control, and obesity.

People who experience neck pain and headaches may seek relief via either pharmacological or conservative manual procedure(s). The intent of this case report is not to extend the debate regarding the role of and/or potential risks associated with cervical spinal manipulation regardless of the type of provider performing the procedure. Rather, it is hoped this case report will accentuate the importance of the early recognition of classic symptoms associated with vascular deficiency in the brain when possible regardless of the causal factor.

Practitioners should be aware of the classic symptom picture of pain, dizziness, headache, visual and hearing disturbances, sensory disturbances, loss of balance, and nausea. When a vascular deficiency is suspected, immediate appropriate action is required. The action items include the following: (1) the withholding of manipulative procedures of the neck, (2) advanced imaging (MR and CT), (3) neurological consultation, and (4) pharmaceutical support. The goal is to prevent exacerbation and avoid progression of a developing

and potentially serious condition. We suggest that this case be considered as an example of an appropriate course of care.

Limitations

While this particular patient had a spontaneous vertebral artery dissection, not all cases with a similar signs or symptoms will result in similar diagnoses, and some positive cases may exhibit asymptomatic presentations. Nevertheless, when patients present with symptoms that are suggestive of a possible cerebral vascular event, caution in providing manipulative care seems advisable until the vascular disruption has been ruled out through proper examination procedures. This procedure may be construed as an error on the side of excessive caution or defensive medicine that requires unnecessary costly additional procedures and patient anxiety, but in the opinions of the authors, the potential for significant adverse results justifies these actions.

Conclusion

This case exemplifies a symptom picture of a potential vascular deficiency problem to the brain. Presentation of the classic symptom picture of pain, dizziness, headache, visual and hearing disturbances, sensory disturbances, loss of balance, and nausea requires immediate appropriate actions such as withholding manipulative procedures of the neck, advanced imaging (MR and CT), neurological consultation, and pharmaceutical support. Recognition and rapid response by the chiropractic physician provided the optimum outcome for this particular patient.

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Vertebral artery dissection in a patient practicing self-manipulation of the neck

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Abstract

Objective: The purpose of this case report is to describe a patient who regularly practiced self-manipulation of her neck who presented with shoulder and neck pain and was undergoing a vertebral artery dissection.

Clinical Features: A 42-year-old female patient sought care for left shoulder pain with a secondary complaint of left lower neck pain. Twelve days prior, she had had "the worst headache of her life," which began in her left lower cervical spine and extended to her left temporal region. The pain was sudden and severe, was described as sharp and burning, and lasted 3 hours. She reported nausea, vomiting, and blurred vision.

Intervention and Outcome: Initial history and examination suggested that the patient's head and neck pain was not musculoskeletal in origin, but vascular. She repeatedly requested that an adjustment be performed, but instead was referred to the local emergency department for further evaluation. Magnetic resonance angiogram revealed a dissection of the left vertebral artery from C6 to the C2-C3 interspace and a 3-mm dissecting pseudoaneurysm at the C3 level. She underwent stent-assisted percutaneous transluminal angioplasty combined with antiplatelet therapy (clopidogrel) and experienced a good outcome.

Conclusion: This case suggests that careful history taking and awareness of the symptoms of VAD are necessary in cases of sudden head and neck pain. More research is needed on the relationship between vertebral artery dissection and self-manipulation of the neck.

Introduction

Vertebral artery dissection (VAD) is one cause of stroke in patients who are younger than 45 years old.[1-4] It is estimated that 1 to 1.5 per 100 000 individuals in the United States will experience this condition.[5,6] Common presenting symptoms are headache and neck pain; thus, many of these patients may present for chiropractic care. As these symptoms are nonspecific and may be related to a number of underlying conditions, it can be difficult to properly diagnose a VAD.[7] Currently, medical treatment of

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this condition includes administration of anticoagulant drugs.[8]

Vertebral artery dissection is the result of a flap-like tear in the tunica intima of the vertebral artery. Because of this tear, blood enters into the tunica media causing a hematoma in the vessel wall. Although the mechanism of this condition is well documented, little research has been conducted concerning the clinical presentation of VAD.[9] Cassidy et al[10] and Murphy[11] recently suggested that some patients visiting chiropractic clinics with complaints of head and neck pain may have undiagnosed VAD. These patients may undergo cervical spinal manipulation for this pain, further complicating their VAD through a thromboembolic event.[10] This can lead to the assumption that manipulation caused the dissection. In light of this, it is critical that doctors of chiropractic be able to differentially diagnose VAD from benign causes of head and neck pain to avoid catastrophic complications. The purpose of this case report is to describe a patient with VAD who reported that she regularly practiced self-manipulation of her neck and to present guidelines to identify and properly manage VAD.

Case report

A 42-year-old female patient complained of left-sided neck pain and shoulder pain at a chiropractic college community outreach clinic. The patient had not seen a chiropractor for 8 years according to records; however, she reported that she would regularly self-manipulate or "crack" her neck to reduce neck pain. She reported that she had performed this self-manipulation of her neck several times a day for the past several years. She was not a chiropractor and had no training in manipulative therapy. When she arrived at the clinic, she appeared tired and distressed. She stated that she had burning, sharp pain and requested that her neck and shoulder be adjusted.

A chiropractic intern performed a routine initial evaluation to determine the diagnosis. Bilateral pulse, respiration, and seated blood pressure were measured within normal limits. Palpation indicated burning on the left side of C7, myospasms on the right side paraspinal muscles between T4-T9, myospasms on the left side paraspinal muscles between L2-L4, and a high right hip. Cervical compression and shoulder depressor test caused pain in the left lower cervical region.

The supervising doctor of chiropractic requested a more detailed history based upon the distressed appearance of the patient. As the patient was further questioned, she reported a persistent headache that started 12 days prior while driving her vehicle. The pain was in her lower neck and shoulder and ascended to the temporal region on her left side. She described her headache as a stabbing pain, worse than she had ever experienced before, that moved throughout her head and occurred for approximately 5 to 10 minutes at a time. This admission raised red flags for both the intern and the supervising chiropractor. The pain was intense and burning, rating a 10/10 on a numerical rating scale. This pain was followed by episodes of nausea and vomiting. She stated that she would have these headaches for 3 hours per day and, for most of the time, she would be on her hands and knees in a dark corner of a room. She denied any tobacco or oral contraceptive use and noted drinking socially. Throughout the visit, she repeatedly requested that she wanted to have her neck manipulated. The supervising chiropractor stated that he would not perform a chiropractic manipulation due to the seriousness of her suspected condition. He quickly referred her out to an emergency department for consult and advised her not to self-manipulate her neck.

The patient refused the immediate emergency attention recommended by the supervising chiropractor and instead waited until the following day because of insurance reasons before she went to a university hospital. At admission to the hospital, she reported no dizziness, lightheadedness, weakness, or other focal motor or sensory changes, consistent with her presentation at the chiropractic clinic. Her physical examination and blood profile showed no abnormalities. A magnetic resonance imaging was conducted to rule out the possibility of stroke, and the findings were negative. A magnetic resonance angiogram with contrast was ordered to evaluate the integrity of the vertebral arteries. The results of this test showed left vertebral artery dissection extending from C6 to the C2-C3 interspace with poststenosis and a 3-mm pseudoaneurysm at the C3 level. The dissection is best visualized in Fig 1 near the arrow as the decreased luminal caliber with increased signal intensity medial to the vessel. The emergency department doctor explained to her that the chiropractor recognized the need for emergency care and referring her to the hospital may have saved her life.

The emergency department physician determined that she needed immediate surgical attention. She subsequently underwent diagnostic cerebral angiogram and stent-assisted percutaneous transluminal angioplasty of the dissected left vertebral artery involving 3

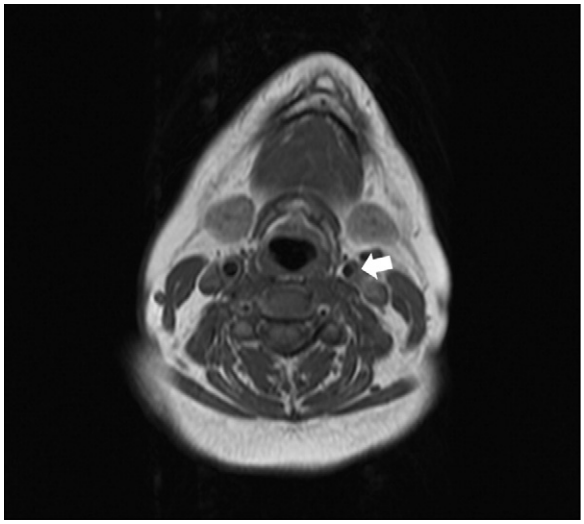

Fig. 1. Presurgical magnetic resonance angiogram showing arterial narrowing as indicated by arrow.

overlapping stents Aspirin and clopidogrel were given for blood-clotting protection, and omeprazole was prescribed for stomach protection while on aspirin. She was instructed by her medical physician to avoid abrupt neck maneuvers and only perform physical activity that she could tolerate. As of the submission of this case report, she has resumed her working duties and is living a healthy, normal life.

Discussion

In writing this case, the literature was searched to determine if self-manipulation has been published in relation to VAD. At present, it was determined that this is the first published case of a person who claims to self-manipulate presenting with VAD.

It should be stressed that, although cervical spinal manipulation has been implicated in prior research as a possible causative event in VAD, there are many others including sneezing, violent coughing, turning the head while driving, kneeling at prayer, yoga, and sexual intercourse.[12-14] Given the mundane nature of these activities and the fact that the vast majority of the population practices them without ever developing VAD (a rare condition), it is unlikely that they could be considered a "cause" of the condition. Recent research suggests that there may be no causal relationship[15] and that general forces of manipulation may not be enough to cause VAD.[16] It is more likely that previous damage or a preexisting defect was present and that an otherwise trivial trauma triggered the VAD. This hypothesis fits with new research by Cassidy et al[10] who reason that patients who are undergoing a VAD may present to a chiropractic clinic with neck pain and headaches similar to

Patient History

1. Ipsilateral facial dysesthesia (pain and numbness)- Most common symptom
2. Dysarthria or hoarseness (cranial nerves [CN] IX and X)
3. Contralateral loss of pain and temperature sensation in the trunk and limbs
4. Ipsilateral loss of taste (nucleus and tractus solitarius)
5. Hiccups
6. Vertigo
7. Nausea and vomiting
8. Diplopia or oscillopsia (image movement experienced with head motion)
9. Dysphagia (CN IX and X)
10. Disequilibrium
11. Unilateral hearing loss
12. Contralateral weakness or paralysis (pyramidal tract)
13. Contralateral numbness (medial lemniscus)

Clinical findings

1. Limb or truncal ataxia
2. Nystagmus
3. Ipsilateral Horner syndrome in as many as one third of patients with VAD (ie, impairment of descending sympathetic tract)
4. Ipsilateral hypogeusia or ageusia (ie, diminished or absent sense of taste)
5. Lateral medullary syndrome
6. Medial medullary syndrome
7. Tongue deviation to the side of the lesion (impairment of CN XII)
8. Contralateral hemiparesis
9. Internuclear ophthalmoplegia (lesion of the medial longitudinal fasciculus)
10. Ipsilateral impairment of fine touch and proprioception
11. Contralateral impairment of pain and thermal sensation in the extremities (ie, spinothalamic tract)

Fig. 2. Potential patient history and clinical signs or symptoms indicating possible VAD. Adapted with permission from eMedicine.com, 2010. Available from: emedicine.medscape.com/article/761451-overview.[11]

neuromusculoskeletal conditions. Oftentimes, the chiropractor may misdiagnose this as a more benign condition and then adjust the patient, which can complicate the underlying VAD. Thus, chiropractors need to recognize the initial symptoms of VAD so that diagnosis and treatment can be administered without further harm caused by adjusting the patient.[11] Cassidy et al[10] note risk factors for VAD independent of manipulation. These factors include connective tissue disorders, hypertension, recent infection, vessel abnormalities, and atherosclerosis. A patient who presents with symptoms similar to this patient, or parts of the history in Fig 2, should be screened for these risk factors before cervical manipulation is given to prevent serious complications due to underlying VAD.

Limitations

There are several important limitations to this case report. Although the present report represents the first to describe a case of VAD for a patient who habitually practiced self-manipulation before the onset of symptoms, a sample of 1 cannot "prove" that a relationship exists between self-manipulation of the neck and VAD. It merely suggests a chronological association and need for future studies to determine causality. Second, as this is a retrospective study, it was not possible to determine the exact interval of time between the last cervical self-manipulation and the onset of symptoms. All that is known, as stated earlier, is that the patient reportedly self-manipulated her neck several times a day. This raises the question of whether or not the patient was undergoing a VAD and had resultant head and neck pain for which she tried to self-manipulate, leading to further complication of the condition. This also raises another question of whether her crude attempts at replicating a chiropractic adjustment were the cause of the VAD in the first place. Although this fits the narrative portrayed by Smith, Rothwell, and others, it does not correspond to the recent prevailing thoughts of Cassidy or Murphy. The exact mechanism of any reported case of VAD is beyond the realm of a case study or case series; but because temporality is one of Sir Bradford Hill's requirements for determining causality, manipulation before VAD detection cannot be ruled out as a cause without specific research, which has yet to be conducted.

Conclusion

It is critical for doctors of chiropractic to exercise proper clinical evaluation and treatment when addressing their patients, specifically when dealing with suspected VAD. This case report should serve as a reminder that recognizing "red flags" is critical to a proper diagnosis. By taking a proper history, realizing the warning signs, and performing the right action plan (ie, immediate referral to an emergency department), the chiropractic doctor and intern contributed to the preservation of this patient's life.

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SCIENTIFIC INVESTIGATIONS

Treatment of Sleep Disorders after Traumatic Brain Injury

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Study Objectives: Determine whether treatment of sleep disorders identified in brain injured adults would result in resolution of those sleep disorders and improvement of symptoms and daytime function.

Methods: Prospective evaluation of unselected traumatic brain injury patients with nocturnal polysomnography (NPSG), multiple sleep latency test (MSLT), Epworth Sleepiness Scale (ESS), and neuropsychological testing including Psychomotor Vigilance Test (PVT), Profile of Mood States (POMS), and Functional Outcome of Sleep Questionnaire (FOSQ) before and after treatment with continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA), modafinil (200 mg) for narcolepsy and posttraumatic hypersomnia (PTH), or pramipexole (0.375 mg) for periodic limb movements in sleep (PLMS).

Setting: Three academic medical centers.

Participants: Fifty-seven (57) adults ≥ 3 months post traumatic brain injury (TBI).

Measurements And Results: Abnormal sleep studies were found in 22 subjects (39%), of whom 13 (23%) had OSA, 2 (3%) had PTH, 3 (5%) had narcolepsy, 4 (7%) had PLMS, and 12 had objective excessive daytime sleepiness with MSLT score < 10 minutes. Apneas, hypopneas, and snoring were eliminated by CPAP in OSA subjects, but there was no significant change in MSLT scores. Periodic limb movements were eliminated with pramipexole. One of 3 narcolepsy subjects and 1 of 2 PTH subjects had resolution of hypersomnia with modafinil. There was no significant change in FOSQ, POMS, or PVT results after treatment.

Conclusions: Treatment of sleep disorders after TBI may result in polysomnographic resolution without change in sleepiness or neuropsychological function.

Key Words: Trauma, brain injury, hypersomnia, sleep apnea, narcolepsy, sleep disorders, MSLT, continuous positive airway pressure.

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Traumatic brain injury (TBI) has been increasingly recognized as a major health problem in both the civilian and military population as a consequence of motor vehicle accidents and explosive devices.[1] Every year, over 124,000 civilians in the U.S. who sustain a TBI develop a long-term disability. Presently, there are over 3.3 million Americans living with a TBI-related long-term disability. Recent studies have revealed a high prevalence of sleep disorders in the TBI population, including narcolepsy, posttraumatic hypersomnia (PTH), periodic limb movements in sleep (PLMS), and especially obstructive sleep apnea (OSA), with serious consequences.[2-8] Very little, however, has been published about treatment of these problems.[9] Recent reports of long-term studies of patients with OSA have revealed a significantly higher risk of both cardiovascular and all-cause mortality,[10,11] as well as reduced cardiac function[12] and hypertension.[13,14] OSA has been linked with structural changes in the brain[15] as well as neurocognitive deficits.[16] Both narcolepsy and OSA are significant risk factors for motor vehicle accidents.[17,18] The purpose of this present study was to determine whether treatment of specific sleep disorders identified in brain injured adults would result in resolution of those sleep disorders and improvement of symptoms and daytime function.

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METHODS

Subjects

Subjects older than 18 years of age who were ≥ 3 months post TBI were recruited from the rehabilitative services at 3 academic medical centers: Memorial Hermann Hospital–Texas Medical Center (Houston, TX), Transitional Learning Center (Galveston, TX), and Philadelphia Veterans Administration Medical Center (Philadelphia, PA). The study was approved by the Committee for the Protection of Human Subjects/Institutional Review Board of all participating institutions. Exclusion criteria were as follows: (1) presence of circadian rhythm disorder, (2) inability to give informed consent, and (3) use of sedating medications. Each consented subject was scheduled to undergo nocturnal and daytime sleep studies along with neuropsychological testing. TBI severity was classified by considering both emergency room Glasgow Coma Scale (GCS) and

CT scan findings according to established criteria.[19,20] Subjects were classified as having a severe TBI if their GCS score was < 9, regardless of CT scan findings. Subjects were classified as having had a moderate TBI if they had a GCS of 9-12 regardless of CT findings, or if they had a GCS of 13-15 and a positive CT scan.[21,22] Subjects were classified as having a moderate/severe TBI if they had a positive CT scan but there was no GCS available to make a finer characterization. Subjects were classified as having a mild TBI if their GCS score was 13-15 and the CT scan was negative.[22]

METHODS

Sleep Studies

An Epworth Sleepiness Score (ESS) questionnaire[23] was completed by each subject on the night of polysomnography. Nocturnal polysomnograms (NPSG) were performed ≥ 3 months post injury in sleep laboratories in each center. Using standard techniques,[24,25] a computer data acquisition and analysis system recorded the following signals: electroencephalogram (C3A2, C4A1, O1A2, and O2A1), bilateral electroculogram, submental and bilateral anterior tibialis electromyogram, thoracic and abdominal excursion by piezocrystals, oral and nasal airflow by thermistor and breath sounds, body position, oxygen saturation by pulse oximeter, and electrocardiogram. Throughout the study, subjects were monitored with an infrared video camera and a one-way intercom, which connects the bedroom with the monitoring room. All studies were attended by polysomnographic technologists who also scored the studies using 30-sec epochs by Rechtschaffen and Kales criteria,[26] and each was interpreted by a physician certified by the American Board of Sleep Medicine.

During the day subsequent to the sleep study, a multiple sleep latency test (MSLT) was used to assess objective physiologic sleepiness. The test was performed using standard techniques; sleep onset was defined as the first epoch of sleep, (> 50% of the 30-sec epoch of any sleep stage).[27] Each subject took 5 naps of 20-min duration at 2 hour intervals. The following signals were recorded during the naps: EEG (C3A2, C4A1, O1A2 and O2A1), bilateral electroculograms, submental electromyogram, and electrocardiogram. The average sleep latency over these 5 naps was the MSLT score. Those with an MSLT score < 10 min were termed sleepy and those with an MSLT score ≥ 10 min were non-sleepy. A urine sample was collected after the NPSG and during the MSLT with analysis for possible opiates, benzodiazepines, cannabinoids, amphetamines, and adrenergic drugs.

Respiratory events were scored as previously described.[28] Obstructive apnea was defined by cessation of breathing > 10 sec with ≥ 4% fall in oxygen saturation and/or EEG arousal accompanied by continuous respiratory effort. Central apnea was defined by a cessation of breathing > 10 sec with ≥ 4% fall in oxygen saturation and/or EEG arousal without respiratory effort. Hypopnea was defined as > 50% reduction in airflow > 10 sec accompanied by ≥ 4% fall in oxygen saturation and/or EEG arousal. The diagnosis of obstructive sleep apnea (OSA) was made with ≥ 5 apneas/hour of sleep and/or ≥ 10 apneas + hypopneas/hour of sleep. Narcolepsy was defined as an MSLT score (average sleep latency) < 5 min with ≥ 2 sleep onset REM periods (SOREMPs) after an unremarkable NPSG with adequate total sleep and REM sleep and negative urine drug screen. Posttraumatic hypersomnia (PTH) was defined as an MSLT score ≤ 10 min with < 2 SOREMPs after an unremarkable NPSG and no history of hypersomnolence prior to TBI. Periodic limb movements in sleep (PLMS) were defined as > 5 periodic limb movements (PLMs)/hour of sleep; PLMs were scored according to the standard criteria prevailing at the time the study was designed and initiated.[29,30]

Neuropsychological Evaluation

Each subject underwent a brief neuropsychological evaluation and completed several self-report measures. All subjects were evaluated on 2 occasions. To control for diurnal variations, all evaluations took place beginning at 10:30, between the second and third MSLT naps. The measures used are described below.

Psychomotor Vigilance Test (PVT): Sustained attention was evaluated with the Psychomotor Vigilance Test (PVT). The PVT was chosen because it is sensitive to the effects of sleepiness on cognitive functioning as well as cognitive problems associated with OSA and its treatment.[31-33] The PVT is administered via a small hand-held computerized device with a 3-digit millisecond LED counter and display window (PVT-192: Ambulatory Monitoring Inc, Ardsley, NY). Subjects are presented with a 10-min trial in which they press a response button as soon as a number counting up from 0 is seen. Once the response button is pressed, the counter stops and feedback is given on their reaction time. The amount of time between stimulus presentations varies between minimum and maximum interstimulus intervals of 2000 and 10,000 ms. Performances are recorded in the PVT device and downloaded into a database after the testing bout. For the purposes of this study, the average of the fastest 10% of reaction times, the average of the slowest 10% reaction times, and the number of lapses (reaction times ≥ 500 ms) from the PVT were selected for this analysis because these variables have been shown in prior research to be sensitive to sustained attention under conditions of sleep deprivation and in sleep disorders.[31-33] Normally, the PVT is given in several testing bouts across time. Owing to the time constraints involved in this study, each subject was exposed to the PVT once.

Profile of Mood States (POMS): The Profile of Mood States (POMS)[34] is a self-report measure in which subjects rate themselves on each of 65 adjectives using a 1-5 scale. These 65 responses yield 6 mood state scales which are: Anger-Hostility; Vigor-Activity, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, and Confusion-Bewilderment. This measure enjoys wide use in sleep research and has been shown to be sensitive to sleep disorder-related mood problems.[35,36]

Functional Outcome of Sleep Questionnaire (FOSQ): The Functional Outcome of Sleep Questionnaire (FOSQ) is a self-report measure designed to assess the impact of sleep disorders on daily functioning.[37] It has been used in sleep research and appears sensitive to treatment related change.[38-40] There are 30 items, which are divided into 5 scales: Activity, Vigilance, General Productivity, Social Outcome, and Intimacy and Sexual Relationships. These scales are summed to make a total score.

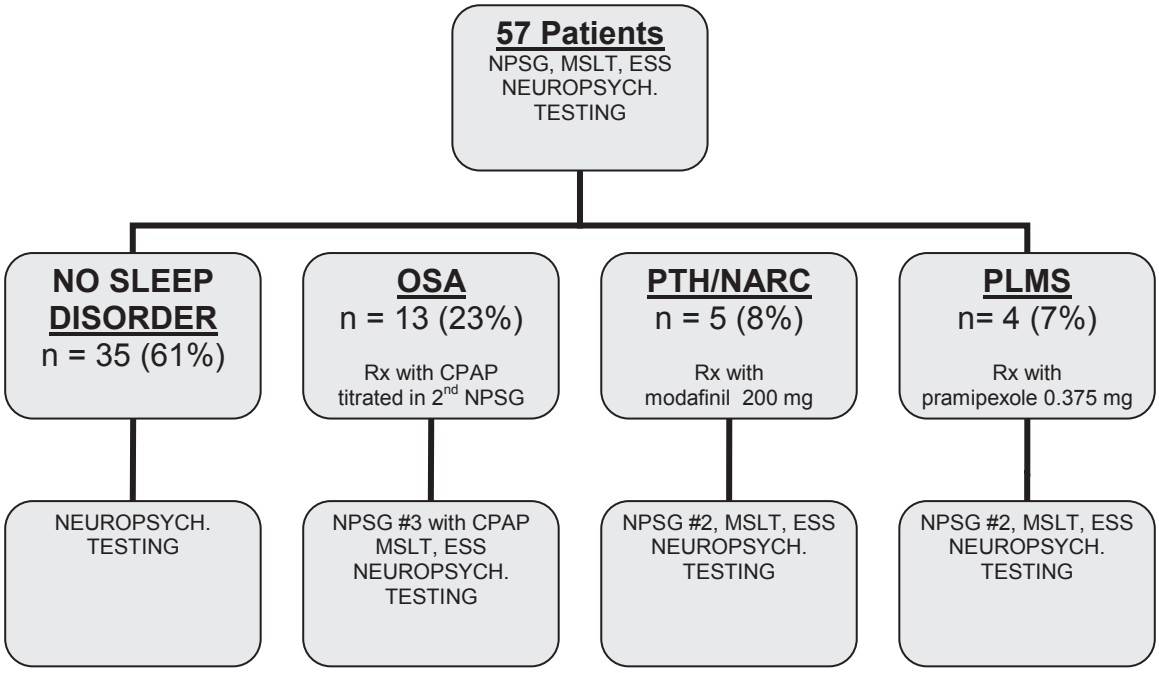

Figure 1—Flow of study participants. OSA = obstructive sleep apnea; PTH – post-traumatic hypersomnia; NARC = narcolepsy; PLMS = periodic limb movements in sleep; NPSG = nocturnal polysomnographu; MSLT = multiple sleep latency test; CPAP = continuous positive airway pressure.

Higher scores on the FOSQ indicate self-perceived better daily functioning. The total score was used for this analysis.

Patients with diagnosed sleep disorders were offered one of the following treatment plans: (1) OSA patients were treated with nasal continuous positive airway pressure (CPAP) and returned subsequent to diagnosis for repeat NPSG with appropriate titration of CPAP to eliminate apneas, hypopneas, and snoring; (2) Subjects with PLMS were treated with pramipexole 0.375 mg by mouth each night; (3) Those diagnosed with narcolepsy or PTH were treated with modafinil 200 mg by mouth each morning. The patients were not seen in closer follow-up unless there was an adverse event. Thus medications were not titrated up or down.

Three-Month Follow-up

The patients were re-examined after ≥ 3 months of treatment. Those subjects without a sleep disorder were also seen at 3 months. The sleep study, MSLT, and neuropsychologic evaluation were repeated in those patients with a sleep disorder. Those without a sleep disorder participated in the neuropsychologic testing only.

STATISTICAL ANALYSIS

Comparability of demographic and baseline characteristics were summarized by subgroups using means and standard deviations (quantitative data), or frequency of counts (qualitative /categorical data). Parametric *t* tests for independent samples were used to evaluate group differences when distributions were normal. Categorical data was analyzed using chi square tests. Where small cell sizes precluded the use of chi square, Fisher exact test was employed.

RESULTS

Overview of the Sample

There were 87 subjects initially studied, of whom a total of 57 patients completed the protocol (Figure 1). Of those, 35 subjects (61%) were free of a sleep disorder, 13 (23%) had OSA, 3 (5%) had narcolepsy without cataplexy, 2 (3%) had PTH, and 4 (7%) had PLMS. There were 12 (25%) female and 36 (75%) male participants. Forty-four subjects (77%) were Caucasian, 8 (14%) were African American, and 5 (9%) were Hispanic. Of those who had complete data upon which severity could be determined, 17 subjects (30%) had severe injuries, 3 (5%) had moderate or severe injury, 10 (18%) had moderate injuries, and 5 (9%) had mild injuries. Forty-four (77%) subjects incurred TBI as a result of a motor vehicle accident, 4 (7%) were assaulted, 5 (9%) had a fall, and 4 (7%) were injured by a falling object. The average age, education, and number of months post injury for the entire sample were 38.56 (± 14.75) years, 12.65 (± 1.88) years, and 67.84 (± 126.34) months.

Did Patients Improve?

We next evaluated the degree to which TBI patients with sleep disorders benefited from treatment. Baseline sleep and demographic data are depicted in Tables 1 and 2. In order to determine if OSA patients were effectively treated, the apnea hypopnea index (AHI), amount of REM sleep, MSLT, and ESS were compared pre and post treatment using a paired samples *t* test. These comparisons disclosed that the AHI improved dramatically from pretreatment to post treatment ($p = 0.001$). The amount of REM sleep increased from pre to post treatment ($p = 0.04$), but there was no change in total sleep time ($p = 0.38$).

Table 1—Sleep Study Data for TBI Patients with Sleep Disorders

	OSA				NAR PTH				PLM			
	aRx		pRx		aRx		pRx		aRx		pRx	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
TST	5.9	1.5	6.1	1.1	7.0	0.7	6.6	0.6	5.7	1.8	6.3	0.5
ESS	12.2	6.2	13.0	6.4	7.8	3.6	6.4	5.0	17.0	2.0	8.5	2.1
%N1	15.8	12.3	12.3	8.3	11.6	3.5	11.0	6.6	8.7	2.6	8.6	4.4
%N2	61.4	11.7	63.7	13.6	62.2	21.6	58.4	17.7	69.8	13.0	74.8	7.6
%N3	3.8	8.8	4.7	8.4	9.2	8.1	10.6	13.2	7.8	7.5	5.7	6.0
%REM	20.3	9.8	19.2	9.8	18.4	1.8	19.6	6.8	13.5	10.1	10.9	8.5
SL	50.9	127	25.7	37.1	10.3	10.4	27.6	39.6	38.9	50.3	9.0	6.9
SOREM	1.42	3.1	0.8	2.6	2.4	3.1	0.6	0.9	3.0	6.0	2.6	5.3
AHI	31.4*	21.5	3.8*	3.7	0.8	1.3	1.6	1.3	1.2	1.7	2.9	3.2
PLMI	9.9	17.1	19.8	28.8	1.8	3.5	1.8	4.0	17.7#	7.2	1.3#	2.5
MSLT	10.3	6.2	12.1	5.1	5.7	1.7	9.3	6.9	13.1	3.6	13.2	7.7

OSA = obstructive sleep apnea; NAR = narcolepsy; PTH = post-traumatic hypersomnia; PLM = periodic limb movements; aRx = before treatment; pRx = after treatment (with CPAP for OSA, modafinil for NAR/PTH, pramipexole for PLM); M = mean; SD = standard deviation; TST = total sleep time (in hours); ESS = Epworth sleepiness score; %N1 = percent of Stage 1 sleep; %N2 = percent of Stage 2 sleep; %N3 = percent of Stage 3 and 4 (slow-wave or delta) sleep; %REM = percent of stage REM (rapid eye movement) sleep; SE = sleep latency (from time in minutes from lights out to sleep onset) on nocturnal polysomnography; SOREM = number of sleep-onset REM periods on multiple sleep latency test; AHI = apnea-hypopnea index (number of apneas and hypopneas per hour of sleep); PLMI = periodic limb movement index (number of periodic limb movements per hour of sleep); MSLT = MSLT score = mean sleep latency (in minutes) over 5 naps on multiple sleep latency test. *p = 0.001 (before and after treatment with CPAP); #p = 0.03 (before and after treatment with pramipexole)

There was no significant change in MSLT score ($p = 0.66$) or ESS ($p = 0.43$). In order to determine if there had been significant treatment related improvement in those with narcolepsy and PTH, the pre and post treatment MSLT and ESS scores were evaluated using a paired samples *t* test for the pooled group. These findings disclosed no statistically significant differences from pretreatment to posttreatment on the MSLT or the ESS. However the mean MSLT scores increased from 5.65 ± 1.7 to 9.3 ± 6.9 min in this small group from before treatment to after treatment with modafinil 200 mg daily for narcolepsy or PTH. There were improvements in MSLT scores in one of 3 narcolepsy subjects (from 4.3 to 19 min) and one of 2 PTH subjects (from 6 to 13 min). To determine if there had been a significant treatment-related improvement in those with PLMS, pre and post treatment periodic limb movement index (PLMI) as well as the ESS and MSLT scores were compared using a paired samples *t* test. These findings revealed a significant decrease in the PLMI from pre (17.7 ± 7.2) to post treatment (1.25 ± 2.5) with 0.375 mg of pramipexole ($p = 0.03$). There was no significant change in MSLT score from pre (13.1 ± 3.6) to post treatment (13.2 ± 7.7) in this patient group, but these were normal MSLT scores at the outset.

Outcome Of Sleep Disordered And Non–Sleep Disordered Patients: Neuropsychology And Quality Of Life Measures

In order to examine the relationship between sleepiness, cognitive functioning, mood state, and quality of life, the FOSQ total score, the 6 scales from the POMS, and the average of the fastest 10% of reaction times, the average of the slowest 10% reaction times, and the number of lapses (reaction times $\geq$500 ms) from the PVT were selected for this analysis. The amount of change from pretreatment to post treatment served as the dependent measure in these analyses. The distributions are depicted in Table 3. This analysis was based on 22 sleep disordered and 33 non–sleep disordered patients. The average age for the sleep disorder and non–sleep disorder groups were 42 (± 15.29) years and 36.34 (± 14.18) years respectively. The average years of education was 12.64 (± 2.08) for those with and 12.66 (± 1.76) years without sleep disorders. The individuals with sleep disorders were on average 98.86 (± 165.05) months post injury while those without sleep disorders were 48.32 (± 91.47) months post injury. The distributions of gender, race and cause of injury were all similar between the groups ($p > 0.05$). There were more patients with severe injuries in the sleep disordered group. There were no differences between the groups in terms of age, education, or number of months post injury ($p > 0.05$). Glasgow Coma Scale scores (GCS) ($p < 0.05$) were significantly lower in the sleep disordered group. The results of group comparisons of the outcome measures disclosed: (1) a significant difference in the amount of change in POMS Tension and Anger scales, indicating that the sleep disordered patients had greater reductions in tension and anger than the non sleep disordered patients ($p = 0.04$); (2) that the sleep disordered patients showed a marginally significant greater reduction in self-reported sleepiness on the ESS ($p = 0.05$); (3) that the sleep disordered patients did not differ from the non–sleep disordered patients in the amount of change from pre to post treatment on the FOSQ or the PVT measures (all $p > 0.05$). However, given the number of statistical comparisons performed, these differences are likely the result of chance.

Sleepy and Non-Sleepy Patients

There were 12 sleepy and 10 non-sleepy patients who completed the study. There were 16 males and 6 females in the sample. The average age, education and time post injury for the sample was 40.80 (± 14.45), 12.70 (± 2.18), and 75.25 (± 126.18), respectively. The distributions of baseline sleep and demographic data for the 2 groups are depicted in Tables 4 and 5. The average age, education, and time post injury for the sleepy and not sleepy groups were 38 (± 12.86) and 43.20 (± 16.20); 12.30

Table 2—Demographic Data for the TBI Patients with and without Sleep Disorders

	NO SLEEP DISORDER N (%)	SLEEP DISORDER N (%)
N	35	22
Sex		
Male	25 (44)	16 (11)
Female	10 (17)	6 (28)
Race		
Caucasian	27 (47)	17 (30)
African American	5 (9)	3 (5)
Hispanic	3 (5)	2 (4)
Cause of Injury		
Assault	2 (4)	2 (4)
Auto/Vehicle	29 (51)	15 (26)
Fall	3 (5)	2 (4)
Hit by Falling Object	1 (6)	3 (5)
CT Scan Findings		
Unknown	12 (21)	11 (19)
Negative	6 (11)	0 (0)
Positive	17 (30)	11 (19)
Brain Injury Severity		
Unknown	11 (50)	11 (53)
Mild	5	
Moderate	2 (12)	1 (16)
Moderate/Severe	9 (19)	1 (5)
Severe	8 (19)	9 (26)

Table 3—Neuropsychological Test Performance Data for TBI Patients with and without Sleep Disorders

	NON SLEEP DISORDERED		SLEEP DISORDERED	
	M	SD	M	SD
ΔPVT Lapses[2]	-1.90	7.87	-4.00	15.67
ΔPVT Fastest 10% RT[23]	5.45	24.97	0.73	28.86
ΔPVT Slowest 10% RT[24]	-42.34	214.48	-34.27	351.77
ΔPOMS Fatigue[2]	-1.24	6.46	1.50	5.07
ΔPOMS Confusion[2]	-1.64	4.34	0.40	7.37
ΔPOMS Tension[2]	-1.68	6.37	2.05	5.43
ΔPOMS Vigor[2]	-1.08	4.88	0.20	7.28
ΔPOMS Depression[2]	-2.24	10.54	2.40	11.68
ΔPOMS Anger[2]	-2.48	9.64	3.70	9.98
ΔFOSQ Total Score[3]	0.36	1.99	-0.75	3.12
ΔEpworth	-2.40	3.69	0.84	4.50

[1]N for NonOSA group = 16 N for OSA group 19; [2]N for NonOSA group = 16 N for OSA group 18; [3]PVT Fastest 10% Reaction Times; [4]PVT Slowest 10% Reaction Times; PVT = Psychomotor Vigilance Test; POMS = Profile of Mood States; FOSQ = Functional Outscome of Sleep Questionnaire.

Table 4—Sleep Study Data for Sleepy and Non-Sleepy Patients

N	NON-SLEEPY 10		SLEEPY 12	
Total Sleep (h)	5.81	1.52[1]	6.86	0.86[1]
Epworth Sleepiness Scale	12.78	11.55	11.08	4.98
Percent Stage 1[2]	14.67	13.74	12.56	5.50
Percent Stage 2[3]	60.11	12.55	65.63	15.50
Percent Stage 3 & 4[4]	7.90	10.02	3.96	6.46
Percent REM Sleep[5]	18.92	10.52	18.36	7.46
Apnea Hypopnea Index[6]	18.85	14.58	23.16	27.05
MSLT Score[7]	14.77	3.95	5.53	2.01

[1]Standard Deviation; [2]Percentage of total sleep time that is stage 1 sleep; [3]Percentage of total sleep time that is stage 2 sleep; [4]Percentage of total sleep time that is stage 3 and 4 sleep; [5]Percentage of sleep time that is spent in REM sleep; [6]The number of apnea and hypopnea events per hour of sleep; [7]The average time to sleep onset across five Multiple Sleep Latency Test naps.

(± 1.42) and 13.10 (± 2.77); and 66.80 (± 148.61) and 83.70 (± 106.62). The distributions of gender, severity, race, and cause of injury were all similar between the groups ($p > 0.05$). There were no differences between the groups in terms of age, education, number of months post injury, and GCS. To examine the relationship between sleepiness, cognitive functioning, mood state, and quality of life, the FOSQ total score, the 6 scales from the POMS and the average of the fastest 10% of reaction times, the average of the slowest 10% reaction times, and the number of lapses (reaction times ≥ 500 ms) from the PVT were selected for this analysis. The amount of change from pretreatment to post treatment served as the dependent measure in these analyses. The distributions for demographic and outcome data are depicted in Table 6. Note that there were missing PVT data and thus, this analysis was based on 8 sleepy and 11 non-sleepy patients. The results of these group comparisons disclosed no significant differences between the groups on any of the measures (all $p > 0.05$).

DISCUSSION

In this paper, we report the results of a prospective evaluation of unselected traumatic brain injury patients with PSG, MSLT, ESS, and neuropsychological as well as functional outcome measures before and after treatment of OSA, narcolepsy, PTH, and PLMS. An analysis of pre and post treatment results disclosed a polysomnographic reversal of OSA with CPAP and in PLMS with pramipexole. In subjects with OSA there was no demonstrable improvement in excessive daytime sleepiness as defined by the MSLT or ESS after treatment with CPAP, despite polysomnographic resolution of OSA. One of 3 narcolepsy subjects and one of 2 PTH subjects demonstrated resolution of hypersomnia by MSLT with modafinil 200 mg daily. There were no significant changes in measures of mood, quality of life and cognitive performance in TBI patients after treatment of their sleep disorders. There are a number of methodological factors that must be considered in evaluating these results.

Is the MSLT the Right Outcome Measure?

We are not the first investigators to find that the MSLT does not change with treatment. In a trial of modafinil for the treatment of residual excessive daytime sleepiness in obstructive sleep apnea, modafinil had no effect on sleepiness as measured by the multiple sleep latency test; however, significant improvements in alertness were found with the maintenance of wakefulness test.[41] In another study,[42] 142 patients with sleep apnea-hypopnea syndrome (AHI = 10-30) were randomly assigned to

Table 5—Demographic Data for Sleepy and Non-Sleepy TBI Patients

	SLEEPY	NOT SLEEPY
	N (%)	N (%)
N	12	10
Sex		
Male	9 (75)	7 (70)
Female	3 (25)	3 (30)
Race		
Caucasian	9 (75)	8 (80)
African American	2 (17)	1 (10)
Hispanic	1 (8)	1 (10)
Cause of Injury		
Assault	1 (5)	1 (5)
Auto/Vehicle	10 (40)	5 (25)
Fall	0 (0)	2 (10)
Hit by Falling Object	1 (5)	2 (10)
CT Scan Findings		
Unknown	6 (50)	5 (50)
Positive	6 (50)	5 (50)
Negative	0	0
Brain Injury Severity		
Unknown	6 (50)	5 (50)
Mild	0	0
Moderate	0	1 (10)
Moderate/Severe	0	1 (10)
Severe	6 (50)	3 (30)
Sleep Disorder Diagnosis		
Narcolepsy	3 (25)	0
OSA[1]	7 (58)	6 (60)
PLM[2]	0	4 (40)
PTH[3]	2 (17)	0

[1]Obstructive Sleep Apnea; [2]Periodic Limb Movements in Sleep; [3]Posttraumatic Hypersomnia.

Table 6—Neuropsychological Test Performance Data for TBI Patients with and without Sleep Disorders

	NOT SLEEPY		SLEEPY	
	M	SD	M	SD
ΔPVT Lapses[2]	-0.33	2.54	-8.20	21.69
ΔPVT Fastest 10% RT	8.89	33.28	-5.95	24.88
ΔPVT Slowest 10% RT	-120.49	202.33	-39.94	470.59
ΔPOMS Fatigue[2]	1.88	5.30	1.30	5.39
ΔPOMS Confusion[2]	2.11	6.51	-1.30	5.39
ΔPOMS Tension[2]	2.22	4.84	2.30	6.29
ΔPOMS Vigor[2]	0.80	8.24	-0.40	6.68
ΔPOMS Depression[2]	2.66	16.44	2.90	6.41
ΔPOMS Anger[2]	7.44	11.46	0.80	8.24
ΔFOSQ Total Score[3]	-1.37	3.14	0.20	3.25
ΔEpworth	0.80	3.91	1.62	5.19

PVT = Psychomotor Vigilance Test; POMS = Profile of Mood States; FOSQ = Functional Outscome of Sleep Questionnaire

receive conservative treatment (sleep hygiene and weight loss) or conservative treatment plus CPAP. There was no significant improvement in MSLT scores in the CPAP group at 3 and 6 months. A trial conducted to assess the efficacy of modafinil (200-400 mg/day) for the treatment of EDS in Parkinson disease failed to show a significant improvement in MSLT scores compared with placebo.[43]

A review of 75 studies concluded that MSLT and MWT have limited clinical utility for confirming response to treatment in groups of patients with different sleep disorders.[44] A meta-analysis[45] of randomized controlled trials where CPAP was compared with either a placebo or with conservative management in the treatment of OSA showed that CPAP: (1) significantly reduced subjective daytime sleepiness (ESS), (2) improved objective daytime wakefulness (MWT), but (3) did not affect objective daytime sleepiness (MSLT).

Why is the MSLT Unresponsive to Treatment?

One explanation may be that sleep and wakefulness are 2 separate active processes. The active process of sleep and propensity to fall asleep are measured by MSLT. The active process of wakefulness and the ability to stay awake are measured by MWT. It is possible that CPAP and modafinil treatment did not affect the propensity to fall asleep as measured by MSLT. Both treatments may have enhanced the ability to stay awake, but we did not measure the MWT to obtain this data. In support of this view, the meta-analysis reported above found improvement by MWT in spite of observing no change in MSLT with CPAP treatment.[45] On the basis of our study and what has been discussed above, it is possible that the MWT may be a better outcome measure than MSLT in future clinical trials. While there was an improvement of borderline significance ($p = 0.05$) in ESS, there is good reason to doubt the validity of self-report in this patient population.[2]

Other Methodological Issues

The sample sizes were small, and, in addition, complete data on severity of injury was not available on all subjects. For this reason we were unable to address the possibility of a relationship between injury severity and outcome of treatment for sleep disorders. We did not have sufficient numbers to evaluate outcomes in narcolepsy and PTH. Significant effects might have been detected with larger sample sizes. In this study we planned to recruit 90 TBI subjects, expecting that approximately 40% would have sleep disorders and excessive daytime sleepiness. In actuality, 47% had sleep disorders, but only 26% had excessive daytime sleepiness as measured by MSLT. Of those who returned for the second study, 39% had a sleep disorder and 21% had excessive daytime sleepiness. There was an attrition rate of 35% between the initial evaluation and the post treatment phase. This is not unusual for research with TBI patients. Future investigations of TBI patients and sleep disorders need to recruit very large numbers of TBI patients in order to adequately sample the heterogeneity of sleep disorders in this population. This would be best and most economically accomplished with large-scale multicenter investigations by collaborative investigators.[46]

While CPAP treatment of OSA patients was properly titrated in the laboratory, dosages of modafinil and pramipexole were fixed *a priori* by the study protocol with no accommodation made for individual responses and related dose titration. For this reason, patients with PTH or narcolepsy may have been undertreated and remained sleepy on the 200 mg dose of modafinil, yet might have improved with a higher dose. However, titration of modafinil would have required accurate self-report from

patients, which remains problematic in this patient population.[2] Perhaps this could have been addressed with periodic MWTs as an aid to modafinil dosage titration. Periodic limb movements improved in all patients with 0.375 mg of pramipexole, but this is a fairly high dose. It is known that some OSA patients have residual hypersomnia despite adequate treatment with CPAP.[47,48] Thus, the lack of improvement in MSLT scores in these patients may not be entirely surprising.

We did not find any significant change on the neuropsychological test scores or quality of life measures. It has been reported in some, but not all, studies that some OSA patients show improvement on neuropsychological measures while others do not.[47] There may be some permanent deficits in OSA that are not reversed by CPAP.[47] It is also possible that neuropsychological and quality of life measures did not improve because of residual sleepiness despite treatment.

This study represents the first attempt at assessing the effectiveness of treatment of sleep disorders in patients with traumatic brain injury. The difficulties encountered in this endeavor illustrate the importance of large multicenter collaborative studies. Alternative methodological tools will be necessary for assessing sleepiness/wakefulness and for capturing the extra cognitive burden produced by sleep disorders in TBI patients as well as assessing any improvement after treatment.

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DISCLOSURE STATEMENT

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Treating Sleep Disorders in People with Traumatic Brain Injury May not Eliminate Daytime Symptoms

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American Academy of Sleep Medicine
Wednesday, April 15, 2009

Westchester, Ill. – A study in the April 15 issue of the *Journal of Clinical Sleep Medicine* is the first to assess the effectiveness of treating sleep disorders in adults with a traumatic brain injury (TBI). Results indicate that treatment may result in the objective resolution of the sleep disorder without improvements in daytime sleepiness or neuropsychological function.

Results show that in brain-injured subjects with obstructive sleep apnea (OSA), three months of treatment with continuous positive airway pressure (CPAP) therapy dramatically reduced the severity of OSA from 31.4 to 3.8 apneas and hypopneas per hour of sleep; however, there was no demonstrable improvement in measures of daytime sleepiness. Participants experienced no significant changes in measures of mood, quality of life and cognitive performance after treatment for a sleep disorder.

According to principal investigator Richard J. Castriotta, M.D., director of the division of Pulmonary, Critical Care and Sleep Medicine at the University of Texas Health Science Center in Houston, researchers were not surprised by the fact that patients with sleep disorders had more severe injuries; however the lack of improvement in excessive sleepiness and neuropsychological testing after treatment was unexpected.

"The TBI patients with sleep apnea and no improvement in sleepiness may have had a combination of pre-existing sleep apnea and posttraumatic hypersomnia, causing sleepiness after the injury," said Castriotta. "These patients may need stimulant therapy in addition to CPAP in order to improve symptoms."

The study involved 57 adults with an average age of 39 years who had suffered a traumatic brain injury at least three months earlier (average 68 months). Seventy-seven percent of the injuries (44) were incurred as a result of a motor-vehicle accident; other causes were assault, a fall or a falling object. Sixty-one percent of the subjects (35) were free of a sleep disorder, while 23 percent (13) had OSA, 7 percent (4) had periodic limb movements in sleep (PLMS), 5 percent (3) had narcolepsy without cataplexy and 3 percent (2) had post-traumatic hypersomnia.

Participants underwent objective evaluation by overnight polysomnography to detect the presence of sleep disorders, and both objective and subjective tests were used to measure daytime sleepiness, mood, quality of life and cognitive performance. Subjects who were diagnosed with OSA received individualized treatment with CPAP therapy while those suffering from narcolepsy, post-traumatic hypersomnia and PLMS received predetermined dosages of medications that were not adjusted after assessment.

According to the authors, research has shown that some OSA patients have residual hypersomnia despite adequate CPAP therapy, which may explain the lack of improvement in measures of daytime sleepiness. Castriotta stated that the study illustrates how difficult it can be to measure the burden of sleep disorders in people with traumatic brain injuries.

A media fact sheet about obstructive sleep apnea is available from the AASM at http://www.aasmnet.org/Resources/FactSheets/SleepApnea.pdf. Information from the AASM for patients and the public is available about sleep apnea at http://www.sleepeducation.com/Disorder.aspx?id=7 and about CPAP at http://www.sleepeducation.com/CPAPCentral/

The Journal of Clinical Sleep Medicine (JCSM) contains published papers related to the clinical practice of sleep medicine, including original manuscripts such as clinical trials, clinical reviews, clinical commentary and debate, medical economic/practice perspectives, case series and novel/interesting case reports. In addition, the JCSM publishes proceedings from conferences, workshops and symposia sponsored by the American Academy of Sleep Medicine or other organizations related to improving the practice of sleep medicine

For a copy of the study, "Treatment of Sleep Disorders after Traumatic Brain Injury," or to arrange an interview with an AASM spokesperson, please contact Kelly Wagner, AASM public relations coordinator, at (708) 492-0930, ext. 9331, or kwagner@aasmnet.org.

AASM is a professional membership organization dedicated to the advancement of sleep medicine and sleep-related research. As the national accrediting body for sleep disorders centers and laboratories for sleep related breathing disorders, the AASM promotes the highest standards of patient care. The organization serves its members and advances the field of sleep health care by setting the clinical standards for the field of sleep medicine, advocating for recognition, diagnosis and treatment of sleep disorders, educating professionals dedicated to providing optimal sleep health care and fostering the development and application of scientific knowledge.

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Trauma Associated With Cardiac Dysrhythmias: Results From a Large Matched Case–Control Study

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Background: **Various cardiac dysrhythmias such as supraventricular and ventricular premature beats, supraventricular and ventricular paroxysmal tachycardia, atrial and ventricular fibrillation and atrial flutter have been reported in case series, as complications of blunt cardiac and thoracic trauma. The objective of this research was to determine whether thoracic or blunt cardiac injury is associated with cardiac dysrhythmia in a large multistate hospitalized population.**

Methods: **Cases and matched (by age) controls were identified based on hospital discharge information that was collected from 986 acute general hospitals across 33 states in 2001. Both the exposure (thoracic trauma and blunt cardiac injury) and the outcome (cardiac dysrhythmias) were identified based on ICD-9-CM discharge diagnoses. Unadjusted and conditional adjusted (for gender, race, length of stay, and primary source of payment) multivariate logistic regression analyses were performed.**

Results: **After adjusting for potential confounders, patients 50 years and younger diagnosed with blunt cardiac injury had a fourfold (95% confidence interval, 1.40–11.60) increase in the risk of cardiac dysrhythmia. Independent of potential confounding factors, discharge for blunt cardiac injury among patients 51 to 70 years old was associated with a twofold (95% confidence interval, 1.36–3.82) increased risk for cardiac dysrhythmia.**

Conclusion: **Blunt cardiac injury was found to be a significant risk factor for cardiac dysrhythmia. Longitudinal studies are needed to better establish the association between trauma and cardiac dysrhythmias.**

Key Words: **Trauma, Cardiac dysrhythmias.**

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Cardiac dysrhythmias have been frequently reported in case reports as a complication of trauma.[1–17] Thoracic trauma and blunt cardiac injury have been shown to produce various types of dysrhythmias such as ventricular and supraventricular extrasystoles,[18–21] atrial fibrillation and flutter,[4–6,8,11,22,23] supraventricular and ventricular paroxysmal tachycardia,[6,8,12–15,20,24] and ventricular fibrillation.[16,23,25] Traumatic cardiac dysrhythmias have been observed after being hit by a brick,[4] by a steering column,[24] and by a soccer ball.[12] Fabian et al.[8] described 92 patients who experienced various cardiac dysrhythmias after anterior chest impact (i.e. sternal or rib fractures) and Leor et al.[12] observed multiple ventricular premature contractions in patient with blunt trauma to the left precordium. In some studies, patients who developed cardiac dysrhythmia had no history of cardiovascular diseases.[1,15] Traumatic cardiac dysrhythmias usually developed within the first several hours[26,27] or within 24 to 48 hours after injury;[19,28–30] however, some patients with trauma experienced life-threatening dysrhythmias several days after an episode of injury.[2]

To our knowledge, no population-based studies have examined the relationship between thoracic trauma and cardiac dysrhythmias. Our previous study showed that trauma may be independently associated with such serious cardiac events as acute myocardial infarction[31] and cardiac valve insufficiency.[32] Although potentially treatable, cardiac complications of thoracic or cardiac trauma such as heart failure or cardiac dysrhythmias are difficult to predict.[33,34] The objective of this research, therefore, was to determine whether thoracic and blunt cardiac injuries are significantly associated with certain cardiac dysrhythmias. A matched case–control study of the association between thoracic and blunt cardiac injuries and cardiac dysrhythmias was conducted based on a database of all hospital discharges from 33 states in the United States.

MATERIALS AND METHODS

The Agency for Healthcare Research and Quality developed the 2001 Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS; http://www.hcup-us.ahrq.gov/db/nation/nis/Overview_of_NIS_2001_25Jul03.pdf). The 2001 NIS file has 7.45 million uniform hospital discharge abstracts for all inpatient stays. Such discharge information was collected from 986 acute care general hospitals across 33 states (Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Maine, Minnesota, Missouri, Montana, Nebraska, North Carolina, New Jersey, New York,

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Oregon, Pennsylvania, Richmond, South Carolina, Tennessee, Texas, Utah, Virginia, Vermont, Washington, Wisconsin, West Virginia). The NIS contains patient-level characteristics, types and sources of admissions, International Classification of Diseases-9th Rev.-Clinical Modification (ICD-9-CM) diagnosis codes, procedure codes, diagnosis-related groups, total charges, primary and secondary sources of payment, insurance coverage, discharge status, length of stay, and procedure days from admission.[35,36]

Cardiac dysrhythmias were identified based on ICD-9-CM codes. These included premature supraventricular beats (ICD-9-CM 427.61), paroxysmal supraventricular (427.0), atrial flutter (427.32), atrial fibrillation (427.31), premature ventricular beats (427.69), paroxysmal ventricular tachycardia (427.1), and ventricular fibrillation (427.41).

There were 672,043 cases with the dysrhythmia of interest. All dysrhythmias of interest were combined into a single outcome. Controls were matched for age (±1.5 years) in the ratio 1:1 by random selection of individuals within the database. All controls were free of reported dysrhythmia based on ICD-9-CM codes.

Thoracic trauma was identified based on ICD-9-CM diagnostic codes: 807.0–807.4, 839.61–839.71, 848.3, 848.4, 860–862, 875, 879.0, 879.1, 901, 927.0, 922.1, and 942.x1–942.x2. Body part groupings were based on an early version of the Barell Matrix developed by Barell et al.[37] Blunt cardiac injury was identified based on ICD-9-CM diagnostic code (861.01).

Potential confounding factors included patient-level demographic characteristics such as age, race (white vs. nonwhite), and gender (male vs. female). Length of stay was categorized as a categorical variable (≤3 days vs. >3 days). Primary source of payment included Medicare, Medicaid, private including HMO, self-pay, no charge, and other.

Paired case–control analyses were conducted with results reported for analyses and subset analyses where the number of observations (i.e., individual discharge records) in any given cell of tabulated data was >10.[35] Data cells where the number of observations was ≤10 were collapsed.[36]

Analyses initially employed unadjusted conditional logistic regression to examine the relationships among thoracic trauma, blunt cardiac injury, and cardiac dysrhythmia. Subsequently, covariates were introduced using the multivariate extension for McNemar Test for matched case–control studies (conditional logistic regression) to assess the relationship between trauma and dysrhythmias adjusting for patient-level characteristics. To test for interactions, a product term was calculated by multiplying the dichotomized exposure of interest (i.e., thoracic or blunt cardiac injury) with variables reflecting each 10-year age group strata. The interaction term was included in a model along with all available potentially confounding covariates: gender, race, length of stay, and source of payment. Models with and without interaction terms were analyzed revealing thoracic injury-age 51 to 60 and thoracic injury-age 61 to 70 interaction product terms that were statistically significant. Therefore, we stratified our analyses by age groups of ≤50 years, 51 to 70 years, and ≥71 years. This stratification is also relatively consistent with age grouping (≤45 years vs. ≥46 years) used previously by us[31] and others.[38,39] When appropriate, odds ratios and 95% confidence intervals (CIs) were calculated from logistic models. Calculations were performed using SPSS for Windows (version 12.0; SPSS, Chicago, IL).

RESULTS

Among 672,042 cases of dysrhythmia, 988 (0.15%) had thoracic trauma and 126 (0.02%) had blunt cardiac injury. Among 672,042 controls, 1,193 (0.18%) had thoracic trauma and 90 (0.01%) had blunt cardiac injury. Social and demographic characteristics of cases and controls are presented in Table 1. There were fewer female patients (50.9 vs. 59.3) and more white patients diagnosed with cardiac dysrhythmia (64.9 vs. 59.8) compared with controls. Almost 80% of cases had atrial fibrillation, the most prevalent type of dysrhythmia in our study, followed by paroxysmal ventricular tachycardia and atrial flutter (about 7% each) and other dysrhythmias (about 1% each).

In unadjusted logistic regression analyses, thoracic trauma was significantly associated with a moderate decrease in the risk for cardiac dysrhythmia among patients 71 years and older whereas blunt cardiac injury was significantly associated with increased risk for cardiac dysrhythmia among all age groups; however, this result was not statistically significant (Tables 2 and 3). In the multivariate conditional logistic regression analyses, patients ≤50 years old diagnosed with blunt cardiac injury had a fourfold (95% CI, 1.40–11.60) increase in the risk of cardiac dysrhythmia (Table 2). Independent of potential confounding factors, discharge for blunt cardiac injury among patients 51 to 70 years was associated with a twofold (95% CI, 1.36–3.82) increased risk for cardiac dysrhythmia (Table 2). After adjusting for potential confounders, discharge for thoracic trauma was found to have moderately decreased risk for cardiac dysrhythmia among people 71 years and older (Table 3).

Table 1 Social and Demographic Characteristics of Cases and Controls

Characteristics	Cases (672,043)	Controls (672,043)
Female (%)	342,565 (50.9)	398,295 (59.3)
White (%)	436,232 (64.9)	401,572 (59.8)
Length of stay (median)	5	4
Medicare	522,193 (77.7)	515,303 (76.7)
Medicaid	21,100 (3.1)	25,881 (3.9)
HMO	109,719 (16.3)	108,155 (16.1)
Self-pay	8,842 (1.3)	10,299 (1.5)
No-charge	641 (0.1)	686 (0.1)
Thoracic trauma	988 (0.1)	1,193 (0.2)
Blunt cardiac injury	126 (0.02)	90 (0.01)

Table 2 Conditional Multivariate Logistic Regression Analysis on Blunt Cardiac Injury and Cardiac Dysrhythmias

	≤50 Years Old			51–70 Years Old			≥71 Years Old		
	OR	*p*	95% CI	OR	*p*	95% CI	OR	*p*	95% CI
Blunt cardiac injury, unadjusted	1.67	0.32	0.61–4.59	1.39	0.19	0.84–2.31	1.38	0.06	0.98–1.93
Blunt cardiac injury, adjusted*	4.03	0.01	1.40–11.60	2.28	<0.01	1.36–3.82	0.78	0.16	0.55–1.10

* Adjusted for gender, race, length of stay, and source of payment.
CI, confidence interval; OR, odds ratio.

Table 3 Results of the Conditional Multivariate Logistic Regression Analysis on Thoracic Injury and Cardiac Dysrhythmias

	≤50 Years Old			51–70 Years Old			≥71 Years Old		
	OR	*p*	95% CI	OR	*p*	95% CI	OR	*p*	95% CI
Thoracic injury, unadjusted	0.94	0.76	0.64–1.41	0.90	0.24	0.76–1.07	0.80	<0.01	0.72–0.88
Thoracic injury, adjusted*	1.35	0.11	0.93–1.97	1.11	0.26	0.93–1.34	0.72	<0.01	0.65–0.80

* Adjusted for gender, race, length of stay, and source of payment.
CI, confidence interval; OR, odds ratio.

DISCUSSION

This article represents the first attempt to look at the association between thoracic and cardiac trauma and cardiac dysrhythmias at a large population-based level. Population-based studies are important in that they reduce the potential for selection bias and confounding, both of which may limit the interpretation of case reports. In addition, population-based studies that include control groups provide quantitative estimates of association as well as better estimates of public health impact.

We found that patients 50 years and younger diagnosed with blunt cardiac injury had a fourfold increase, whereas patients 51 to 70 years old diagnosed with the same type of injury had a twofold increase in the risk of cardiac dysrhythmia. Several mechanisms have been hypothesized to explain cardiac dysrhythmias resulting from trauma, including abnormal perfusion patterns, vagal sympathetic reflex, and abberant conduction by damaged myocardial cells.[40] Local hypoxia and ischemia caused by increased intravascular rouleaux formation owing to trauma[41] may also contribute to the mechanism of traumatic cardiac dysrhythmias. The mechanism of traumatic cardiac dysrhythmias was studied in animals. Schlomka conducted a series of experiments where he traumatized the heart by direct blows. Both ventricular tachycardia and fibrillation were observed.[42] Link et al.[43] conducted a series of low-energy impacts to the chest wall in a swine model. It has been demonstrated that the risk and type of dysrhythmia depend on when the impact occurred during the cardiac electric cycle.[43,44] In addition, the risk of cardiac dysrhythmia was found to be directly proportional to both the force and speed of the impact and inversely proportional to the size of the contact area.[43] Evidence that cardiac dysrhythmias may result from relatively "mild" sports trauma, perhaps suggesting that the strength of the impact is less important, has been also introduced by various researchers who noticed that various types of dysrhythmias may appear from usually innocent-appearing chest blows in various sport activities.[45] On the other hand, by using the swine model it was shown that even low-energy impact can have immediate and significant effect if applied during a short and vulnerable time interval (i.e. upstroke of the T wave), resulting in ventricular fibrillation.[43]

Atrial fibrillation, one of the most common cardiac dysrhythmias encountered in clinical practice[46] was found to be the most common form of dysrhythmia that presents after chest injury.[4–8,11,22,23,30,47–49] In the study conducted by Seguin et al.,[50] independent of confounding factors, blunt thoracic trauma was associated with a 17-fold increased risk for atrial fibrillation. The relatively short observation of patients for the presence of some confounding factors such as the presence or absence of shock as well as the relatively low incidence of atrial fibrillation were the main limitations of this study. Another limitation of this study was the lack of assessment for blunt cardiac injury among patients with blunt thoracic injury, which may explain the disagreement in results between this and our study.

Although chronic cardiovascular conditions, such as ischemic heart disease or rheumatic diseases, are major cause of atrial fibrillation, in about 10% of people with this type of dysrhythmia, the "true" cause is unknown.[51,52] Blunt cardiac injury was found to be one of the causes of atrial fibrillation but this type of injury is difficult to diagnose.[7,30,49] In a previous study, we have found that blunt cardiac injury is much less frequent when identified through ICD-9-CM and when compared with thoracic injury (57,270 vs. 2,709 respectively).[31] In addition, relatively mild mechanical impact to the chest can result in serious cardiac dysrhythmia even without significant blunt cardiac injury.[53,54] On the

other hand, cardiac injury may be produced by external traumatic agent without symptoms of significant chest trauma.[55] This probably can explain the lack of association between chest trauma and cardiac injury in our study.

Both supraventricular and ventricular paroxysmal tachycardia have been reported after thoracic and cardiac trauma.[6,8,12–15,20,24] Most traumatic cardiac dysrhythmias and electrocardiogram (ECG) changes are transitory conditions that are usually represented as ST-T changes of extrasystoles.[11,15,17–21] Some traumatic cardiac dysrhythmias such as ventricular fibrillation, however, may lead to immediate death.[16,23,25] This phenomenon is poorly understood and in some cases is described as commotion cordis, a life-threatening event occurring mostly in young sportsmen.[56–59] Although commotion cordis is a relatively rare event, its prevalence is likely underestimated.[43,54,57]

We found that thoracic trauma was not a risk factor for cardiac dysrhythmias among patients 70 years and younger. Among elderly patients (≥71 years old) thoracic trauma was related to moderately decreased risk for cardiac dysrhythmias after adjusting for other variables. Readers should bear in mind that cardiac injury (i.e., areas of patchy necrosis, local hypoxia, and ischemia) may be produced by external traumatic agent without significant damage to the chest wall.[60,61] On the other hand, the existing Barrel matrix provides only limited information about the anatomic site of thoracic trauma (for instance, whether the impact was toward the left precordium). Future population-based studies are warranted to better understand the relationship between thoracic trauma and cardiac dysrhythmias.

There are several limitations related to this study. Because of the nature of the data (i.e. administrative), temporal trends between trauma and cardiac dysrhythmias could not be established. There might be a higher probability of sustaining cardiac dysrhythmia in the presence of pre-existing cardiac disease; however, this database cannot provide any insight into this issue, since administrative data may not provide accurate insight into timing of events. Certain other problems such as coding accuracy and variation as well as a limited insight into temporal relationship between events have been related to administrative data.[62–64] In addition, such data may not provide full clinical information on certain important confounders such as smoking status or seat belt use.[62–64] Medical chart review, although more expensive, may provide more detailed information on both the exposure and the disease,[65] whereas longitudinal studies would provide in-depth insight into timing of events and mortality. Finally, although we have gained power by combining all dysrhythmias into one group, we have lost the precision of the individual types of dysrhythmia.

It is important to establish the nature and degree of association between certain types of trauma, such as cardiac and thoracic, and dysrhythmias. Ventricular paroxysmal tachycardia can degenerate spontaneously into ventricular fibrillation or may result in congestive heart failure.[66,67] However, it may be even more important to establish a link between trauma and supraventricular paroxysmal tachycardia, since such patients may be completely asymptomatic. Nevertheless, depending on coexisting cardiac diseases, such dysrhythmia can cause pulmonary edema or myocardial ischemia.[68,69] Patients with blunt cardiac injury, therefore, might benefit from certain screening procedures for cardiac dysrhythmias such as ECG, although normal ECG at admission and during 24 hours in the intensive care unit does not exclude fatal cardiac dysrhythmias after discharge.[2] Results of this study, however, do not lend themselves to aggressive screening for cardiac dysrhythmias; rather, they suggest more research in this particular direction. Future research should also focus on possible association between other types of trauma such as back or abdominal trauma and cardiac dysrhythmias.

CONCLUSION

Blunt cardiac injury was found to be a significant risk factor for cardiac dysrhythmia. Longitudinal studies are needed to better establish the association between trauma and cardiac dysrhythmias.

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The Effect of Hyperbaric Oxygen on Persistent Postconcussion Symptoms

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Background: The high incidence of persistent postconcussion symptoms in service members with combat-related mild traumatic brain injury has prompted research in the use of hyperbaric oxygen (HBO_2) for management. **Objective:** The effects of HBO_2 on persistent postconcussion symptoms in 60 military service members with at least 1 combat-related mild traumatic brain injury were examined in a single-center, double-blind, randomized, sham-controlled, prospective trial at the Naval Medicine Operational Training Center at Naval Air Station Pensacola. **Methods:** Over a 10-week period, subjects received a series of 40, once-daily, hyperbaric chamber compressions at 2.0 atmospheres absolute (ATA). During each session, subjects breathed 1 of 3 preassigned oxygen fractions (10.5%, 75%, or 100%) for 60 minutes, resulting in an oxygen exposure equivalent to breathing surface air, 100% oxygen at 1.5 ATA, or 100% oxygen at 2.0 ATA, respectively. Individual, subscale and total item responses on the Rivermead Postconcussion Symptom Questionnaire and individual and total Posttraumatic Disorder Checklist–Military Version were measured just prior to intervention and immediately postintervention. **Results:** Between-group testing of pre- and postintervention means revealed no significant differences on individual or total scores on the Posttraumatic Disorder Checklist–Military Version or Rivermead Postconcussion Symptom Questionnaire, demonstrating a successful randomization and no significant main effect for HBO_2 at 1.5 or 2.0 ATA equivalent compared with the sham compression. Within-group testing of pre- and postintervention means revealed significant differences on several individual items for each group and difference in the Posttraumatic Disorder Checklist–Military Version total score for the 2.0 ATA HBO_2 group. **Discussion:** The primary analyses of between group differences found no evidence of efficacy for HBO_2. The scattered within group differences are threatened by Type 2 errors and could be explained by nonspecific effects. **Conclusion:** This study demonstrated that HBO_2 at either 1.5 or 2.0 ATA equivalent had no effect on postconcussion symptoms after mild traumatic brain injury when compared with sham compression. **Key words:** *hyperbaric oxygen therapy*, *postconcussion syndrome*, *traumatic brain injury*

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WITH the onset of the Afghanistan and Iraq wars in October 2001, the US Departments of Defense (DoD) and Veterans Affairs (VA) have established a worldwide system of care to assess and manage the significant numbers of service members (SMs) and Veterans who have sustained mild traumatic brain injury (mTBI).[1] Aggregated screening data of all Operation Enduring Freedom (Afghanistan War) and Operation Iraqi Freedom (Iraq War) Veterans enrolled in the VA system of care through 2011 reveal that 9.6% experienced at least 1 mTBI during their deployments.[2] Of note, more than 90% of these individuals have at least 1 concomitant secondary diagnosis (eg, posttraumatic

stress disorder [PTSD], pain) that may confound both the clinical presentation and subsequent treatment.[2,3] This condition has been labeled postdeployment multisymptom disorder,[4] or more commonly postdeployment syndrome,[5] and may be one of the reasons for the higher rate of persistent postconcussion syndrome (PPCS) in military personnel than in civilian individuals.[3] The broad range and high frequency of various symptoms are the clinical hallmarks of these syndromes. In addition, many in the military have had repetitive blast exposures, potentially with associated head trauma and associated cumulative brain injury, that may further complicate symptom attribution and recovery.[6]

In an effort to evaluate the effectiveness of innovative treatment options for the array of symptoms seen with PPCS in US combatants, the DoD and VA have developed an initiative involving 3 ongoing independent, randomized, blinded trials to assess the utility of hyperbaric oxygen (HBO_2).[7] Together, these complementary investigations objectively study the effect on symptoms of a range of hyperbaric exposures on military and Veteran populations. The administration of HBO_2 involves breathing high levels of oxygen, usually 100%, at an increased pressure at least 1.4 times greater than the atmospheric absolute pressure at sea level (1 atmospheres absolute or ATA, which is equivalent to 760 mm Hg partial pressure of oxygen).[8] The partial pressure of oxygen will increase proportionally with an increase in the hyperbaric chamber compression pressure, consequently the intent of HBO_2 is to increase the oxygenation of the patient's blood and tissues to supraphysiologic levels as a stimulus to cellular growth and repair. The use of HBO_2 for treating TBI is based on the still unproven theory that functionally retrievable neurons, adjacent to severely damaged or dead neurons, exposed to HBO_2 may return to normal function or near normal function by reactivating metabolic or electrical pathways. Other possible mechanisms of benefit to TBI patients include stem cell mobilization to sites of injury, immunomodulation, and impact on fundamental neurotransmitters such as nitric oxide.[9] While these theories hold promise for future identification of those patients most likely to respond, in practical terms, symptom improvement remains the current metric for a positive therapeutic outcome.[7]

To date, the evidence for efficacy of HBO_2 in TBI is inconclusive. Randomized trials support the use of HBO_2 to improve survival after acute, severe TBI; however, there is no appreciable effect in functional outcomes.[10,11] Primarily anecdotal evidence exists to support HBO_2 for chronic TBI (ie, >3 months postevent), and the only published randomized clinical trial investigating HBO_2 for postconcussion syndrome demonstrated no effect.[9]

A typical HBO_2 clinical treatment uses oxygen at 2.0 to 3.0 ATA for the duration of 90 to 120 minutes; however, individualization based on diagnosis and patient symptoms has been advocated,[8] and anecdotal evidence exists to support efficacy in TBI at lower dosages (1.5 ATA).[10,12,13] A randomized, controlled trial using 2.4 ATA HBO_2 exposure compared with sham (room air at 1.3 ATA) failed to demonstrate any differences in symptoms in SMs with PPCS.[9] Given these results and the anecdotal reports of efficacy at lower, potentially safer pressures, the second phase of the DoD-VA research initiative focused on the effect of 1.5 and 2.0 ATA equivalent HBO_2 dosing. To this end, this investigation examined the effects of HBO_2 exposure on a population of active-duty SMs with PPCS following combat-related mTBI in a 3-arm, randomized, blinded, sham-controlled trial.

MATERIALS AND METHODS

Commencing in 2009, the Defense Advanced Research Projects Agency and the US Navy Bureau of Medicine and Surgery (as part of the DoD-VA collaborative research program) sponsored this single-center, 3-arm, randomized, blinded, sham-controlled trial of HBO_2 exposure on symptomatic mTBI patients. The logistics and challenges of double-blinding hyperbaric chamber interventions have been described previously.[14] This study received appropriate institutional review board and governmental approvals. Sixty-one active-duty military SMs with PPCS were recruited from US military bases. Inclusion criteria were TBI specialist–confirmed diagnosis of mTBI based on the DoD definition of TBI (Health Affairs 2007),[15] postconcussive symptoms from mTBI for at least 3 months, injury occurrence in the past 3 years, psychiatric status (if any) stable for 2 months, stable psychotropic medication history for at least 1 month, and ability to use computerized testing. The diagnosis of TBI was confirmed by the study physiatrist's history, physical examination, and a review of all the acute medical records, including any available battlefield information, from the time of the traumatic event to the present, using the DoD definition of TBI. The only exclusion criteria were the presence of a disorder that contraindicated hyperbaric exposure or previous exposure to HBO_2. Volunteers were recruited from a pool of full-duty Marines from Camp Lejeune Marine Base (North Carolina) and a few from Marine Base Quantico (Virginia) whose symptoms were being managed by the TBI clinic but who were otherwise without medical or military limitations. The Marines from Quantico received additional duty orders to relocate to Naval Medicine Operational Training Center at Naval Air Station Pensacola, Florida, for 2 months to receive the investigative exposures in a hyperbaric chamber.

Demographic information, clinical parameters, and baseline physical, cognitive, and behavioral functioning measures were obtained. Participants were randomly assigned to breathe 1 of 3 oxygen mediums in the hyperbaric chamber at 2.0 ATA, specifically 10.5%, 75%, or 100% oxygen. The sham control (10.5% oxygen at 2.0 ATA) simulated a placebo exposure. The intervention dosing used in this study was chosen on the basis of consensus opinion of the DoD and VA.[16] To maximize participant blinding, oxygen concentrations were varied while maintaining 2.0 ATA to minimize the likelihood of participants noting differential pressures. Randomization to 1 of the 3 groups was accomplished using a computer-generated number assignment (randomizer.org).

Exposures were conducted in a multiplace chamber, with the breathing medium delivered at gas flow rates of 20 L/min or more, using an oxygen treatment hood once the 2.0 ATA exposure pressure was reached, to ensure a consistent dose (Amron International Inc, Vista, California). The Naval Medicine Operational Training Center hyperbaric chamber was elevated less than 50 ft above mean sea level. Exposures in this study were delivered using modifications of established protocols developed by the Navy's Bureau of Medicine and Surgery (BUMED) Undersea Medicine Department. To ensure distributional uniformity among the 3 experimental exposures, subjects were accessioned in 5 separate blocks of 11 to 15 subjects, based on subject availability. Each group of subjects was randomly assigned to receive 1 of the 3 experimental conditions. Once assigned to a particular treatment group, the subjects' experimental condition did not vary over the 40-exposure course. To ensure subject and investigator blinding to the specific treatment exposure being received, all subjects were pressurized inside the chamber to a pressure equivalent of 2.0 ATA. This is equivalent to the atmospheric pressure attained during underwater diving to 33 ft of seawater. Subjects breathed an oxygen-nitrogen treatment gas blended to achieve the oxygen pressure equivalents to which they were assigned. Specifically, 3 gas mixtures were used: (1) a sham air equivalent of 10.5% oxygen (balance 89.5% nitrogen); (2) a 1.5 ATA oxygen exposure equivalent of 75% oxygen (balance 25% nitrogen); and (3) a 2.0 ATA oxygen exposure equivalent of 100% oxygen (0% nitrogen). Chamber compression to 2.0 ATA generally required less than 3 minutes to attain. Once at 2.0 ATA of pressure, each subject was instructed to sit quietly and breathed the assigned gas mixture for a period of 60 minutes (SD = ±1 minute). Chamber decompression to 1.0 ATA (ie, an average room air pressure of 759 mm Hg) similarly required less than 3 minutes to attain. Each participant underwent 40 compressions lasting 60 minutes over a 10-week period. During compression to and decompression from 2.0 ATA, all subjects breathed ambient chamber air. Taking into account the National Fire Protection Agency, US Navy Diving Manual Class A chamber operation standards and local Naval Medicine Operational Training Center control levels, the oxygen content of chamber air was closely regulated to remain between 19% and 23.5% surface equivalents (ie, sea level). This protocol was selected because it most closely approximated the community standard of care and met all safety guidelines.[7,8]

Any subject unable to complete a scheduled treatment due to transient contraindications to hyperbaric chamber exposure (ie, fevers, congestion, inability to equalize sinus or ear pressure) was allowed to make up the missed treatment at the next available opportunity (ie, later the same day, on weekends when treatments were not normally scheduled, or, if necessary, during the transition period between the five 12-subject blocks).

Statistical analyses

This segment of the study focused on an analysis of the effects of these exposures on the primary outcome measure, the Rivermead Postconcussion Symptom Questionnaire (RPQ), by comparing baseline measures with initial postcompression outcomes. Subsequent analyses of all outcome measures at both the initial and 3-month time periods will be completed later. Initial postcompression outcome measurements were obtained within the first week following last exposure. While a broad array of outcome batteries was used for all participants, this initial article presents main findings on the symptomatic effects of the chamber exposures measured by the primary outcome tool, the RPQ.[17] The RPQ is a widely used Likert-type symptom inventory consisting of 16 items (and a 17th narrative item) designed to evaluate the somatic, cognitive, and emotional functioning of individuals who have PPCS following a brain injury.[17] A study of the psychometric properties of the RPQ found that it is most appropriately scored and analyzed using 2 subscales, items 1 to 3 constituting the RPQ-3 and the remaining 13 items constituting the RPQ-13.[17] The appropriate sample size estimates were calculated for a 10% difference (equal to a decrease of 7 total score points) on the primary outcome of postconcussion symptom severity as measured by the RPQ,[17] which required 20 subjects in each group after adjusting for 10% attrition (1-way analysis of variance [ANOVA]; power = 0.80; α = .05). Given the significant co-occurrence of PTSD in military populations with mTBI[1–4] and the overlap of many symptoms to either condition, several behavior measures were included in this investigation. For this article, we selected the Posttraumatic Disorder Checklist–Military Version (PCL-M) to assess symptoms associated with PTSD.[16,18] The PCL-M is a 17-item self-report measure of symptoms suggestive of PTSD and is often used

as an aid in screening for and measuring PTSD. For both the RPQ and the PCL-M, improvement in symptoms is denoted by lower scores.

All analyses were conducted using SPSS 16.0. Demographic characteristics were analyzed using descriptive statistics. Main effect concussive symptom changes were examined using 1-way ANOVA of scores pre- and postcompression on RPQ individual items, RPQ subscales (RPQ-3; RPQ-13), and RPQ total score. Potential secondary effects of hyperbaric treatment on posttraumatic stress was analyzed using 1-way ANOVA on PCL individual item scores pre- and postcompression as well as PLC total score. Statistical level of significance was set at .05.

RESULTS

One hundred twenty eight SMs met preliminary study eligibility and consented for evaluation. Sixty-one of 128 candidates met the full-study criteria and were randomly assigned into the sham control or 1 of 2 HBO_2 exposure groups. The primary reasons for exclusion were the inability to confirm the diagnosis of mTBI, active medication changes, and schedule conflicts. One participant was unavailable for the immediate postintervention assessment, leaving a total of 60 subjects for this analysis. All study subjects experienced at least 1 mTBI, with the most recent TBI occurring at a mean of 8.5 months (SD = 6.58 months; range = 3-39 months) prior to the baseline assessments. All subjects were men. Etiology of concussion included improvised explosive device blast (85.3%), rocket-propelled grenades (3.0%), and mortar attacks (1.7%). The remaining 10% were uncategorized blasts. Slightly more than a quarter of the participants self-reported concussions ($M = 2.1$, SD = 0.95; range = 1-4) prior to the most recent blast injury. Of the 60 subjects who completed the pre- and postcompression procedures, there were 21 subjects in the sham compression group, 18 in the 1.5 ATA equivalent group, and 21 in the 2.0 ATA equivalent group. There were no precompression between-group differences on these variables.

The final sample of 60 subjects had a mean age of 23.2 years (SD = 2.95). Two subjects (3.0%) were African American, 47 (78.3%) were white, 10 (16.6%) were Hispanic, and 1 (1.6%) was Native American. Of the 60 subjects, 19 were married, 3 were divorced, and 38 were single. Pay grades E1 to E6 comprised 97% of the sample. One-way ANOVA and χ^2 analysis revealed no between-group differences with respect to age, pay grade, marital status, or race /ethnicity.

To determine whether a main effect existed, between-group analyses, using SPSS with 1-way ANOVA, were conducted for the pre- and postcompression RPQ items, subscales (RPQ-3; RPQ-13), and total scores. As a secondary analysis, PCL-M item responses and total score, again using SPSS with 1-way ANOVA, were also conducted. At pretreatment, there were no significant differences between groups for symptom inventory items, verifying the efficacy of randomization. At postcompression, no significant differences were found between the 3 groups on any individual symptom inventory items, subscale scores (RPQ-3; RPQ-13), or total scores on the RPQ or PCL-M (see Tables 1 and 2).

Within-group analyses were conducted for all 3 groups, using paired *t* tests, comparing pre- and postcompression RPQ item responses. The sham (2.0 ATA-10.5% O_2) group showed no significant differences on symptom inventory items, subscale scores (RPQ-3; RPQ-13), or total score. The 1.5 ATA equivalent (2.0 ATA-75% O_2) group showed a statistically significant increase (ie, worsening) on item 14 (light sensitivity), but no significant differences were noted for other symptom individual items, subscale scores (RPQ-3; RPQ-13), or total score. The 2.0 ATA equivalent (2.0 ATA-100% O_2) group showed a statistically significant decrease on items 4 (noise sensitivity) and 9 (frustration, impatience), but no other significant differences were noted for symptom individual items, subscale scores (RPQ-3; RPQ-13), or total score (see Table 3).

Within-group analyses were then conducted for all 3 groups, using paired *t* tests, comparing pre- and postcompression PCL-M item responses. Items 16 (being super alert; watchful) and 17 (easily startled) were significantly decreased within the sham (2.0 ATA-10.5% O_2) group, but no other significant differences were noted for individual symptom inventory items or total score. The 1.5 ATA equivalent (2.0 ATA-75% O_2) group showed a significant decrease on item 16 (being super alert; watchful), but no other significant differences were noted for individual symptom inventory items or total score. The 2.0 ATA equivalent (2.0 ATA-100% O_2) group demonstrated significant decreases on PCL-M items 4 (upset when reminded of stressful past event) and 16 (being super alert; watchful) and total score (see Table 4).

DISCUSSION

This investigation represents the second DoD-VA collaborative, randomized, controlled clinical trial studying clinically relevant effects of HBO_2 on PPCS. In this study, none of the groups achieved the hypothesized clinically significant improvement (ie, 7 points) on the primary outcome measure for PPCS (ie, RPQ). In addition, there were no significant differences between groups on any of the RPQ-3, RPQ-13, or PCL-M total scores postcompression. While there were within-group improvements on several of the items for each of the 3 compression groups, analysis of individual symptom items revealed that there were no between-group

TABLE 1 *Between-group analysis of RPQ item means*

	Precompression				Postcompression			
Item no.	**Sham**	**1.5 ATA equivalent**	**2.0 ATA equivalent**	***P***	**Sham**	**1.5 ATA equivalent**	**2.0 ATA equivalent**	***P***
1	2.9	3	2.83	.83	2.62	2.90	2.39	.35
2	1.57	1.43	1.22	.63	1.76	1.52	1.28	.27
3	0.76	0.62	0.55	.78	0.71	0.76	0.33	.24
4	2.7	2.10	2.72	.28	2.43	2.48	2.00	.32
5	2.52	2.86	2.83	.63	2.86	2.86	2.61	.75
6	2.24	1.7	1.72	.28	2.24	1.76	1.78	.31
7	2.62	2.38	3.05	.16	2.48	2.62	2.50	.92
8	1.38	1.0	1.17	.60	1.24	1.10	0.94	.77
9	2.52	2.43	2.67	.78	2.33	2.19	2.11	.79
10	3.14	3.05	3.06	.94	3.05	3.0	2.78	.67
11	2.43	2.19	2.44	.75	2.52	2.29	2.39	.75
12	2.57	2.29	2.39	.69	2.33	2.38	2.06	.58
13	1.29	0.71	0.67	.15	1.48	1.0	0.67	.06
14	1.62	1.10	0.94	.18	1.90	1.62	1.11	.16
15	0.48	0.43	0.28	.58	0.81	0.33	0.22	.07
16	2.05	2.05	1.94	.96	2.10	1.76	1.50	.36
RPQ-3	5.20	5.04	4.6	.72	5.10	5.19	4.00	.20
RPQ-13	27.57	24.29	25.83	.48	27.76	25.38	22.67	.23
Total score	32.81	29.33	30.44	.53	32.86	30.57	26.67	.19

Abbreviations: ATA, atmospheres absolute; RPQ, Rivermead Postconcussion Symptom Questionnaire.

differences. These findings are similar to the first DoD-VA collaborative trial.[9] The lack of between-group differences among the 3 experimental conditions on the primary outcome measure suggests that there was no treatment effect that could be attributed to the HBO_2 parameters studied. These current findings, which parallel the earlier work of Wolf and colleagues,[9] are particularly important in that this study used the more typical treatment pressures advocated by hyperbaric clinicians.[8,10,12,13]

TABLE 2 *Between-group analysis of PCL-M item means*

	Precompression				Postcompression			
Item no.	**Sham**	**1.5 ATA equivalent**	**2.0 ATA equivalent**	***P***	**Sham**	**1.5 ATA equivalent**	**2.0 ATA equivalent**	***P***
1	2.95	2.81	3.39	.24	2.71	2.67	2.83	.90
2	2.43	2.86	3.16	.11	2.38	2.76	3.00	.25
3	2.10	1.76	2.39	.15	1.90	1.95	2.00	.96
4	2.52	2.52	2.94	.46	2.48	2.48	2.28	.80
5	2.71	2.57	2.72	.93	2.76	2.52	2.52	.56
6	2.57	2.57	2.72	.92	2.52	2.57	2.39	.89
7	2.0	2.05	2.22	.82	1.90	2.14	1.83	.62
8	2.0	2.38	2.28	.63	2.24	2.43	2.17	.82
9	2.19	2.10	2.61	.49	2.19	1.71	2.17	.31
10	2.29	2.33	3.00	.15	2.42	2.29	2.50	.87
11	2.57	2.33	2.89	.47	2.48	2.19	2.33	.80
12	1.71	1.57	1.61	.91	1.71	1.81	1.28	.23
13	3.71	3.86	3.83	.93	3.95	3.76	3.50	.53
14	3.38	3.38	3.55	.87	3.14	3.05	3.14	.91
15	3.33	3.10	3.44	.58	3.43	3.24	3.33	.86
16	3.24	3.29	3.11	.88	2.76	2.86	2.39	.52
17	3.43	3.19	3.43	.69	2.90	2.86	3.00	.94
Total score	45.14	44.67	49.39	.45	43.9	43.29	42.56	.96

Abbreviations: ATA, atmospheres absolute; PCL-M, Posttraumatic Disorder Checklist–Military Version.

TABLE 3 *Within-group analysis of RPQ item means*[a]

	Sham			1.5 ATA equivalent			2.0 ATA equivalent		
Item no.	Precompression mean	Postcompression mean	*P*	Precompression mean	Postcompression mean	*P*	Postcompression mean	Precompression mean	*P*
1	2.9	2.62	.23	3.00	2.90	.71	2.83	2.39	.12
2	1.57	1.76	.33	1.43	1.53	.73	1.22	1.28	.83
3	0.76	0.71	.83	0.62	0.76	.48	0.55	0.33	.33
4	2.7	2.43	.21	2.10	2.48	.23	2.72	2.00	.04[b]
5	2.52	2.86	.18	2.86	2.86	1.0	2.83	2.61	.33
6	2.24	2.24	1.0	1.71	1.76	.88	1.72	1.77	.88
7	2.62	2.48	.51	2.38	2.62	.26	3.06	2.50	.10
8	1.38	1.24	.42	1.00	1.10	.72	1.17	0.94	.22
9	2.52	2.33	.38	2.43	2.19	.37	2.67	2.11	.05[b]
10	3.14	3.05	.65	3.05	3.00	.72	3.06	2.78	.45
11	2.43	2.52	.68	2.19	2.29	.68	2.44	2.39	.88
12	2.57	2.33	.40	2.29	2.38	.75	2.38	2.06	.33
13	1.29	1.48	.30	0.71	1.00	.21	0.67	0.67	1.0
14	1.62	1.90	.28	1.10	1.62	.04[b]	0.94	1.11	.64
15	0.48	0.81	.11	0.43	0.33	.49	0.22	0.22	1.0
16	2.05	2.10	.87	2.05	1.76	.44	1.94	1.50	.15
RPQ-3	5.20	5.10	.84	5.04	5.19	.8	4.6	4.0	.32
RPQ-13	27.57	27.76	.91	24.29	25.38	.59	25.83	22.67	.21
Total score	32.81	32.86	.98	29.33	30.57	.61	30.44	26.67	.19

Abbreviations: ATA, atmospheres absolute; RPQ, Rivermead Postconcussion Symptom Questionnaire.
[a] Significant items were #4 (noise sensitivity), #9 (frustration, impatience), and #14 (light sensitivity).
[b] Significant.

TABLE 4 *Within-group analysis of PCL-M item means*[a]

	Sham			1.5 ATA equivalent			2.0 ATA equivalent		
Item no.	Precompression mean	Postcompression mean	*P*	Precompression mean	Postcompression mean	*P*	Precompression mean	Postcompression mean	*P*
1	2.95	2.71	.37	2.81	2.67	.63	3.39	2.83	.14
2	2.43	2.38	.86	2.86	2.76	.68	3.16	3.00	.51
3	2.10	1.90	.46	1.76	1.95	.43	2.39	2.00	.13
4	2.52	2.48	.88	2.52	2.48	.85	2.94	2.28	.02[b]
5	2.71	2.76	.88	2.57	2.52	.83	2.72	2.52	.30
6	2.57	2.52	.88	2.57	2.57	1.0	2.72	2.39	.21
7	2.0	1.90	.68	2.05	2.14	.75	2.22	1.83	.15
8	2.0	2.24	.46	2.38	2.43	.89	2.28	2.17	.54
9	2.19	2.19	1.0	2.10	1.71	.23	2.61	2.17	.16
10	2.29	2.42	.64	2.33	2.29	.87	3.00	2.50	.07
11	2.57	2.48	.72	2.33	2.19	.65	2.89	2.33	.22
12	1.71	1.71	1.0	1.57	1.81	.17	1.61	1.28	.11
13	3.71	3.95	.33	3.86	3.76	.80	3.83	3.50	.32
14	3.38	3.14	.31	3.38	3.05	.23	3.55	3.14	.32
15	3.33	3.43	.74	3.10	3.24	.58	3.44	3.33	.71
16	3.24	2.76	.03[b]	3.29	2.86	.05[b]	3.11	2.39	.04[b]
17	3.43	2.90	.03[b]	3.19	2.86	.15	3.43	3.00	.19
Total score	45.14	43.9	.67	44.67	43.29	.64	49.39	42.56	.05[b]

Abbreviations: ATA, atmospheres absolute; PCL-M, Posttraumatic Disorder Checklist–Military Version.

[a]Significant items were #4 (upset when reminded of past stressful event), #9 (being super alert; watchful), and #17 (easily startled).

[b]Significant.

While no main treatment effect was found at any exposure level, within-group analyses were noteworthy for improvements on 1 to 2 items from both the RPQ and the PCL-M within each experimental condition. In addition, the total score for the 2.0 ATA equivalent group for the PCL-M was found to improve. A statistical argument could be made that the total score is subject to family-wise error rate, and a post hoc test (eg, Bonferonni correction or a similar test) should have been conducted to reduce the likelihood of false-positives by lowering the α value. It was determined, given the exploratory nature of this feasibility study, that doing so would have increased the number of false-negatives, obscuring statistically significant results. Future studies should apply the more rigorous post hoc corrections to ensure that false-positives are not included (ie, type I error). However, it is interesting to note that even with a more "liberal" α value, these significant results represented only a small fraction of the item inventory and a restricted symptom array. The 6 symptoms that significantly varied within any of the groups were noise sensitivity, light sensitivity, easily frustrated, easily upset by past events, being super alert, and easily startled. Three of these symptoms (being super alert, easily upset, and easily startled) are hallmarks of PTSD but are not typical for mTBI. One of them (easily frustrated) may be seen in either condition, and the remaining 2 symptoms (noise and light sensitivity) are more commonly associated with mTBI. The finding of symptoms consistent with mTBI or PTSD or both was expected in this cohort because of the nature of postdeployment syndrome.[1–6] While one of the symptoms (noise sensitivity) that improved within the 2.0 ATA equivalent exposure group is most commonly associated with mTBI, none of the symptoms improved differentially in the main analysis between groups.

The decision to use the RPQ as the primary outcome measure was driven by its worldwide acceptance in the study of mTBI and specifically PPCS.[15,19,20] However, it is most commonly used for individuals who are within 1 year of their symptom-generating mTBI, when these symptoms are most likely to improve or resolve. In this investigation, while the mean time post-mTBI was 8.5 months, many of the subjects had multiple mTBIs, some as distant as 39 months previously, and symptom onset could not be easily discerned. Moreover, these subjects had most likely already experienced the bulk of the recovery typically seen following mTBI, but persistent residual symptoms remained at the time of study enrollment. However, the baseline mean individual item score on the RPQ for all groups was 1.93; therefore, these subjects could only have improved in a limited fashion as compared with individuals with the more typical moderate-severe symptoms seen with acute concussion. The preestablished clinically significant RPQ total score criterion threshold of a 7-point improvement was not approached in any of the groups. Of interest, we found that the sham and 1.5 ATA equivalent groups demonstrated nonsignificant increase (worsening) in their raw total RPQ scores, whereas the 2.0 ATA equivalent group demonstrated a 3.77-point nonsignificant decrease (improvement).

We believe that the improvements seen in this investigation, as well as in the study of Wolf and colleagues and prior case reports,[11,12,21–23] can be best explained by factors other than the effect of HBO_2 on PPCS. As has been reported in depression, anxiety, and PTSD randomized sham-controlled trials, one would expect a placebo and/or Hawthorne effect on symptoms, given the intense nature of the intervention.[24–26] For example, the Marines in this study were temporarily reassigned to Naval Air Station Pensacola and had greatly reduced duty schedules. In addition, they had enhanced access to leisure time and activities in a noncombat, semitropical beach environment. The significant improvement on the PCL-M total score in the 2.0 ATA equivalent group is of interest, but its implications are unclear. Given evidence from animal research on the positive effects of HBO_2 on behavioral factors[27] and the minor benefits seen on the PCL-M in the 2.4 ATA DoD trial,[9] further prospective investigations may be warranted.

This trial represents the second randomized, double-blinded, sham-controlled, prospective study of HBO_2 in the population of subjects with symptomatic chronic mTBI and demonstrates no significant symptomatic improvements from PPCS of HBO_2 at either 1.5 or 2.0 ATA equivalent over sham control. This investigation incorporated many features lacking in prior studies, such as randomization, blinding, and control groups. The inclusion of this level of scientific rigor in this study and the study of Wolf and colleagues support the conclusion that the minor benefits seen on the RPQ, the PCL-M, and other similar measures are not the result of HBO_2.

These studies demonstrated that individuals with PPCS could be recruited into and safely tolerate this study protocol. Future studies, which are currently underway, will benefit from the addition of a waiting list or standard concussion care third arm to account for the nonspecific effects possible in sham control treatment and longer duration of follow-up to assess for the durability of any initial improvements.

This study has several inherent limitations. The small sample size limits the power of the study. Generalizability may be limited by gender. In addition, the high follow-up rate seen secondary to the paid travel and active-duty status (ie, they received additional duty orders to be on the base) may be atypical of nonmilitary populations. The combat exposure experienced by all study participants introduces the possible influence of posttraumatic stress, depression, anxiety, substance abuse, and pain, which have been associated

with deployment,[3,4] likely had confounding effects on HBO_2. The diagnosis of TBI relies on participant self-report, which is sensitive to subjective patient interpretation, memory, social desirability, and other covariates such as personality factors and willingness to reveal problems. As noted, a confounding role of PTSD symptoms may be especially important, as our study demonstrated a significant reduction in some individual items on both the RPQ and the PCL-M that are commonly attributed to stress in both the sham control group and the HBO_2 group over time. Better understanding of this influence and other possible variables, such as time postinjury, medication usage and adjustments, and the role of repetitive mTBI in postconcussion recovery, would allow for a greater refinement of treatment protocols.

CONCLUSIONS

HBO_2 therapy is a proven intervention for treating select acute and chronic ischemic injuries that have well-established theoretical underpinnings and a well-documented role in dive-related injuries, soft-tissue healing, and carbon monoxide poisoning treatment. Prior human research trials with acute, severe TBI have been inconclusive, and previous studies among participants with long-standing postconcussion syndrome have demonstrated no symptom relief with HBO_2. This study, which used a randomized, controlled, double-blinded design conducted at total oxygen doses most commonly used by clinicians, did not demonstrate significant effects of HBO_2 in individuals with symptoms of chronic mTBI when compared with sham compression.

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Traumatic Brain Injury: A Disease Process, Not an Event

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Abstract

Traumatic brain injury (TBI) is seen by the insurance industry and many health care providers as an "event." Once treated and provided with a brief period of rehabilitation, the perception exists that patients with a TBI require little further treatment and face no lasting effects on the central nervous system or other organ systems. In fact, TBI is a chronic disease process, one that fits the World Health Organization definition as having one or more of the following characteristics: it is permanent, caused by non-reversible pathological alterations, requires special training of the patient for rehabilitation, and/or may require a long period of observation, supervision, or care. TBI increases long-term mortality and reduces life expectancy. It is associated with increased incidences of seizures, sleep disorders, neurodegenerative diseases, neuroendocrine dysregulation, and psychiatric diseases, as well as non-neurological disorders such as sexual dysfunction, bladder and bowel incontinence, and systemic metabolic dysregulation that may arise and/or persist for months to years post-injury. The purpose of this article is to encourage the classification of TBI as the beginning of an ongoing, perhaps lifelong process, that impacts multiple organ systems and may be disease causative and accelerative. Our intent is not to discourage patients with TBI or their families and caregivers, but rather to emphasize that TBI should be managed as a chronic disease and defined as such by health care and insurance providers. Furthermore, if the chronic nature of TBI is recognized by government and private funding agencies, research can be directed at discovering therapies that may interrupt the disease processes months or even years after the initiating event.

Key words: brain injury morbidity; chronic disease; head injury; head trauma; rehabilitation; traumatic brain injury

Introduction

THE FUNK AND WAGNALL'S STANDARD DICTIONARY (Funk, 1980) defines an event as: "the final result; the outcome." Traumatic damage to the brain is seen by the insurance industry as well as many health care providers as an "event." Thus a broken brain is the equivalent of a broken bone—the final outcome of an insult to an isolated body system. Once "fixed," the brain requires no further treatment beyond a relatively brief period of rehabilitation, and there certainly will be no lasting effects on other organ systems. In contrast, the World Health Organization (WHO) defines a chronic disease as having one or more of the following characteristics: it is permanent, caused by non-reversible pathological alterations, requires special training of the patient for rehabilitation, and/or may require a long period of observation, supervision, or care (World Health Organization, 2002).

The purpose of this article is to encourage the classification of traumatic brain injury (TBI) as the beginning of a chronic disease process, rather than an event or final outcome. Head trauma is the beginning of an ongoing, perhaps lifelong, process that impacts multiple organ systems and may be disease causative and accelerative. Our intent is not to discourage patients with TBI or their families and caregivers, but rather to emphasize that TBI should managed as a chronic disease, and defined as such by health care and insurance providers. Furthermore, if the chronic nature of TBI is recognized by government and private funding agencies, research can be directed at discovering therapies that may interrupt the disease processes months or even years after the initiating event.

Post-Traumatic Mortality

Traumatic brain injury increases long-term mortality and reduces life expectancy (Table 1). In a 2004 study of mortality at 1 year post-injury among 2178 moderate to severe TBI patients, Harrison-Felix and associates reported that individuals with a TBI were twice as likely to die as a similar non-brain-injured cohort, and had a life expectancy reduction of 7 years (Harrison-Felix et al., 2004). A follow-up study on causes of death revealed that individuals surviving more than 1 year

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Table 1. Relationship between Traumatic Brain Injury and Mortality

n	*Increase in mortality*	*Cause of death*	*Reference*
1448	5.29 MRR, mod-sev 1.33 MRR, mild	Not stated	(Brown et al., 2004)
642	2.78 SMR	Not stated	(Ratcliff et al., 2005)
3679	7 times[a]	Not stated	(Selassie et al., 2005)
2140	37 times[a]	Seizures	(Harrison-Felix et al., 2006)
	12 times	Septicemia	
	4 times	Pneumonia	
	3 times	Respiratory disorders	
1678	49 times[a]	Aspiration pneumonia	(Harrison-Felix et al., 2009)
	22 times	Seizures	
	4 times	Pneumonia	
	3 times	Suicide	
	2.5 times	Digestive disorders	

[a]Greater than in a general population matched for age, race, and gender.
MRR, mortality risk ratio; mod-sev, moderate to severe TBI; SMR, standardized mortality ratio; TBI, traumatic brain injury.

post-injury were 37 times more likely to die from seizures, 12 times more likely to die from septicemia, 4 times more likely to die from pneumonia, and 3 times more likely to die from other respiratory conditions, than a matched cohort from the general population (Harrison-Felix et al., 2006). The greatest proportion of deaths (29%) was from circulatory problems. Although this number was not significantly greater than that of the general population, there was still a 34% increase over the expected number of circulatory-related deaths. In their most recent study, a retrospective analysis of charts from 1678 TBI patients admitted between 1961 and 2002, Harrison-Felix and colleagues observed that TBI patients were 49 times more likely to die of aspiration pneumonia, 22 times more likely to die of seizures, 3 times more likely to die of suicide, and 2.5 times more likely to die of digestive disorders than the general population matched for age, race, and gender (Harrison-Felix et al., 2009).

Shavelle and colleagues (Shavelle et al., 2001) reported that individuals with a TBI were three times more likely to die of circulatory conditions. Although it is somewhat intuitive that individuals with moderate to severe TBI would have a higher mortality rate than the general population, even individuals with mild TBI exhibited a small but statistically significant reduction in long-term survival (Brown et al., 2004).

Based on an examination of mortality among 3679 TBI patients within 1 year of discharge from acute care hospitals in South Carolina, Selassie and colleagues observed a sevenfold increased risk of death overall (standardized mortality ratio [SMR] = 7.1; 95% CI 6.3,7.9) within 15 months of discharge compared with the general U.S. population (Selassie et al., 2005). Patients treated at level 1 trauma centers were 44% (95% CI 0.4,0.8) less likely to die during the follow-up period than those treated at hospitals without a trauma center. Interestingly, patients with a TBI who were insured by Medicare were 1.6 times (95% CI 1.1,2.5) more likely to die than patients covered by commercial insurance.

In a retrospective cohort design study of 642 patients with a TBI discharged from a large rehabilitation hospital in the years 1974–1984, 1988, and 1989, Ratcliff and associates used a Poisson regression to estimate the ratio of the observed number of deaths to the expected number of deaths. The resulting SMR was 2.78 ($w^2 = 96.35$, $df = 1$, $p < 0.0001$), indicating more than a 2.5-fold increase in mortality rates in TBI patients (Ratcliff et al., 2005).

Brown and associates (Brown et al., 2004) conducted a population-based, retrospective, chart-review cohort study of 1448 TBI patients (164 moderate to severe and 1284 mild) from Olmsted County, Minnesota during the years 1985–2000. The mortality risk ratio (95% CI = 22.0–35.9) was 5.29 (range 4.11–6.71) in moderate to severe, and 1.33 (range 1.05–1.65) in mild TBI patients. This indicates that patients with mild TBI exhibited a small but statistically significant reduction in long-term survival compared to the general population. Considering the far greater numbers of mild than moderate to severe TBI patients, the increased mortality among patients with mild TBI would result in considerable numbers of TBI-related deaths.

Post-Traumatic Morbidity

Although many patients survive the initial insult, TBI initiates a chronic disease process that may ultimately contribute to their deaths months to years later.

Neurological disorders

Epilepsy. Traumatic brain injuries are a major cause of epilepsy, accounting for 5% of all epilepsy in the general population (Hauser et al., 1991; Table 2). Individuals with a TBI are 1.5–17 times (depending on the severity of the TBI) more likely than the general population to develop seizures (Annegers et al., 1998). Brain injury is the leading cause of epilepsy in the young adult population. Seizures were observed over a week after a penetrating TBI in 35–65% of individuals. In a study of 309 individuals with moderate to severe TBI followed as long as 24 years post-injury, 9% were being treated for epilepsy (Yasseen et al., 2008). In general, the risk of developing post-traumatic epilepsy (PTE) after a penetrating TBI is higher than after the most severe closed head injury. Englander and colleagues (Englander et al., 2003) studied risk factors for the development of PTE in 647 patients with moderate to severe TBI. The highest probabilities of PTE were seen in individuals with dural penetration by bone and metal, bi-parietal contusions, multiple intracranial operations, multiple subdural contusions, subdural hematoma requiring evacuation, and/or midline shift of >5 mm. As the time from

TABLE 2. INCIDENCE OF SUBSEQUENT NEUROLOGICAL AND NEUROENDOCRINE DISORDERS AFTER TRAUMATIC BRAIN INJURY (TBI)

Disorder	n	*Incidence after TBI*	*Reference*
PTE	4541	Severe TBI: 16.7% Moderate TBI: 4.2%	(Annegers et al., 1998)
	137	13.1% late seizures in admitted patients	(Angeleri et al., 1999)
	490	25.3% late seizures in TBI rehab patients	(Asikainen et al., 1999)
	647	11% seizures within 2 years of TBI	(Englander et al., 2003)
SD	71	45% SD averaging 3 years	(Masel et al., 2001)
	87	46% SD; 23% OSA	(Castriotta et al., 2007)
	35	54% OSA; significantly worse performance on verbal and visual delayed recall and attention tests versus TBI patients without OSA	(Wilde et al., 2007)
PTH	100	35% severe GH deficiency in 21% of patients	(Aimaretti et al., 2004)
	70	33% at 3 months, 23% at 12 months	(Aimaretti et al., 2005)
	1137	27.5% in combined data from 19 studies	(Schneider et al., 2007a)

GH, growth hormone; OSA, obstructive sleep apnea; PTH, post-traumatic hypopituitarism; PTE, post-traumatic epilepsy; SD, sleep disorders.

injury to the time of the first post-TBI seizure may be as long as 12 years (Aarabi et al., 2000), there is need for heightened awareness of the development of epilepsy on the part of the patient, family, and treating medical personnel.

Sleep disorders. Sleep complaints are common following TBI. Subjective complaints of sleep disturbances have been reported in 70% of TBI outpatients (McLean et al., 1984). Disturbed sleep as measured by polysomnography was reported in 45% of a group of 71 individuals averaging 3 years post-injury (Masel et al., 2001).

There is an increased incidence of obstructive sleep apnea (OSA) in TBI patients (Castriotta et al., 2007). OSA is not only associated with decreased cognitive functioning (Wilde et al., 2007), but also with hemodynamic changes and severe cardiac arrhythmias during sleep. Such changes may be profound, with normotensive individuals developing systolic pressures approaching 300 mm Hg after apnea termination (Weiss et al., 1999). Even individuals with mild OSA have significant mortality risks (Partinen, 1988).

Neurodegenerative diseases

It is generally assumed that the cognitive gains made during the acute and post-acute period following TBI are maintained or may increase over the long term. There is a growing body of evidence, however, that suggests that a subset of individuals exhibits gradual declines in cognitive function after their injury (Tables 3 and 4). Till and colleagues (Till et al., 2008) performed serial neuropsychological assessments on 33 individuals with moderate to severe TBI over the first 5 years post-injury. Statistically significant cognitive declines on at least two neuropsychological measures were observed in 27.3% of subjects. Interestingly, the best predictor of

TABLE 3. CLINICAL EVIDENCE OF A RELATIONSHIP BETWEEN TRAUMATIC BRAIN INJURY (TBI) AND SUBSEQUENT NEURODEGENERATIVE DISEASES

Disease	*Effects of TBI*	*Reference*
AD, PD, LBD	Increased NF, BACE, APP, PS-1, α-syn, and Aβ levels in brain tissue samples from TBI patients	(Uryu et al., 2007)
PD	30–60% reduction in antioxidant glutathione and increased iron levels in the substantia nigra of PD patients	(Dunnett and Bjorklund, 1999)
PD	Odds ratio for PD after severe TBI = 11.0 ($p = 0.02$)	(Bower et al., 2003)
AD	Aβ present at autopsy in 30% of severe TBI patients	(Roberts et al., 1994)
AD	Aβ present in 30% of severe TBI patients as early as 2 hours	(Ikonomovic et al., 2004)
AD	Meta-analysis of 15 studies found that TBI is a risk factor for AD, but only in males	(Fleminger et al., 2003)

Aβ, amyloid-β; AD, Alzheimer's dementia; APP, amyloid precursor protein; α-syn, α-synuclein; BACE, β-site APP cleavage enzyme; LBD, Lewy body dementia; NF, neurofilament proteins; PD, Parkinson's disease; PS-1, presenilin 1.

TABLE 4. EXPERIMENTAL EVIDENCE OF A RELATIONSHIP BETWEEN TRAUMATIC BRAIN INJURY (TBI) AND SUBSEQUENT NEURODEGENERATIVE DISEASES

Animal	*TBI model*	*Neurodegenerative disease*	*Effects of TBI*	*Reference*
Mouse	CCI	MS, AD	Increased MMP expression; MMP KO led to reduced lesion volume, improved cognitive performance	(Wang et al., 2000)
Mouse	CCI	AD	Elevated Aβ levels and deposition impaired memory, increased lipid peroxidation	(Uryu et al., 2002)
Pig	RA	AD, PD	APP, Aβ, BACE, PS, and caspases-3 accumulation up to 6 months post-TBI	(Chen, 2004)
Rat	CCI	AD	Increased BACE-1 mRNA and protein expression and enzyme activity	(Blasko et al., 2004)
Rat	CCI	AD	Increased apolipoprotein D mRNA and protein expression	(Franz et al., 1999)
Rat	FPI	AD	Increased APP gene expression PID 2-7 days post-TBI; increased Aβ immunoreactivity and protein expression up to 1 year post-TBI	(Iwata et al., 2002)
Rat	FPI	AD	Increased APP in axons after TBI	(Bramlett and Dietrich, 2002)
Mouse	WDI	AD	Increased expression of PS and Nct in astrocytes and microglia after TBI	(Nadler et al., 2008)
Mouse	WDI	AD	Increased PS1 expression after TBI	(Cribbs et al., 1996)

Aβ, amyloid-β; AD, Alzheimer's dementia; APP, amyloid precursor protein; BACE, β-site APP cleavage enzyme; CCI, controlled cortical impact; FPI, fluid percussion injury; KO, knock-out; MMP, matrix metalloproteinase; MS, multiple sclerosis; Nct, nicastrin; PS-1, presenilin 1; RA, rotational acceleration; WDI, weight-drop injury.

decline was the amount of therapy received at 5 months post-injury. Those who received more therapy in the early post-injury months, regardless of severity of injury and level of neuropsychological impairment, were less likely to show declines over the long term. In its report on the Gulf War and Health, the Institute of Medicine concluded: "there is sufficient evidence of a relationship between sustaining a penetrating TBI and decline in neurocognitive function associated with the affected region of the brain and the volume of brain tissue lost" (Institute of Medicine, 2009). In addition, age is clearly a factor in long-term cognitive outcome after TBI. Older patients show a greater decline over the first 5 years following a TBI than younger patients (Marquez de la Plata et al., 2008)

Alzheimer's disease. Although the precise cause of Alzheimer's disease (AD) is unknown, numerous studies have shown that TBI may be a risk factor (Jellinger et al., 2001). In a large study of World War II veterans, Plassman and colleagues (Plassman et al., 2000) found that any history of brain injury more than doubled the risk of developing AD, as well as the chances of developing non-Alzheimer's dementia. They also observed that the worse the brain injury, the higher the risk for AD. Moderate brain injury was associated with a 2.3-fold increase in the risk, while severe head injury more than quadrupled the risk of the subsequent development of AD. Even individuals with no known cognitive impairments after TBI exhibited an increased risk of an earlier onset of AD (Schofield et al., 1997).

In their excellent review on this subject, Lye and Shores suggested many possible etiologies for this connection: damage to the blood–brain barrier causing leakage of plasma proteins into the brain, liberation of free oxygen radicals, and loss of brain reserve capacity, as well as the deposition of amyloid-β (Aβ) plaques (Lye and Shores, 2000).

Neurofilament proteins (NF), amyloid precursor protein (APP), β-site APP cleaving enzyme (BACE), presenilin-1 (PS-1), α-synuclein protein (α-syn), and Aβ were detected in brain tissue samples harvested 4 weeks after TBI (Uryu et al., 2007). Aβ plaques and neurofibrillary tangles comprised of tau protein are pathological characteristics of AD (Braak and Braak, 1991; Forman et al., 2004). BACE and PS-1 are critical components of the anabolic pathway that cleaves APP into Aβ (DeStrooper et al., 1998. Selkoe, 2001).

Iwata and associates reported increased expression of the APP gene, APP751/770, 2–7 days after fluid percussion TBI in rats (Iwata et al., 2002). Interestingly, Aβ immunoreactivity and protein expression increased for as long as a year post-injury, indicating that Aβ accumulation may continue long after APP gene expression returns to normal. Apolipoprotein D (ApoD) mRNA and protein expression were increased in the cortex and hippocampus of adult rats 2–14 days after concussion. ApoD may contribute to neurodegeneration in AD, since elevated ApoD levels have been observed in the CSF and hippocampus of AD patients (Terrisse et al., 1998).

Acute and chronic systemic inflammation/infections are associated with increases in serum tumor necrosis factor-α (TNF-α), resulting in a twofold increase in the rate of cognitive decline over a 6-month period in individuals with AD. Those with high baseline TNF-α levels had a fourfold increase in the rate of cognitive decline (Holmes et al., 2009).

Chronic traumatic encephalopathy. Chronic traumatic encephalopathy (CTE, aka "punch drunk" or dementia pugilistica) is a distinct neuropathological entity caused by repetitive blows to the head. CTE begins insidiously with

deterioration in concentration, attention, and memory, eventually affecting the pyramidal tract, resulting in disturbed coordination and gait, slurred speech, and tremors (McCrory et al., 2007). Although once thought to be a disease only seen in older retired boxers, the sporting world has recently been made aware of autopsy-confirmed findings of CTE in retired professional football players (Omalu et al., 2006). As repetitive head injuries occur in a wide variety of contact sports beginning at the junior high school level, there is clearly need for further study of this entity.

Parkinson's disease. Parkinson's disease (PD) has classically been characterized pathologically by the loss of neurons in the substantia nigra, leading to a selective loss of dopamine and its metabolites. Symptoms of PD include dementia, rigidity, tremor, postural instability, and slowness of movement (Dunnett and Bjorklund, 1999). Lewy bodies (concentric inclusion bodies in the neurons) are considered the histopathological signature of the disease (Zhang et al., 2000). Dopaminergic and noradrenergic neuronal loss have been observed in the locus caeruleus, as have Lewy bodies and neuronal loss in the cerebral cortex, anterior thalamus, hypothalamus, amygdala, and basal forebrain (Zhang et al., 2000).

Although the pathology of PD is well recognized, the mechanisms of neuronal death are uncertain. Experimental studies have implicated oxygen free radicals and oxidative stress (Zhang et al., 2000). α-Syn, which is implicated in other neurodegenerative diseases such as AD, may play a role in the development of PD after TBI (Bramlett and Dietrich, 2003). α-Syn immunoreactivity is a hallmark pathological finding in PD, Lewy body dementia, and multi-system atrophy (Norris et al., 2004; Smith et al., 2003). Increased brain tissue α-syn levels have been observed in brain tissue samples from TBI patients (Uryu et al., 2007). Other putative pathophysiological mechanisms of PD include endogenous and exogenous toxins, mitochondrial abnormalities (Rango et al., 2006), perturbations in the neuronal cytoskeleton and axonal transport, and calcium-induced injury, as well as apoptotic cell death (Dunnett and Bjorklund, 1999; Jenner and Olanow, 1998). Many of these mechanisms are thought to contribute to the pathophysiology of TBI (Bramlett and Dietrich, 2004)

Based on a study of 93 pairs of twins from a database of World War II veterans, Goldman and colleagues observed that if both twins had PD, the one with a TBI was more likely to have an earlier onset of the disease (Goldman et al., 2006). If only one twin had PD, that individual was more likely to have sustained a TBI. In a review of records of 196 PD patients from Olmstead County, Minnesota, Bower and colleagues observed an increased risk of PD in individuals who had sustained a TBI, a risk that increased with injury severity (Bower et al., 2003).

Neuroendocrine disorders

Post-traumatic hypopituitarism. TBI is associated with a host of neuroendocrine disorders, due perhaps to the induction of complex hormonal responses in the hypothalamic-pituitary-end-organ axes that ultimately lead to acute and/or chronic post-traumatic hypopituitarism (PTH). Hypopituitarism was reported in approximately 30% of moderate to severe TBI patients over the first year after injury (Schneider et al., 2007a). To date, studies on the relationship of PTH to mild TBI are lacking. In contrast to TBI patients who develop PTH that resolves over time, Aimaretti and colleagues reported that 5% of TBI patients studied had normal pituitary functioning at 3 months, but developed deficits a year post-injury, perhaps due to the loss of pituitary neuronal reserve (Aimaretti et al., 2005).

Although the underlying causes of PTH are unclear, vascular and structural changes to the hypothalamus, pituitary stalk, and the pituitary itself have been theorized (Edwards and Clark, 1986; Kelly et al., 2000). Current routine clinical imaging techniques may be inadequate for clearly visualizing structural pathology in the pituitary gland and tiny (2–3 mm in diameter) pituitary stalk. Normal imaging does not rule out the possibility of PTH (Agha et al., 2004; Schneider et al., 2007b)

Chronic PTH results in several related neuroendocrine conditions, including growth hormone (GH) and gonadotropin deficiencies and hypothyroidism. GH deficiency/insufficiency was found in approximately 20% of moderate to severe TBI patients (Agha and Thompson, 2006). GH deficiency (regardless of cause) was associated with an increased risk of fatigue, decreased exercise tolerance, depression, osteoporosis, hypercholesterolemia, and atherosclerosis, as well as a significant increase in mortality from vascular disease (Rosen and Bengtsson, 1990). Insulin-like growth factor-1 (IGF-1) is the major mediator of the actions of GH, and a low IGF-1 level is a hallmark of GH deficiency (Carro et al., 2002). In addition to enhancing neurogenesis and increasing neuronal excitability, IGF-1 enhances the clearance of Aβ from the brain (Carro et al., 2002).

Gonadotropin deficiency was observed in approximately 10–15% of individuals post-TBI (Agha and Thompson, 2006). Symptoms in adult males include decreased libido, muscle mass, and strength. A correlation has been found between low free testosterone levels and impaired cognitive function, although there is no clear consensus about testosterone supplementation therapy for cognition (Papaliagkas et al., 2008).

Hypothyroidism was found in approximately 5% of individuals post-TBI (Agha and Thompson, 2006). Associated signs and symptoms included weight gain, dyspnea, bradycardia, intellectual impairment (Agha and Thompson, 2006), hyperlipidemia, depression, hypothermia, and cold intolerance, as well as irregular menses and infertility (Garber and Bergmann Khoury, 2009). A recent study revealed a connection between hypothyroidism in females and the subsequent development of AD (Tan et al., 2008).

The need for monitoring for the development of PTH was emphatically stated in the 2009 Institute of Medicine report on the Gulf War: "That hormonal alterations substantially modify the posttraumatic clinical course and the success of therapy and rehabilitation underscores the need for the identification and appropriate timely management of hormone deficiencies to optimize patient recovery from head trauma, to improve quality of life, and to avoid the long-term adverse consequences of untreated hypopituitarism" (Institute of Medicine, 2009).

Psychiatric disease

In terms of impact on patients and their families and cost to society, psychiatric disorders are among the most important

TABLE 5. RELATIONSHIP BETWEEN TRAUMATIC BRAIN INJURY (TBI) AND PSYCHIATRIC DISORDERS

Disorder	n	*Incidence after TBI*	*Reference*
Depression	722	42% MDD in 30-month study period	(Kreutzer et al., 2001)
	66	42% MDD in 1-year study period	(Jorge et al., 1993)
	100	48% MDD in 8-year study period	(Hibbard et al., 1998)
	666	27% MDD in 35.3-month study period	(Seel et al., 2003)
	1422	7.1% minor depression, 18.5% major depression	(Holsinger et al., 2002)
Psychotic disorder	750	7.5%, latency 15–19 years	(Achte et al., 1991)
	284	8.8%, latency 4.6 ± 4.4 years	(Fujii and Ahmed, 2001)
	60	6.7% in 30-year study period	(Koponen et al., 2002)
Substance abuse	60	11.7% alcohol abuse or dependence	(Koponen et al., 2002)
	361[a]	14%[b] alcohol abuse or dependence; 10.9% drug dependence	(Silver et al., 2001)
Suicide	361[a]	4.5 odds ratio for attempted suicide controlled for alcohol abuse	(Silver et al., 2001)
	145,440	3.02 suicide SMR for concussion	
		2.69 suicide SMR for fracture	(Teasdale and Engberg, 2001)
		4.05 suicide SMR for lesion[c]	
	39	33% considered at risk for suicide	(Leon-Carrion et al., 2001)

[a]5034 study subjects, 361 with TBI, 4673 without TBI

[b]24.5% alcohol abuse in TBI patients, 10.5% in control subjects (24.5–10.5 = 14%).

[c]SMR, standardized mortality ratio (observed suicides in study population/predicted suicides in a matched population); concussion, TBI without fracture or lesion; fracture, TBI with cranial fracture; lesion, TBI with contusion or traumatic intracranial hemorrhage.

MDD, major depressive disorder.

of the nation's health care issues. Current estimates in the U.S. suggest that the collective cost of psychiatric diseases could be as high as one-third of the total health care budget (Voshol et al., 2003). It is therefore critical to note that psychiatric and psychological deficits are among the most disabling consequences of TBI (Table 5). Many individuals with a mild TBI, and the majority of those who survive moderate to severe TBI, are left with significant long-term neurobehavioral sequelae.

In addition to the aggression, confusion, and agitation seen in the acute stages, TBI is associated with an increased risk of developing numerous psychiatric diseases, including obsessive-compulsive disorder, anxiety disorders, psychotic disorders, mood disorders, and major depression (Fleminger, 2008; Zasler et al., 2007), as well as substance abuse or dependence (Hibbard et al., 1998; Holsinger et al., 2002; Koponen et al., 2002; Silver et al., 2001). TBI is associated with high rates of suicidal ideation (Kishi et al., 2001; Leon-Carrion et al., 2001), attempted suicide (Silver et al., 2001), and completed suicide (Teasdale and Enberg, 2001). In chronic TBI, the incidence of psychosis is 20%. The prevalence in TBI patients was 18–61% for depression, 1–22% for mania, 3–59% for post-traumatic stress disorder, and 20–40% for post-traumatic aggression (Kim et al., 2007).

In a study of 60 patients with TBI followed for up to 30 years post-injury, Koponen and colleagues observed that 50% developed a major mental disorder that began after their TBI (Koponen et al., 2002). In a long-term follow-up study of 254 individuals at 2 and 5 years post-TBI, it was found that there was a higher incidence of cognitive, behavioral, and emotional changes at 5 years than at 2 years post-TBI (Olver et al., 1996). Thirty-two percent of those working at 2 years were unemployed at 5 years. Thus in many patients TBI results in long-term or perhaps permanent vulnerability to psychiatric illness.

This lasting susceptibility to psychiatric disorders may be especially prominent in children, perhaps due to frequent damage to pre-frontal brain structures (Anderson et al., 1999). Many functions subserved by the frontal lobes are more severely affected if the injury occurs in the early childhood years (Anderson et al., 1999). Moreover, as opposed to the anticipated improvement in behavior and cognitive functioning that normally occurs as a child matures, young children who have sustained a TBI tend to worsen over time. Even mild TBI in childhood may lead to psychiatric issues in adolescence and early adulthood. McKinlay and colleagues, who followed 1000 infants in New Zealand from birth, reported that children who required overnight hospitalization due to mild TBI showed no academic or cognitive differences from the uninjured cohort before age 10 (McKinlay et al., 2002). However, by ages 10–13 this group showed an increase in conduct disorder, oppositional-defiant disorder, and attention-deficit hyperactivity disorder.

Non-neurological disorders

Sexual dysfunction. Sexuality, both physiological and functional, plays an enormous role in our lives. Sexual dysfunction is an important issue in the general population, and is a major ongoing problem in the TBI population. Between 40 and 60% of TBI patients complain of sexual dysfunction (Zasler et al., 2007). As noted previously, transient hypogonadism is common acutely following TBI, yet it persists in 10–17% of long-term survivors (Agha and Thompson, 2005). Beyond just the fertility and psychosocial issues presented by hypogonadism, muscle weakness and osteoporosis may have a significant impact on long-term function and health, with the consequences exacerbated by prolonged immobility following a TBI (Agha and Thompson, 2005).

Incontinence. One of the most frequent and psychologically devastating consequences of TBI is bladder and bowel incontinence. Brain injury frequently affects the cerebral

structures that control bladder storage and emptying functions, resulting in a neurogenic bladder. Based on a review of the records of over 1000 TBI patients, Foxx-Orenstein and colleagues observed that one-third were incontinent of bowel at admission, 12% at discharge, and 5% at 1 year post-TBI (Foxx-Orenstein et al., 2003). In their review of medical complications in 116 individuals with moderate to severe TBI, Safaz and colleagues found that 14% had fecal incontinence at over 1 year post-injury (Safaz et al., 2008). Fecal incontinence is not only socially devastating, but it may contribute to skin breakdown, decubitus ulcers, and skin infections (Foxx-Orenstein et al., 2003).

Urinary incontinence is an enormous social and medical problem. Chua and associates reviewed the records of 84 patients admitted to a rehabilitation unit within 6 weeks of injury and observed that 62% reported urinary incontinence (Chua et al., 2003). This improved to 36% at discharge; however, 18% remained incontinent at 6 months. Safaz and colleagues found urinary incontinence in 14% of their cohort over a year post-injury (Safaz et al., 2008). Urinary incontinence is associated with the development of frequent urinary tract infections and decubitus ulcers.

Musculoskeletal dysfunction. Spasticity, a common problem after moderate to severe TBI, is characterized by increased muscle tone that results in abnormal motor patterns that may interfere with general functioning, and limit self-care, mobility, and independence in the activities of daily living (Elovic et al., 2004). Untreated, it will eventually lead to muscle contractures, tissue breakdown, and skin ulceration (Zafonte et al., 2004).

The incidence of fractures in TBI is approximately 30%. TBI patients with fractures, especially fractures of the long bones, are at risk for heterotopic ossification (HO), which may develop as late as 3 months post-injury. HO is defined as "the development of new bone formation in soft tissue planes surrounding neurologically affected joints," and has in incidence of 10–20% following TBI (State of Colorado Department of Labor and Employment, 2006). This ectopic bone formation may eventually lead to limited joint mobility, pain, increased spasticity, neurovascular entrapment, and pressure ulcers. Safaz and colleagues found HO in 17% of their cohort over a year post-injury (Safaz et al., 2008). Brain injury severity and autonomic dysregulation accurately predict HO in patients with TBI (Hendricks et al., 2007).

One explanation for the development of HO is that osteoblasts (the pluripotent mesenchymal cells responsible for bone formation) undergo inappropriate differentiation within muscles. Prostaglandins normally help regulate osteoclast and osteoblast function, and it has been suggested that prostaglandin dysregulation after TBI may be a factor in the development of HO (Vanden Bossche and Vanderstraeten, 2005). The mechanism behind increased post-traumatic osteogenesis is not fully understood; however, it is clear that there are unknown centrally-released osteogenic factors that that enter into the systemic circulation following brain injury (Toffoli et al., 2008).

Metabolic dysfunction. A TBI appears to impact the way the body absorbs, utilizes, and converts amino acids. Amino acids play a critical role in brain function because they are incorporated into functional and structural proteins, and are the precursors of neurotransmitters involved in cognitive, motor, neuroendocrine, and behavioral functions. Aquilani and colleagues found significant plasma amino acid abnormalities in individuals with an acute (30–75 days) TBI (Aquilani et al., 2000). All the essential amino acids (EAA, those that cannot be synthesized by the body), and 50% of the non-essential amino acids (NEAA, those that can be synthesized by the body), were significantly lower in individuals with brain injuries than in controls. The same group also found that significant abnormalities at admission were essentially unchanged upon discharge. Most notable was a reduction in tyrosine, a NEAA precursor to serotonin (Aquilani et al., 2003).

Although the amino acid abnormalities in the acute and subacute phases of TBI could be due in part to muscle tissue depletion, hypercatabolic states, and inadequate nutritional supply, Borsheim and associates found significant abnormalities in plasma EAA and NEAA concentrations in chronic moderate to severe TBI patients (Borsheim et al., 2007). Compared to controls, TBI patients (17 ± 4 months post-injury) consuming a 2000-cal/d dietician-approved diet were found to have significantly lower plasma levels of the EAA valine. Valine competes with tryptophan for the same transporter system into the brain, and low valine levels will increase tryptophan concentrations in the brain (Borsheim et al., 2007). As tryptophan is a precursor to serotonin, an increase in tryptophan may increase serotonin production and consequently increase central fatigue.

When administered a drink containing 7 g of EAA, patients with TBI had significantly lower plasma levels of NEAA and valine than control subjects. The NEAA with the smallest increases in the TBI group were alanine and glutamine, which is a precursor to the excitatory neurotransmitter glutamate. Remarkably, TBI patients who were eating a normal diet and were partially back into society and performing activities of daily living, still exhibited abnormalities in plasma amino acids more than 1.5 years post-injury (Borsheim et al., 2007). Glutamine concentrations were reduced by 14% in temporal lobe biopsies in patients with AD, suggesting a glutaminergic cause for the decline in memory and learning seen in that disease (Francis et al., 1993). Moreover, abnormalities in amino acid metabolism may contribute to some of the symptoms (fatigue, decreased memory, and poor learning) seen in patients with TBI.

Etiology

Traumatic central nervous system injury often results in chronic disability with lasting cognitive and motor disorders (Levin et al., 1987). However, what remains uncertain is whether chronic damage is due to long-term consequences of the initial traumatic insult (i.e., Wallerian degeneration) (Adams et al., 2000; Graham et al., 1995), or progressive secondary injury (Bramlett and Dietrich, 2002; Bramlett et al. 1997; Dixon et al., 1999; Smith et al., 1997). Ng and associates (Ng et al., 2008) used MRI to evaluate 14 patients 4.5 months and 29 months post-moderate to severe TBI. In 10 individuals the MRIs showed progression of encephalomalacia. Greenberg and colleagues (Greenberg et al., 2008) studied a similar cohort of 13 patients 4.5 months and 29 months following moderate to severe TBI using diffusion tensor imaging. The studies showed subacute white-matter injury progression in

the frontal and temporal lobes bilaterally. Clinical (Anderson and Bigler, 1995) and experimental (Bramlett and Dietrich, 2002; Dixon et al., 1999; Smith et al., 1997) research has demonstrated progressive CNS atrophy after TBI. Anderson and Bigler (1995) reported widespread white- and gray-matter atrophy in TBI patients, and observed that the extent of ventricular expansion positively correlated with severe memory deficits. Furthermore, dilation of the anterior horn of the lateral ventricle was associated with atrophy of the corpus callosum (Anderson and Bigler, 1995). MRI images recorded as long as 603 days after TBI revealed significant atrophy of the anterior hippocampus. Interestingly, the atrophy involved both anterior hippocampal regions, regardless of the location of the primary injury (Ariza et al., 2006). A positive correlation between cognitive outcome and extent of brain atrophy has been observed in other studies of the chronic effects of TBI (Cullum and Bigler, 1986; Reider-Groswasser et al., 1993).

These studies suggest that the progression of symptoms seen in chronic TBI is due in part to defective apoptotic rather than necrotic cell death mechanisms. Genetic changes affecting cellular demise by apoptosis has also been proposed as a mechanism in delayed radiation vasculopathy syndrome (O'Connor and Mayberg, 2000).

The mechanisms by which a brain injury can impact other organs is not known, but clearly there is an indirect effect. Mirzayan and colleagues (Mirzayan et al., 2008) subjected mice to a controlled cortical impact brain injury and sacrificed them at 96 h. Histopathological changes were found in the liver and lung, suggesting that an isolated TBI can lead to the migration of immune incompetent cells to the peripheral organs, thus potentially leading to their dysfunction. The immune response is significantly impaired acutely following TBI ("post-traumatic immune paralysis"), and may be associated with the high prevalence of infections seen in TBI patients (Kox et al., 2008).

Polio and subsequent post-polio syndrome (PPS) may well serve as a model for chronic post-traumatic disease (CPD). A 1987 National Health Interview Survey estimated that after a period of neurological and functional stability, of the 640,000 survivors of polio surveyed, approximately half had new late manifestations of the disease, with an average latency of 35 years. Weakness and fatigue were the most common symptoms (Jubelt et al., 1999).

In the PPS patient, the terminal axons of the surviving motor neurons sprouted in an attempt to reinnervate muscle fibers that had lost innervation from non-surviving motor neurons (Dalakas 1995). The phenomenon can be captured by single-fiber EMG measuring increased jitter in these patients (Jubelt and Agre, 2000). Jitter measures the time difference of the depolarization of two muscle fiber potentials within the same motor unit upon successive firings. Jitter increases after an attack of polio and persists indefinitely, suggesting ongoing denervation and reinnervation (Jubelt et al., 1999). Although the jitter in the axons of the peripheral nervous system cannot be measured within the axons of the brain, the concept of ongoing denervation and reinnervation within those axons certainly remains a possible explanation for the varying symptomatology displayed over time by individuals with TBI. This "impaired transmission model" may partly explain why some individuals with TBI have benefited from anticholinesterase medications (Silver et al., 2006). This ongoing process of denervation and reinnervation can be stressing to the neuronal cell bodies, that may not be able to keep up with the required metabolic demands, causing them to fail. It is certainly possible that "injured" neurons may have a shorter-than-normal lifespan, and may succumb earlier to the normal aging process (Dalakas, 1995).

Discussion

Historically, individuals living with a brain injury have been referred to as brain injury "survivors." Perhaps the concept of merely "staying alive" was used, because as few as 30 years ago the majority of individuals with a moderate to severe TBI succumbed soon after their injury. Perhaps it was used to imply that the individual "outlived" their injury and persevered despite the hardship of the trauma.

This term, however, does not address the reality of brain injury. Cancer survivors are believed to be cured; they have outlived their disease. Many individuals who sustain a TBI recover completely; they have truly survived their injury. However, annually in the United States alone, over 90,000 TBI patients become disabled (Thurman et al., 1999). In this article we have discussed only a small percentage of the causes of TBI-induced disability and the ongoing and developing medical conditions faced by TBI patients and their families. Presently, well over 3.5 million individuals in the U.S. are disabled due to the myriad sequelae of TBI (Zaloshnja et al., 2008). Brain trauma has resulted in a condition that may be disease-causative and disease-accelerative. As a result of their brain trauma, those 3.5 million Americans now have a lifelong condition that might be termed "chronic traumatic brain injury disease." Certainly by suggesting that a TBI should be approached differently than in the past, the authors do not wish to appear to depersonalize the individual with this disease. Rather, we would hope to achieve one of the goals of chronic disease management: to develop "expert patients" (Tattersall, 2002), who truly understand their disease and can therefore take steps to mitigate all the medical issues that develop after a TBI. The goal is to treat the patient with the disease, as opposed to merely treating the disease in the patient.

Chronic traumatic brain injury disease should be reimbursed and managed on a par with all other chronic diseases. Only then will the individuals with this condition get the medical surveillance, support, and treatment they so richly deserve. Only then will brain-injury research receive the funding it requires. Only then will we be able to truly talk about a cure.

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The Ophthalmology of TBI-Associated Sleep Apnea

Eric L. Singman, M.D.,Ph.D.

Sleep apnea is a type of disturbance during which the sleeping patient either fails to breathe intermittently or does not breathe with sufficient strength or frequency, thereby developing low blood oxygen levels during sleep. Patients with sleep apnea often have no idea they are affected, and might complain of fatigue, drowsiness, or awakening without a feeling of being refreshed. Their spouses might even be more aware of a problem, being kept awake by the patient's loud snoring or choking sounds, or watching with concern as their loved one either stops breathing or gasps while sleeping. Sleep apnea can result from severe brain damage, a condition called central sleep apnea, or from blockage of the airways during sleep. This blockage is referred to as obstructive sleep apnea (OSA).

The risk of developing OSA seems to increase after Traumatic Brain Injury (TBI), and may be related to the development of obesity (a definite cause of OSA) after TBI. Patients with TBI have been reported to eat more and become more sedentary, have lower exercise tolerance and report fatigue more often. Treatment centers caring for TBI patients report having a higher than expected percentage of patients with obesity.

OSA is associated with important and sometimes devastating abnormalities of the visual system. This patient-education module will define and review many of the ophthalmic problems associated with OSA.

OSA patients, more often than other patients, present with a condition called floppy eyelid syndrome. Floppy eyelid syndrome is a condition in which the upper eyelid becomes floppy, rubbery and easier to spontaneously invert. This leads to diminished protection of the ocular surface during sleep, and patients often wake with irritated eyes or even a frank abrasion of the surface of the eye. By the time they see an eye doctor, the objective findings of damage to the ocular surface have usually healed (a process often requiring only a few hours) and the diagnosis can be missed. It is unclear why patients with OSA develop floppy eyelid syndrome more frequently than other patients, but research suggests that obesity leads to both conditions. Other studies suggest chronic allergy and irritation of the upper lids lead to atrophy of the tarsal plate, the firm layer that provides structural support to the eyelid. Floppy eyelid is treatable; the most definitive method is outpatient surgery to tighten the eyelids.

Ischemic optic neuropathy (ION) is a serious condition during which there is swelling and often bleeding at the optic nerve, the nerve that brings information from the eye to the brain. ION can occur at the front-most portion of the optic nerve, a condition called anterior ION (or AION) or in the portion of the nerve behind the eye, a condition called posterior ION (or PION). AION can be diagnosed on physical examination by an eye doctor with the help of special lenses and bright illumination. A diagnosis of PION is made using more indirect imaging tools, such as an ophthalmic sonogram or an MRI.

ION is known to be correlated with OSA and it is likely that sleep apnea is a direct cause of this condition. Its cause is most likely a drop in the blood flow supplying the optic nerve, a condition called ischemia. The optic nerve cannot function correctly during this condition. As the eye deteriorates it begins to swell, further squeezing off its own blood supply. This condition is usually painless, and can be associated with barely noticeable vision loss to complete blindness. The swelling usually resolves spontaneously within a few weeks leaving the normally pink-looking nerve partially or completely pale, a condition called optic atrophy. Not only is visual clarity reduced, but peripheral vision is reduced as well. Patients often report not being able to see the bottom or top half of whatever they are trying to view with the affected eye.

Because there is neither surgery nor medication known to reverse the effects of ION, the most important intervention is to try to prevent the fellow eye from suffering a similar fate. The risk of this occurring is fairly high, and it is important to look for sleep apnea in TBI patients diagnosed with ION and treat them if they experience a sleep disorder.

Chronic glaucoma is a condition in which there is progressive damage to the optic nerve, occurring painlessly over years and without the patient sensing any impairment until late in the disease. It is often associated with an abnormal elevation of fluid pressure within the eye (i.e., intraocular pressure or IOP). The mechanism of glaucoma is not understood but many studies support the concept that there is a mismatch between the IOP and the blood pressure within the vessels supplying the optic nerve.

When the external fluid pressure upon the optic nerve vessels is sufficiently great compared to the

internal blood pressure which helps keep the vessels open, the diameter of the vessels will be reduced and blood flow to the nerve will be compromised. This would be expected to lead to starvation of the nerve, followed by the slow loss of the nerve fibers (or axons) that comprise the nerve.

Another theory of glaucoma is that the naturally thinner portion of the rear wall of the eye where the optic nerve leaves the eye is more susceptible to mechanical damage. When an eye has abnormally high IOP, pressure bows back this thin portion of the wall and crimps the optic nerve and/or the blood vessels feeding the nerve as they pass through the wall, damaging the axons directly, and/or starving them of blood. An eye doctor can see that a nerve may be suffering from glaucoma because the appearance of the nerve changes - the nerve becomes thinner and the center of the nerve head becomes wider and deeper, a condition called optic nerve cupping.

Eye doctors can measure the progress of glaucomatous optic nerve cupping by tracking the reduction of peripheral vision using visual field testing and by tracking the thinning of the axon layer forming the optic nerve using various laser scanning devices. Low pressure (also called normotensive) glaucoma is a variant of glaucoma in which the intraocular pressures seem to be in the normal range. Low pressure glaucoma is definitely associated with OSA and it is likely that OSA is partly causative. The goal when treating low pressure glaucoma is to further lower the IOP and stabilize the visual field loss. It is becoming increasingly important for TBI patients who receive a diagnosis of glaucoma to undergo an exploration for sleep apnea because treatment of sleep apnea might prevent the worsening of, or help in the treatment of, low tension glaucoma.

Papilledema is another type of swelling of the front-most portion of the optic nerve, the portion seen by the eye doctor in the clinic. Papilledema is by caused elevated fluid pressure in the brain, i.e., elevated intracranial pressure. It should be noted that the optic nerve is not only directly connected to the brain, but also that the fibrous layers surrounding the brain (i.e., the meninges) also extend to ensheath the optic nerve.

Between the brain and the meninges circulates the cerebrospinal fluid (or CSF) which supports and cushions the brain and bathes the optic nerve. Normally, the CSF is produced and drained by the brain at such a rate that normal intracranial pressure is maintained. When the CSF drainage is compromised, the

elevated pressure is directly transmitted down the optic nerve. Because the optic nerve sheath ends just at the back of the eyeball, the optic nerve can become squeezed and compressed into the eyeball and the eye doctor can see this swelling occur. Elevated CSF pressure can happen because of brain tumors, bleeding into the brain, congenital deformities in the brain and severe injury to the brain. However, when none of these conditions is present, elevated fluid pressure in the brain is called pseudo-tumor cerebri (PTC).

Notably, OSA is known to cause PTC. Common symptoms of PTC include reduced visual acuity (especially with bending, sneezing or coughing), loss of visual field, headache, double vision and tinnitus (ringing) or whooshing in the ears. Although there are medical and surgical treatments to reduce intracranial pressure in patients with PTC, treating sleep apnea can be an important adjunct to a cure. Therefore, it is critical to specifically evaluate for sleep apnea in TBI patients with PTC.

Stroke, an interruption of blood flow to a portion of the brain, and sleep apnea are intimately associated. Sleep apnea is known to be an important risk factor if not a frank cause of stroke.Stroke patients are known to frequently suffer significant sleep disordered breathing. Because the neurologic pathways serving vision extend the entire length of the brain, stroke, and by extension sleep apnea, can cause significant visual impairment. Common visual problems seen after stroke include double vision, lost visual field, difficulty with eye teaming, reduced visual acuity, impaired visual memory, reduced visual processing speed and visual recognition, and severe glare.Many of these problems can also be a direct result of TBI; as a result, when TBI patients suffer a downturn, caregivers should be wary of both an underlying stroke and undiagnosed sleep apnea leading to stroke.

Microvascular disease, or damage to the smallest blood vessels (i.e., capillaries), is an important problem commonly caused by high blood pressure (hypertension, or HTN) or high blood sugar (diabetes mellitus, or DM). TBI patients seem to be at elevated risk for these conditions, and as with sleep apnea, the connection may be the development of obesity in TBI patients.

Patients will often notice visual impairments prior to becoming aware of the fact that they suffer from HTN or DM. Furthermore, eye doctors commonly diagnose these conditions even when patients do not present with symptoms. OSA appears to make diabetic- and hypertensive-retinal disease more difficult

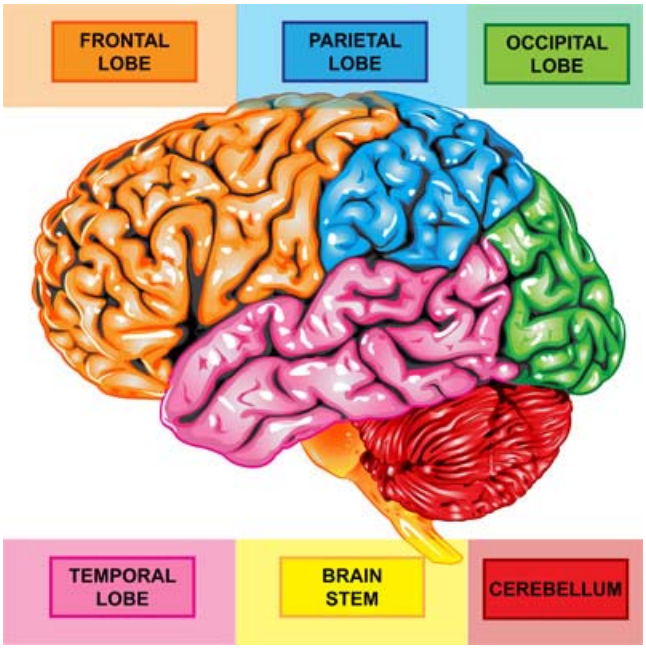
to control and hastens the progression of visual disability. It is therefore important for eye doctors to investigate whether their TBI patients suffer sleep disorders, particularly when retinal vessel disease seems to be progressing faster than expected.

It is probable that the majority of patients with TBI have not been evaluated for sleep disorders; therefore, both patients and caregivers must make an effort to ensure that questions of sleep disorders are raised and addressed. Together, physicians and patients can conquer sleep disorders and the problems they cause. This process of discovery begins with education and awareness. An excellent resource to assist in this process is the National Sleep Foundation (www.sleepfoundation.org).

Brain Injury Alliance
UTAH

Cognitive Skills of the Brain

Because the brain in the central hub for the all of the body's functions, understanding how this organ works can be helpful in terms of understanding Traumatic Brain Injury.



There are six components inside of the brain; the frontal lobe, parietal lobe, occipital lobe, temporal lobe, cerebellum and the brain stem. Read below to understand the functions of each part of the brain, the roles they play in the body's overall health, and observed problems in behavior or well being if that particular part of the brain is injured.

- Frontal Lobe
- Parietal Lobe
- Occipital Lobe
- Temporal Lobe
- Brain Stem
- Cerebellum

Frontal Lobe

The frontal lobe links and integrates all components of behavior at the highest level. Emotion and social adjustment and impulse control are also localized here. Injury to parts of the frontal lobe may cause an inability to move part of the body or the whole side of the body. Speech may become halting, disorganized or be stopped except for single explosive words. Personality may change. Social rules of behavior may be disregarded. The executive functions, planning, abstract reasoning, impulse control, sustained attention and insight are all located here. The frontal lobe is highly susceptible to injury.

Functions

- Initiation
- Problem solving
- Judgment
- Inhibition of behavior
- Planning/anticipation
- Self-monitoring
- Motor planning
- Personality/emotions
- Awareness of abilities/limitations
- Organization
- Attention/concentration
- Mental flexibility
- Speaking (expressive language)

Observed Problems

- Emotion (i.e., depression, anxiety, personality changes, aggression, acting out, and social inappropriateness).

Parietal Lobe

The parietal lobe is largely responsible for construction ability and language. Injury to the front parts of this lobe may cause someone to lose sensation on parts of the body. With an injury in this area, one may become disoriented. Recall of long term memories may be mixed up in time or sequencing. They may become easily lost or confuse left and right. They may have difficulty recognizing or naming what they see. Injury may also produce disorders in the ability to read, write or perform math calculations. This area also includes conscious sensation and voluntary motion.

- Sense of touch
- Differentiation: size, shape, color
- Spatial perception
- Visual perception
- Academic skills (reading)

Observed Problems

- Sensation (i.e., touch, taste, and smell)

Occipital Lobe

Injury to this area usually results in “blindness” to part or all of the visual field. Usually people experience “holes” or “blind spots” in what they see. There may be problems picking things out of space or they may misperceive pictures or objects. Recognition of colors may also be disturbed.

Functions

- Vision
- Reading (perception and recognition of printed words)

Observed Problems

- Depth perception
- Color perception
- Difficulty tracking moving objects
- Partial or total blindness

Temporal Lobe

The temporal lobe perceives and recognizes verbal material. It is among the most frequently injured parts of the brain during head injury. A person may have difficulty screening out distractions. Injury to the upper temporal area can cause someone to misunderstand what is said. They may make sounds like words but which are not recognizable as words at all. They may also misunderstand body language. Emotional changes such as unexplained panic or unexpected tearfulness may be noted. Left temporal area includes production of speech, naming and verbal memory. The right temporal area includes musical abilities, foreign languages, visual memory, and comprehension of the environment.

Functions

- Memory
- Hearing
- Understanding language (receptive language)
- Organization and sequencing
- Musical awareness

Observed Problems

- Thinking (i.e., memory and reasoning)
- Language (i.e., communication, expression, and understanding)

Cerebellum

Obtaining a general understanding of the brain and its functions is important to understanding the rehabilitation process. It is very important, however, to understand that the rehabilitation professional is concerned with the whole person. The identification of individual problems gives the rehabilitation team areas in which to focus treatment plans, all of these plans are designed to work toward the rehabilitation of the whole person. Each problem area affects other areas and many times resolving one problem has a major impact on other problems. For example, reestablishing postural balance and eliminating dizziness greatly enhances concentration and attention which allows for improved cognition and problem solving.

Functions

- Coordination of voluntary movement
- Balance and equilibrium
- Some memory for reflex motor acts

Observed Problems

- Loss of ability to coordinate fine movements
- Loss of ability to walk
- Inability to reach out and grab objects
- Tremors
- Dizziness (vertigo)
- Slurred speech (scanning speech)
- Inability to make rapid movements

Brain Stem

The brain stem plays a vital role in basic attention, arousal, and consciousness. All information to and from our body passes through the brain stem on the way to or from our brain. Like the frontal and temporal lobes, the brain stem is located in an area near bony protrusions making it vulnerable to damage during trauma.

Functions

- Breathing
- Heart Rate
- Swallowing
- Reflexes to seeing and hearing (startling response)
- Controls sweating, blood pressure, digestion, temperature (autonomic nervous system)
- Affects level of alertness
- Ability to sleep
- Sense of balance (vestibular function)

Observed Problems

- Decreased vital capacity in breathing, important for speech
- Swallowing food and water (dysphasia)
- Difficulty with organization/perception of the environment
- Problems with balance and movement
- Dizziness and nausea (vertigo)
- Sleeping difficulties (insomnia, sleep apnea)

Chapter 23

Traumatic Brain Injuries and Sleep/Wake Disorders

Narayan P. Verma and Arunima Verma Jayakar

Additional information is available at the end of the chapter

1. Introduction

Traumatic brain injury (TBI) and sleep/wake disorder/s have a complex relationship [1]. A sleep disorder may make a person more prone to TBI by making him or her drowsy or inattentive and therefore more prone to fall or have an accident [2]. A sleep disorder may also make a person with concussion more prone to develop prolonged concussion or post-concussion syndrome in which symptoms last more than 3 weeks or even more than 3 months [3-7]. Likewise a sleep disorder may make them more prone to future concussions and cumulative injury. [7]

Less known and more common and recently recognized is the sleep/wake disorder caused by TBI itself, most simply termed the post traumatic sleep disorder [8-10] We discourage the use of acronym **PTSD**, however, lest it be confused with post-traumatic stress disorder. We propose the acronym **PTSLD**. This chapter is dedicated to delineating this disorder.

2. TBI

TBI is a problem of significant and increasing proportions-recently described as a silent epidemic [1]. The number of individuals with TBI is expected to climb with the return of Iraq and Afghanistan veterans back to USA. Just like atom bomb induced cancer was the signature injury of World War II and Agent Orange the signature injury of Vietnam War, TBI is the signature injury of Iraq and Afghanistan wars. [1]

Current estimates indicate that the TBI occurs in 100–400 per 100,000 people per year in North America and Europe. Men are more often affected than women. The most common age group which suffers from traumatic brain injury is 15–35 years. It is the most frequent cause of death between the ages 1-15. It accounts for one third of all injury related deaths in the USA. [8]

The TBI may result from fall, domestic violence, street violence, during birth, motor vehicle accidents, war related injuries, a work related injury or due to sports. Falls and motor vehicle accidents are the most common causes in civilian practice. In developing countries such as India with smaller land size, more population density, lax driving law enforcement and booming motor vehicle growth per capita, motor vehicle accidents are as much as 100 times more common than developed countries such as UK or USA.

TBI could be due to a blunt or a penetrating trauma. The trauma may be direct or indirect such from a nearby explosion-as many as 59 percent soldiers exposed to improvised explosive devices (IEDs) develop TBI. [1]

Contrary to popular belief a significant loss of consciousness (LOC) is not always necessary to make a diagnosis especially in so called mild TBI. Per Center of disease control (CDC), a history of clear cut LOC is seen in only less than 10 percent of patients with concussion. [8]

TBI is often described as acute, subacute and chronic-arbitrarily according to the time elapsed. It is also rated as mild, moderate or severe. Although there is no consensus, many prevailing criteria exist. The departments of defense and veterans affairs [3] have attempted to do this as follows:

	GCS	PTA	LOC
Mild	13–15	<1 day	0–30 minutes
Moderate	9–12	>1 to <7 days	>30 min to <24 hours
Severe	3–8	>7 days	>24 hours

GCS-Glasgow coma scale, **LOC**-loss of consciousness, **PTA**-post-traumatic amnesia

Table 1. Severity of traumatic brain injury

Only thing mild about **mild TBI** is the name. It accounts for 75 percent of all TBI. It may potentially be associated with significant, enduring and sometimes devastating consequences, greater likelihood of injury from a repeat concussion and long-term risk of Parkinson's disease, dementia, depression, suicide or homicide. [8] The incidence of mild TBI, also called concussion, is believed to be 6 per 1000 but this may be an underestimate. Per the center of disease control (CDC), a total of 1.4 million visits to hospitals/ER per year in USA are related to concussion/mild TBI. Additional 1.6-3.8 million never visit hospital or the ER. Mild TBI is often considered to occur when Glasgow coma score (GCS) at 24 hours after trauma is 13-15, LOC is 0-30 min and post-traumatic amnesia (PTA) is less than a day. It is often used interchangeably with the term concussion. Sports teams often use the acute concussion evaluation (ACE) questionnaire to evaluate the symptoms of concussion in the sport field.

The ACE questionnaire scores the individual on characteristics of Injury (such as severity and type of trauma, LOC, amnesia and presence or absence of seizures), presence and severity of physical symptoms (such as headache, photophobia, dizziness, nausea, blurred vision etc), cognitive symptoms (fogginess, confusion, forgetfulness, perseveration, slow

cerebration, lack of concentration), emotional symptoms (irritability, sadness, emotional lability, nervousness) and sleep-related symptoms (such as insomnia, hypersomnia, drowsiness, daytime sleepiness, hyperarousal, flashbacks, nightmares), whether they are increased by exertion and how the person feels as compared to before injury on a seven point sale 0-6) and risk factors such as previous history of concussion, headaches, depression anxiety, sleep disorder or developmental disorder such as ADHD or learning disability. This may also be used for serial follow up.

The military equivalent of this scale is called MACE. A score of 25 or above is considered indicative of concussion in MACE. Symptoms persist from 3 weeks to 3 months and are called post-concussive syndrome if they persist beyond 3 months. Although it is believed that concussion results from biomechanical alterations in the brain and there is no structural damage, neuropathological and MRI data with tractography (diffuse tensor imaging or more sophisticated constrained spherical deconvolution) refute this thesis. If *conventional* neuroimaging such as head CT or MRI of the brain is abnormal, the TBI is no longer mild. However moderate to severe TBI may occur with or without abnormal conventional neuroimaging.

Moderate TBI is defined as LOC greater than 30 min but less than 24 hours, GCS 9-12 and/or PTA 1-7 days. It is variously graded by Global assessment of functioning or GAF scale [4] scored from 0-100) or some regional scales such as Rancho Los Amigos Scale [5] which assesses head injured patients on 8 levels of cognitive functioning (LOCF). The GAF score would be expected to be 51-60 with moderate TBI.

Severe TBI is defined as LOC greater than 1 day, GCS 3-8 and/or PTA greater than 7 days. Seizure occurring acutely during the head trauma does not necessarily make the TBI severe but chronic seizure disorder starting 3 months to several years after the head trauma certainly qualifies the TBI as a severe injury. Likewise macro injury, infarction, encephalomalacia, hematoma, persistent focal or lateralized neurological signs, dementia, severe personality change or new onset severe psychiatric disorder stamp an injury as severe. GAF score of 50 or below will indicate a severe head injury even when the neuroimaging is negative. There were 5.3 million people in USA living with severe TBI by 1999 [6]. The number must certainly be higher now. Severe TBI is of 2 types: closed and penetrated.

TBI may occur alone or may be associated with involvement of not just the brain but also skull, scalp, meninges, eyes, ears, sinuses and other neighborhood structures as well as injuries to neck and body.

3. TBI and sleep/wake disorders

Sleep/wake disorders may, in fact, potentially make folks more prone to TBI by making them sleepy and/or inattentive and therefore more likely to be subject of an injury or accident. A preexisting sleep disorder also makes the likelihood of concussion being prolonged and persistent. However, this chapter will mainly deal with the issue of sleep wake disorder/s caused by TBI, a far more common and as yet not well defined problem.

Sleep related problems secondary to chronic TBI have been described anecdotally or in case-report format since 1941. [11-19]. Some commonly reported disorders include hypersomnia, narcolepsy, delayed sleep phase, insomnia, fatigue, alteration of sleep-wake schedule, and movement disorders. It has been found clinically that, insomnia [20], hypersomnia [21-28] and excessive daytime sleepiness (EDS) are common [29, 30] in TBI and may at times occur in the same patient at different intervals from traumatic insult (see below). Only more recently in last 30 years, attempts have been made to explore this relationship in detail. Guilleminault et al in 1982 [13] described impaired daytime functioning and somnolence in 98 percent of all patients with TBI and further expanded their findings in year 2000, [21] extending their observations to even those with cervical whiplash and commenting on the medico-legal dilemma.

Post-traumatic sleep/wake disorders may significantly impair the rehabilitation potential of an injured individual and need to be accurately diagnosed and treated. Organized literature in this important area is sparse and fragmented. An organized account of these disorders is essential not only to improve the rehabilitation potential of these unfortunate individuals but to protect their medical coverage from auto insurers, as they encounter significant skepticism from adjusters regarding their sleep/wake issues to be causally related to their accidents and injury.

To be perfectly accurate, the sleep/wake disorder may not only result from head injury but neck and bodily injuries may cause or contribute to sleep/wake issues equally or even predominantly. [21]

The post-traumatic sleep/wake disorders may evolve, recede or be persistent after TBI. In a prospective study [31], there was found to be a high prevalence of sleep disorders (46%) and of excessive daytime sleepiness (25%) in 87 subjects at least 3 months after TBI [23]. 47% of the subjects in the aforementioned study was found to have a sleep disorder: OSA (23%), PTH (11%), narcolepsy (6%), or PLMS (7%) and 26% of the subjects had EDS [23]. In immediate post-traumatic period, hypersomnia may be common in hospitalized patients due to medications and interrupted nocturnal sleep due to pain and frequent nursing evaluations. Later on, it may be replaced by insomnia. Parasomnias may occur as well. *TBI is now known to cause nearly the entire spectrum of any or all sleep disorders and further may aggravate a pre-existing sleep/wake disorder by potential mechanisms enumerated elsewhere in this chapter.*

4. Acute TBI and sleep-related symptoms

Watson et al in 2007 [32] found in a prospective study of 514 patients that sleep related symptoms are common during acute phase of TBI. As much as 54 percent patients have daytime somnolence, more in those with more severe injury. They result in daytime somnolence which in turn may lead to poor daytime performance, altered sleep-wake schedule, heightened anxiety, and poor individual sense of well-being, insomnia, and depression. Half of these individuals are still sleepy at the end of one year. Relationship with severity or localization of head injury was disputed by Baumann et al [28] who evaluated patients

prospectively as well, but their study ended at 6 months instead of one year in Watson's study.,. However, similar to Watson study, they also found that quality of life was impaired by these symptoms.. CSF hypocretin-1 was found to be significantly reduced levels in those patients with excessive daytime sleepiness (EDS) symptoms.

5. Chronic TBI and sleep related symptoms

Verma et al in 2007 [10] in a retrospective study found that sleep changes and deranged sleep architecture are common in *chronic* TBI patients, arbitrarily defined as 3 months to 2 years after head trauma.. The sleep disorders seen in this population are similar to those seen in the general population but individual percentages are higher. Hypersomnia accounted for 50 percent of all patients and insomnia and parasomnia for quarter each. Global assessment of functioning (GAF) scores correlated with some (stage N1 percentage, impaired sleep efficiency and wake during sleep), but not all (stage shifts and wake before sleep) measures of sleep disruption, indicating a complex and multifactorial pathogenesis.

6. Pathogenesis

The possible pathogenetic mechanisms of TBI causing sleep disorders include: direct brain injury, indirect brain injury, collateral damage to neck and back and resulting pain interfering with sleep, [13] weight gain (secondary to head trauma or medications used to treat head trauma or its sequelae such as posttraumatic mood, anxiety or stress disorder), pre-existing genetic propensity for narcolepsy, which may be clinically aggravated or precipitated by head-trauma [11], a pre-existing anatomical abnormality of sleep-related brain mechanisms, oropharyngeal abnormality aggravated by head trauma or resulting weight gain, anatomical abnormalities caused by head trauma such as jaw dislocation, TMJ problems, and brainstem and forebrain lesions induced by TBI.

Direct brain injury was first described by Strich in 1961 [22] as diffuse degeneration of white matter subsequently termed the diffuse axonal injury (DAI). This was later determined in animal experiments to be the consequence of inertial loading of the head by prolonged coronal angular acceleration [23] with brunt of abnormality in septum pellucidum, corpus callosum, deep gray matter and dorso-lateral pons and midbrain, areas closely associated with sleep-wake mechanisms. The biochemical basis of this injury is excitotoxicity, [24] inflammation, [25] free radicals/eicasanoids, [9] hyperglycolysis, [26] hyperglycemia, [26] and apolipoprotein E e4 synthesis. [27] These mechanisms most likely operate in sleep disorders associated with mild head injury. MRI with tractography may provide a direct evidence of such injury. It has also been hypothesized that the hypocretin system may be partly responsible for the pathophysiology of sleep wake disturbances present post TBI [28].

7. Classification: We propose the following classification of post-traumatic sleep/wake disorders

1. Post-traumatic sleep wake disorder/s-resulting from TBI
2. Post-traumatic sleep/wake disorder/s resulting from neck and/or bodily injuries
3. Post-traumatic sleep/wake disorder/s resulting from both-TBI and neck and/or bodily injuries

Each group has 2 subtypes:

Primary: This group consists of patients who never had any sleep/wake related issues what so ever prior to the accident.

Secondary: These patients have a preexisting sleep/wake disorder which is either aggravated or altered by the accident and in fact may have contributed to the occurrence of accident by making patient inattentive and therefore prone to have an accident. A pre-existing sleep disorder also makes the likelihood of an enduring concussion more as well as increases the proneness to further and cumulative deterioration after repeat concussion.

8. Clinical features

Insomnia: This is the most common consequence of the TBI. It is pretty much universal in all patients with mild TBI at least in initial stages. It is associated with headache, dizziness, mood changes, imbalance and blurred vision and flashbacks in various combinations. It usually resolves in 3 weeks to 3 months in most mild cases but sometimes may be nagging and persistent. It may be sleep onset or sleep maintenance or associated with premature awakening in the morning-the so called the " terminal" insomnia. It may be contributed to by associated anxiety and depression as shown by Verma et al [10] based on Hamilton Anxiety Scale (HAS-appendix 3) and Beck's Depression Inventory (BDI-appendix 4). Nightmares and flashbacks may also contribute. At times it reflects more serious pathology such as sleep apnea caused by TBI and/or neck or spinal injury or periodic limb movements induced by medications used to manage the patient. The medications such as topiramate, methylphenidate etc themselves may aggravate or cause insomnia. Circadian rhythm disorder may complicate insomnia or cause it either due to direct injury to the biological clock or patient's sleep hygiene suffering from frequent examinations by nurses, therapists and other workers, not going to work or office and irregular bedtime and wake up time.

Many patients with more severe head injury initially have hypersomnia due to medications, TBI itself, complicating sleep apnea or narcolepsy but later on after several months or even years develop insomnia. Same factors as listed above operate. Reverse is also true. Patients with mild TBI may develop hypersomnia/ parasomnia or narcolepsy later on even though they had insomnia to begin with. Thus the natural history of sleep/wake disorders is more complicated than the sleep/wake disorders in general as the type of disorder may switch over time.

Although, sleep studies are not generally indicated in patients with most cases of insomnia from other etiologies, the post-traumatic insomnia requires a sleep study for many reasons. It requires documentation as the adjusters frequently look for objective confirmation of subjective symptoms. Also post-traumatic insomnia may not be just pure insomnia but contributed to by sleep apnea, narcolepsy, periodic limb movements, parasomnias such as the REM behavior disorder or a circadian rhythm disorder. In addition, the insomnia may be replaced by hypersomnia or parasomnia and/or even nocturnal seizures later on. The polysomnogram (PSG) should be done with expanded EEG montage with simultaneous video-taping. Traditional investigating methods such as sleep diary, actigraphy and scales such as Hamilton anxiety scale (HAS -appendix 3) and Beck's depression inventory (BDI -appendix 4) also help in dissecting, intellectualizing and treating the issue at hand.

Hypersomnia: This is the second most common consequence. It is quite universal in acute stages of moderate to severe injury as patient is often kept intubated and sedated, on pain medications and primary brain and brainstem pathology from TBI may also contribute. Weight gain from medications to use the consequences of TBI such as antidepressants, anxiolytics or anticonvulsant medications, lack of activity, not working or going to office, being sedentary due to severe TBI and/or neck/bodily injury, overeating due to injury to satiety center of the brain may result in development of obstructive sleep apnea even when there are no oropharyngeal anatomical risk factors. Direct or indirect injury to sleep centers and breathing centers may also contribute. Lowered hypocretin levels may be operative as stated elsewhere. Neck injury may impair diaphragmatic function and add insult to injury. Associated high spinal cord injury may be devastating but cervical whiplash itself is known to cause obstructive sleep apnea [21]. Narcolepsy may be precipitated in a person who is genetically predisposed for it or even be caused by TBI, sometimes even mild TBI. After several years it may be replaced by insomnia in some patients. Hypersomnia with prolonged sleep and even Klein-Levin like syndrome might occur. The periodic limb movements (PLMs) are common either due to medications used to treat TBI or due to unknown reasons such as inactivity or complex chemical changes/alterations, not yet known. Circadian rhythm disorders may contribute. Video-polysomnography with expanded EEG montage and frequently a multiple sleep latency test (MSLT) is addition if the Epworh Sleepiness Scale (ESS-appendix 1) is 11 or more is essential for the diagnosis and should be in-lab and not portable. Actigraphy and sleep diary might help as well.

Parasomnias: These are third most common complications and often co-exist with hypersomnia or insomnia. Each patient may have more than one parasomnia. They may also develop as a remote complication of TBI. As repeated concussions are known to predispose to Parkinson's disease and Parkinson's disease is associated with or even preceded by REM behavior disorder (RBD) by as much as 3 years, this is not entirely unexpected. Sleepwalking, nocturnal eating disorder, nocturnal seizures, nocturnal enuresis either as a part of post-traumatic OSA or due to TBI itself and confusional arousals all are seen and common. In-lab video-polysomnography (video-PSG) with expanded EEG montage is essential for the documentation and diagnosis. The family may also be encouraged to use their smart phones to record these events to help in diagnosis.

9. How to approach a patient with PTSLD

Detailed history is important. One should carefully ascertain if sleep related symptoms started after TBI or preceded that. If latter, document any changes in severity of symptoms or change in symptoms. The routine scales administered in our practice are: Mini mental state examination, ACE questionnaire, Hamilton anxiety Scale (appendix 3), Beck's depression inventory (appendix 4), Epworth sleepiness Scale (appendix 1) and Berlin questionnaire (appendix 2). Careful determination of LOC, PTA and GCS is done based on hospital, ER and other previous records. Computerized psychological and neuropsychological testing (easily administered by even a medical assistant using the 'neurotrax' system) to determine the global assessment of cognitive functioning and levels of anxiety and depression is important to establish a baseline and future follow up. Physical examination should pay careful attention to the HEENT examination, TMJ, neck size, chin (prognathia, retrognathia, micrognathia), oropharyngeal examination for tonsillar size from 1-4 and Mallampati score 1-4, focal and lateralized neurological signs and cardiopulmonary examination. Sleep/wake related history should include details about snoring, witnessed pauses in breathing, bedtime, wake up time, circadian rhythm, gasping and choking in sleep, hypnagogic hallucinations, hypnapompic hallucinations, nightmares, nocturnal incontinence, seizures, sleep walking and acting out of dreams, any falls from bed, restless legs and periodic limb movements (by asking questions such as do you have creepy crawling sensation in your limbs and feet which improve by movement). Wakefulness should be evaluated for alertness, drowsiness, dozing, napping, daydreaming and automatic behaviors. The ESS (appendix 1) is helpful in quantitating sleepiness and Berlin questionnaire (appendix 2) about the probability of sleep related breathing disorder. Sometimes the sleepiness scales are not reliable in patients with severe head injury. Caregiver's input is needed in those situations. Current medication list is critical.

Ancillary tests include an MRI of the head with tractography (diffuse tensor imaging or preferably constrained spherical deconvolution), EEG, an overnight in lab video-PSG with an expanded EEG montage and a 5 nap daytime multiple sleep latency test (MSLT) if ESS is greater than 10. A seven day sleep diary and actigraphy is obtained in those with insomnia or circadian rhythm issues. CSF hypocretin levels may be useful.

Initial follow up visits are monthly for 3 months and then 3 monthly times two. Six monthly visits are obtained after that. Annual ancillary evaluation is more limited and defined by patient's clinical symptomatology. However, sleep disorders may change their characteristics during the course and re-evaluation may need to be tailored accordingly. Therefore a cook book approach is not useful. Maintenance of wakefulness test may be useful in quantitating residual daytime sleepiness.

10. PTSLD

We propose this term as an acronym for post-traumatic sleep/wake disorders to distinguish it from PTSD or post-traumatic stress disorder.

1. Post-traumatic sleep-related breathing disorder:

This is fairly common in general population affecting 2-4 percent of all adults. In patients with TBI, sleep apnea defined as apnea-hypopnea index (AHI) of 10 or greater may be present in up to 30 percent of all patients. Seventy five percent of apneas and hypopneas are obstructive in nature. This condition may present as hypersomnia, insomnia or may only be seen on laboratory evaluation as an unexpected finding. It may cause a secondary REM behavior disorder (RBD -a parasomnia) which may potentially be injurious to the patient if not recognized and treated and further compound the TBI. Mechanisms of post-traumatic sleep related breathing disorder are several. Patient may have pre-existing anatomical abnormalities which were insufficient to cause the sleep related breathing disorder prior to TBI but the occurrence of TBI provides a sufficient milieu for it to clinically manifest. Sedative medications such as clonazapam may potentiate apnea, antidepressants such as sertraline and mitrazepine and anticonvulsants such as valproic acid cause weight gain which is a known risk factor for this condition. Weight gain may also result from physical inactivity and direct damage to hypothalamic centers related to feeding and satiety. Tracheostomy, if done, during the acute management of TBI may further increase the risk especially in children by causing tracheomalacia, as seen in one child by the senior author of this chapter. In addition to known risks of this condition such as premature death, hypertension, heart attack, stroke, dementia and diabetes, this condition may impair the control of patient's seizure disorder if present. Newborns with perinatal head trauma and abused children may develop central apnea due to direct injury to the breathing centers in the brain. In general, more severe the head injury, higher the apnea hypopnea index and hypoxia are. ESS (appendix 1) may be unreliable in those with moderate to severe head injury and should not be used as a sole criterion to order or not order the sleep studies. [10] Berlin questionnaire (appendix 2) also helps in predicting the probability of sleep related breathing disorder.

2. Post-traumatic narcolepsy:

The incidence of narcolepsy in general population is about 1:2000 in the USA. Hormonal change and minor head trauma at puberty are long known to be initiating factors for narcolepsy in neurology text books as the genetic propensity of narcolepsy usually manifests clinically at or after puberty 90 percent of the time. In addition, most patients with narcolepsy remain the same throughout their lifetime. Post-traumatic narcolepsy is different in that it is far more common than general population (it is seen in up to 6-9 percent of all patients with TBI) [10, 11] and down the road, after several years in our experience, symptoms may sometimes abate and even be replaced by insomnia. Hypocretin levels are known to be reduced by TBI and may well play a pathogenetic role. New onset cataplexy might occur after TBI, increasing the risk of falls and therefore repeated TBI. Nightmares are common in TBI and careful history is needed to distinguish them from hypnagogic and hypnapompic hallucinations seen as auxiliary symptoms of narcolepsy. Occurrence of narcolepsy is not correlated with the degree of TBI.

Polysomnogram (PSG) will nearly always show some degree of sleep disruption such as increased percentage of N1, frequent awakenings, reduced sleep efficiency (less than 85

percent), reduced N3 (delta) percentage (less than 15 percent) and sometimes SOREMP (sleep onset REM period or REM sleep occurring with 15 min of sleep onset). The MSLT will show a sleep latency of 8 min or less and 2 or more SOREMPs in 5 naps. [33]

3. Post-traumatic hypersomnia.

Idiopathic hypersomnolence syndrome is long known to often follow TBI and conditions such as Guillaine Barre Syndrome (GBS) or infectious mononucleosis (IM). The PSG shows relatively normal or even improved sleep efficiency sometimes greater than 95 percent, increased or normal delta percentage, relatively few awakenings, minimal sleep disruption if any but severe daytime somnolence on MSLT with no SOREMPs. Medication effect needs to be excluded and one has to be careful not to misdiagnose 15 percent cases of narcolepsy in whom MSLT is initially negative as post-traumatic hypersomnia. The PSG features described above are helpful in distinction and there is no history of hypnagogic or hypnapompic hallucinations or cataplexy. Autonomic symptoms are sometimes present. [33]

4. Post-traumatic periodic limb movement disorder (PLMD):

These may a solitary abnormality on PSG but more often are associated with other conditions such as OSA and narcolepsy. They may have been present premorbidly but are often worsened by medications used for the treatment of TBI. They may be asymptomatic and may not require any treatment or cause significant patient insomnia or spousal discomfort and need treatment. Lower extremities are affected and sometimes only one side but upper extremities may be involved in addition or alone. Neurologic deficit such as hemiparesis or paraparesis may worsen or cause this condition. Anemia of chronic disease may compromise the serum ferritin level and may compound the issue. They are considered significant if more than 15/hour in an adult or 5/hr in a child. [33] Up to 30 percent of all patients may have this condition. [10] They may or may not report RLS in addition when awake.

5. Post-traumatic REM behavior disorder (RBD):

This condition was first described to occur in cats when lesions were created in perilocus coeruleous area to interrupt impulses going down the ventral reticulopsinal tract to spinal motor neurons in REM sleep [10]. Similar mechanisms are operative in humans with TBI. Associated Parkinson's, alcoholism and medications may also contribute. Up to 13 percent patients show symptoms of RBD and/or show increased tone in chin EMG on PSG [10]. Patients typically act out their dreams during last third of sleep at night when REM percentage is the highest and potentially fall from bed, climb out of windows or walk out in freezing weather. It may be secondary to post-traumatic OSA and then it responds to CPAP. If not, RBD precautions and medications are necessary. It may be a precursor of Parkinsonism in patients with punch-drunk syndrome and may precede that condition by as much as 3 years. It should be distinguished from sleep walking which usually occurs during the first half of sleep and there is no dream recall. It should also be distinguished from NREM sleep related confusional arousals which are similar to night terrors.

6. Other post-traumatic parasomnias:

They include sleep paralysis, cataplexy, sleep walking, nightmares, sleep enuresis and nocturnal eating disorder. [33] All parasomnias (these plus RBD) occur in 25 percent of all patients with TBI, either by themselves on in addition to other disorders. Birth injuries to the head may be associated with head banging disorder. [16]

7. Post-traumatic insomnia:

At least one quarter of all patients with TBI have insomnia either sleep onset or sleep maintenance or a combination thereof. [10] Hamilton anxiety scores (appendix 3) are typically elevated in those with sleep onset insomnia and Beck's depression inventory scores (appendix 4) in those with sleep maintenance insomnia. Physical factors such as frequent examination by nurses and respiratory therapists during ICU stay may be the cause at least in acute TBI. Medications such as bronchodilators, anticonvulsants such as topiramate or stimulants such as methylphenidate may cause insomnia. Circadian rhythm abnormalities and not going to regular work and physical inactivity leading to frequent daytime naps may cause insomnia at night. Post traumatic sleep related breathing disorder both of obstructive type or central type may cause insomnia as well. Severe restless leg syndrome (RLS) may cause sleep onset insomnia and PLMs, sleep maintenance insomnia. Patients with post-traumatic narcolepsy may sometimes present initially as insomnia at night and only a careful history uncovers the diagnosis. For example, a patient treated by the senior author was treated for 2 years as insomnia by various physicians, until she disclosed to the author additional history of severe daytime sleepiness and napping since TBI and disturbing "nightmares" (actually hypnagogic hallucinations) with automatic behavior which prevented her from holding onto any job and not succeed in her new marriage. She responded beautifully to sodium oxybutate and was immensely grateful.

8. Post-traumatic circadian rhythm disorder:

This is a fairly common complication. The disorders include a delayed sleep phase syndrome (DSPS), irregular sleep wake cycle, advanced sleep phase syndrome (ASPS) and non-24 hour sleep wake cycle. [33] Irregular sleep wake cycle is common during the acute phase of TBI in moderate to severe cases as nurses and respiratory therapists check on the patient frequently and patient is on medications including sedatives or anesthetic agents such a propofol. It is also common in chronic TBI patients with a psychiatric disorder or blindness. Otherwise DSPS is the most common complication related to circadian rhythm abnormality in patients with TBI and a direct injury to suprachiasmatic nucleus may well be the cause. ASPS is quite frequent in elderly patients with TBI. Non-24 hour cycle is a rare complication in some patients showing a stepladder pattern on actigraphy. [33]

11. Differential diagnosis

Lack of pre-existing history of sleep related symptoms is critical for the diagnosis of the primary post-traumatic sleep disorder, although the TBI may aggravate a pre-existing sleep/

wake disorder or make it more difficult to treat. Secondary gain may need to be excluded but objective confirmation from tests as outlined above, obviates that possibility. Interviewing the family members, friends, golf buddies etc and previous medical records are helpful in determining whether the disorder is primary or secondary. Previous anatomical abnormities do not automatically exclude a primary post traumatic sleep/wake disorder as patient may have been compensated before and the TBI may have been the "last straw which broke the camel's back". Likewise, a positive HLA testing does not automatically make narcolepsy pre-existing or genetic, as head trauma, even mild or minimal is known to be the initiating factor for narcolepsy. Please refer to the international classification of sleep disorders [33] edition 3 for further help in differential diagnosis of post-traumatic sleep disorder/s from non-traumatic etiologies as detailed discussion of that would be tangential to the intent of this chapter.

Treatment : Once it is realized that TBI may cause or aggravate a pre-existing sleep/wake disorder, management is simple. It is treated like any other sleep disorder of another etiology by adding medications, reduction of medications, meditation, machines, devices or behavioral techniques. Treatment is important as it will interfere with rehabilitation potential of the patient unless addressed head on. The treatment modalities outlined below are well described in standard text books of sleep medicine and in the practice guidelines of the American Academy of Sleep Medicine [34] and would only be briefly outlined below without individually referring each modality to prevent unnecessary expansion of the reference list and dilute the intent of this chapter.

Medications and reduction of medications: Mild sleep apnea may be managed with proptriptyline. Periodic limb movements may be helped by Clonazepam, dopamine agonists, gabaergic agents, tonic water and vitamin D. Nocturnal eating disorder often responds to topiramate. REM behavior disorder responds well to Clonazepam and/or melatonin. Nocturnal seizures require anticonvulsants. Carbamazepine is most effective. Hypnagogic hallucinations and nightmares may require clonazepam, imipramine or more complex pharmacological remedies as NMDA agonists.

Reduction of medications may also help by reducing weight, decreasing excessive daytime sleepiness, lessening the aggravation of OSA or reducing PLMs. Some medications such as amitriptyline may induce or aggravate RBD in TBI patients and that might improve by this strategy. Sometimes, reducing topiramate, certain antidepressants, stimulants and wakefulness promoting agents etc may improve insomnia.

Meditation: simple meditation techniques such as Hong-Sau which do not require any special equipment or posture or more complex such techniques such as yoga exercises requiring exercise mats and lotus position may be useful at times in reducing anxiety and improving sleep onset insomnia.

Behavioral techniques: 11 principles of sleep hygiene (appendix 5), 6 Bootzin's principles (appendix 6) and cognitive behavioral therapy for insomnia (appendix 7) are often useful for the management of insomnia. In fact most enduring relief of post-traumatic insomnia comes with non-pharmacological behavioral techniques.

Patients with RBD may require padding around their beds, alarms and double locks at doors and boarding up of windows (RBD precautions). Those with nocturnal eating disorder, may need to have a lock on the refrigerator.

Phototherapy: It is useful in the treatment of post-traumatic delayed sleep phase syndrome and advanced sleep phase syndrome, non 24 hr sleep/wake cycle and insomnia caused by post-traumatic depression. Morning exposure to a standard 2500-10,000 lux lamp from a distance of about 18-24 inches for 30-60 minutes is used in all of these conditions except ASPS in which evening exposure is required. Nausea and queasiness may occur and the duration of exposure may need to be optimized upwards gradually.

Chronotherapy. It will be useful in managing circadian rhythm disorders resulting from head trauma. Advancing the bedtime by 3 hrs a day may help the treatment of DSPS over 8-10 days. It may be used alone or in conjunction with phototherapy and/or melatonin.

CPAP: Continuous positive airway pressure it is the mainstay of treatment for moderate to severe OSA. Patients may experience difficulty in using this device due to facial or TMJ injuries or chest trauma or CHF or if they are claustrophobic.

BIPAP and BIPAP-ST (NIPV)- Bi-level treatment is necessary in some of the patients who have co-morbid muscle disease or CHF. It provides a lesser pressure to facilitate exhalation in an individual with weak muscles or CHF. The inhalation pressures IPAP) are at least 2 cm of H_2O or more than the pressure for exhalation (EPAP). BIPAP-ST or NIPV provides additional protection by backing up ventilation if the respiratory rate falls below a predetermined rate such as 10/min.

Adaptive servo ventilation (ASV): is often useful when nothing else works in complex or central sleep apnea caused by TBI by overwhelming the apneas not only simply by pressure but also volume of the inhaled air and mostly obviates the need for tracheostomy except in acute stages. This device is quite expensive but well worth it as the senior author has never prescribed tracheostomy for sleep-related breathing disorder ever since this device has been commercially available. Prior to that, it was needed at least in one patient every year in our clinic.

Jaw advancement devices: may be useful in those with mild post-traumatic OSA with TMJ issues.

Ongoing follow up is essential by at least 3-6 monthly office visits and yearly sleep studies since post-traumatic sleep disorders are notorious to change during their natural history and may require altogether different treatment as the time passes by.

12. Discussion

A spectrum of sleep disorders are a common finding after the acute phase of TBI [9]. They result in daytime somnolence which in turn may lead to poor daytime performance, altered sleep-wake schedule, heightened anxiety, and poor individual sense of well-being, insomnia

and depression [10] Sleep changes and deranged sleep architecture are more common in *chronic* TBI patients as compared to the general population [10]. Sleep disturbances can compromise the rehabilitation process and the ability to return to work. [20] A high index of suspicion may lead to a diagnosis and subsequent treatment of these disorders and contribute to physical and cognitive rehabilitation of these patients. [10] A proper diagnosis and greater awareness of this complication protects patient's rights for medical care under auto-insurance laws in states such as Michigan [2]. This will also be critical in the management of TBI related symptoms of returning veteran of Iraq and Afghanistan war since TBI is the signature injury of those wars and has become a silent epidemic. [1]

13. Directions for future research and efforts:

The future research and efforts should concentrate on primary prevention of TBI, better delineation of premorbid sleep/wake status by some scales (similar to those which predict premorbid IQ), early identification and accurate diagnosis of post-traumatic sleep/wake disorder, its exact impact on physical, cognitive and occupational rehabilitation, convincing the auto-insurances not to be stingy in the care of these unfortunate individuals and look at sleep/wake related complaints as a medical issue and not a malingering issue, and the US government to provide greater research and medical funds for this important medical condition.

Appendix 1. The epworth sleepiness scale

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

SITUATION	CHANCE OF DOZING
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

Appendix 2. Berlin questionnaire

Top of Form

1. Body Mass Index Information:
Height (in inches):
Weight (in pounds):

CATEGORY 1 QUESTIONS

2. Do you snore?
Yes **
No
I don't know

3. How loud is your snoring?
My snoring is as loud as breathing
My snoring is as loud as talking
My snoring is louder than talking **
My snoring is very loud **

4. How frequently do you snore?
Almost every day **
3-4 times per week **
1-2 times per week
1-2 times per month
Never or almost never

5. Does your snoring bother other people?
Yes **
No

6. How often have your breathing pauses been noticed?
Almost every day **
3-4 times per week **
1-2 times per week
1-2 times per month
Never or almost never

CATEGORY 2 QUESTIONS

7.Are you tired after sleeping?
Almost every day **
3-4 times per week **
1-2 times per week
1-2 times per month
Never or almost never

8. Are you tired during waketime?
Almost every day **
3-4 times per week **
1-2 times per week
1-2 times per month
Never or almost never

9. How often do you nod off or fall asleep while driving?
Almost every day **
3-4 times per week **
1-2 times per week
1-2 times per month
Never or almost never

CATEGORY 3 QUESTIONS

10. Do you have high blood pressure?
Yes **
No
I don't know

BMI (body mass index)
BMI > 30 **

Weight

BMI = ---------- X 703

Height X Height

Weight in pounds, height in inches OR Weight in kilograms, height in meters

Berlin Scoring Results

Any answer followed by double asterisks (**) is a positive response.
Category 1 is positive with 2 or more positive responses to questions 2 through 6
Category 2 is positive with 2 or more positive responses to questions 7 through 9
Category 3 is positive with 1 or more positive responses and/or a BMI>30
2 or more positive categories indicates a high likelihood of sleep apnea

Bottom of Form

Appendix 3. Anxiety rating scales

1. Background
    1. Authored by Max Hamilton in 1959
    2. Public domain anxiety rating scale
2. Symptom Rating Scale (0=Not Present, 4=Disabling)
    1. Anxious Mood
        1.1. Worries
        1.2. Anticipates worst
    2. Tension
        2.1.Startles
        2.2. Cries easily
        2.3. Restless
        2.4. Trembling
    3. Fears
        3.1. Fear of the dark
        3.2. Fear of strangers
        3.3. Fear of being alone
        3.4. Fear of animal
    4. Insomnia
        4.1. Difficulty falling asleep or staying asleep
        4.2. Difficulty with Nightmares
    5. Intellectual

- 5.1. Poor concentration
- 5.2. Memory Impairment

6. Depressed Mood
   - 6.1. Decreased interest in activities
   - 6.2. Anhedonia
   - 6.3. Insomnia
7. Somatic Complaints: Muscular
   - 7.1. Muscle aches or pains
   - 7.2. Bruxism
8. Somatic Complaints: Sensory
   - 8.1. Tinnitus
   - 8.2. Blurred vision
9. Cardiovascular Symptoms
   - 9.1. Tachycardia
   - 9.2. Palpitations
   - 9.3. Chest Pain
   - 9.4. Sensation of feeling faint
10. Respiratory Symptoms
    - 10.1. Chest pressure
    - 10.2. Choking sensation
    - 10.3. Shortness of Breath
11. Gastrointestinal symptoms
    - 11.1. Dysphagia
    - 11.2. Nausea or Vomiting
    - 11.3. Constipation
    - 11.4. Weight loss
    - 11.5. Abdominal fullness
12. Genitourinary symptoms
    - 12.1. Urinary frequency or urgency
    - 12.2. Dysmenorrhea
    - 12.3. Impotence
13. Autonomic Symptoms
    - 13.1. Dry Mouth
    - 13.2. Flushing

13.3. Pallor

13.4. Sweating

14. Behavior at Interview

14.1. Fidgets

14.2. Tremor

14.3. Paces

3. Interpretation

1. Above 14 symptoms are graded on scale

1.1. Not present: 0

1.2. Very severe symptoms: 4

2. Criteria

2.1. Mild Anxiety (minimum for Anxiolytic): 18

2.2. Moderate Anxiety: 25

2.3. Severe Anxiety: 30

4. Other Anxiety Scales

1. Zung Self Rating Scale for Anxiety

2. Beck Anxiety Scale

3. GAD-7

Appendix 4. Beck depression inventory

1. Background

1. Twenty-one question survey completed by patient

2. Answers scored on 0 to 3 scale

1.1. Minimal: 0

1.2. Severe: 3

2. Questions

1. Sadness

2. Hopelessness

3. Past failure

4. Anhedonia

5. Guilt

6. Punishment

7. Self-dislike

8. Self-blame
9. Suicidal thoughts
10. Crying
11. Agitation
12. Loss of interest in activities
13. Indecisiveness
14. Worthlessness
15. Loss of energy
16. Insomnia
17. Irritability
18. Decreased appetite
19. Diminished concentration
20. Fatigue
21. Lack of interest in sex

3. Interpretation
    1. Score <15: Mild Depression
    2. Score 15-30: Moderate Depression
    3. Score >30: Severe Depression

Resources: Beck Depression Inventory

1. General
    1.1. Intended for use by licensed professionals only
    1.2. Copyrighted by the Psychological Corporation
2. Available for purchase from Psychological Corporation
    2.1. http://www.psychcorp.com/

5. Reference
    1. Beck (1996) Beck Depression Inventory, Harcour

Appendix 5. Eleven principles of sleep hygiene

1. Wake up and go to bed at about the same time every night. Bedtime and wake-up time should not differ from working days to weekend nights by more than approximately an hour.

2. Avoid sleeping in on weekends to "catch up" on sleep. This makes it more likely that you will have problems falling asleep.

3. If you take naps, they should be short (no more than an hour) and scheduled in the early to midafternoon. However, if you have a problem with falling asleep at night, napping during the day may make it worse and should be avoided.
4. Spend time outside every day. Exposure to sunlight helps to keep your body's internal clock on track.
5. Exercise regularly. Exercise may help you fall asleep and sleep more deeply.
6. Use your bed for sleeping only. Don't study, read, listen to music, watch television, etc., on your bed.
7. Make the 30–60 minutes before a quiet or wind-down time. Relaxing, calm, enjoyable activities, such as reading a book or listening to calm music, help your body and mind slow down enough to let you get to sleep. Don't study, watch exciting/scary movies, exercise, or get involved in "energizing" activities just before bed.
8. Eat regular meals and don't go to bed hungry. A light snack before bed is a good idea; eating a full meal in the hour before bed is not.
9. Avoid eating or drinking products containing caffeine from dinner time on. These include caffeinated sodas, coffee, tea, and chocolate.
10. Do not use alcohol. Alcohol disrupts sleep and may cause you to awaken throughout the night.
11. Smoking disturbs sleep. Don't smoke at least one hour before bed (and preferably, not at all!).

Appendix 6. Six Bootzin's principles for stimulus control in the treatment of insomnia

1. Go to bed when sleepy.
2. Use the bed for sleeping; do not read, watch television or eat in bed.
3. If you are unable to fall asleep, get up and move to another room; stay up until you are really sleepy, then return to bed; if sleep still does not come easily, get out of bed again. The goal is to associate bed with falling asleep quickly.
4. Repeat step 3 as necessary throughout the night.
5. Set the alarm and get up at the same time every morning regardless of how much you slept through the night. This helps the body acquire a constant sleep-wake rhythm.
6. Do NOT nap during the day.

Appendix 7. Cognitve behavioral therapy for insomnia: weekly for 8-10 weeks:

Sleep hygiene-see above-appendix 5

Stimulus control-see above-appendix 6

Sleep restriction or curtailment

Relaxation, meditation, hypnosis

Reducing muscle tension and hyperarousal by biofeedback

Relapse prevention:

1. Don't compensate for sleep loss
2. Start stimulus control procedures immediately
3. Re-engage sleep restriction should the insomnia persist beyond a few days.

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Scientists hunt for ways to untangle damage of chronic traumatic encephalopathy

Mysteries of the Mind: CTE, Part 2

May 13, 2013 12:00 PM

By Mark Roth Pittsburgh Post-Gazette

Bennet Omalu was the first pathologist in the world to detect CTE in a former football player.

The year was 2002, and the player was former Steelers center Mike Webster, who had died of a heart attack at the age of 50.

Dr. Omalu was a young pathologist working for former Allegheny County Coroner Cyril H. Wecht. As a Nigerian native, he knew very little about American football, except that it was a brutal head-banging sport. Given the reports he had heard about Webster's erratic behavior before his death, he figured the autopsy might show visible evidence of brain damage.

"When I opened up his skull on autopsy, I expected his brain to be all shriveled and small, but lord God almighty, his brain looked normal," he recalled in an interview this year. "It actually confused me more. I thought that means I'm wrong."

Still, with the Webster family's permission, he had a lab prepare the brain for microscopic examination, and weeks later, in his Pittsburgh apartment, he finally looked at the slides. "I pulled out the first slide, and I was munching on an apple, and I thought 'They've made a mistake. This should be the brain of another person.' I looked again and I thought, 'Aha!' "

What he saw were smudges and tangles of tau deposits in the brain, similar to those that would be seen in Alzheimer's disease, but without the accompanying plaques of beta amyloid protein also seen in Alzheimer's. He later named the disorder chronic traumatic encephalopathy, which simply means a long-developing brain injury.

Around the same time, another pathologist, Ann McKee, was amazed at a brain she was examining in her lab outside Boston.

Dr. McKee, now co-director of the Center for Traumatic Encephalopathy at Boston University, had

already studied more than 1,500 brains of Alzheimer's patients, and she knew this one was different. "It was this extraordinary case, florid tauopathy of the likes I had never seen," she said, referring to the harmful form of the protein tau. The brain belonged to a former world-champion boxer, she recalled in an interview last year.

Telltale tangles

We all have tau in our brains. Normally, it makes up part of the skeleton of our brain cells. But in Alzheimer's disease, CTE and some other conditions, the tau becomes damaged and forms tangles and clumps. There is some evidence that this toxic form of the protein can then infect nearby cells, hastening its spread through the brain.

Researchers like Drs. Omalu and McKee knew that the tau they were seeing in CTE was not Alzheimer's because it was showing up in different parts of the brain and advancing with a different pattern.

In Webster's brain, Dr. Omalu said, there was no distorted tau in his hippocampus -- a seahorse-shaped structure lower in the brain that is critical for memory formation and is usually heavily damaged in Alzheimer's disease.

Dr. McKee, who has now examined scores of CTE brains, said the damaged tau shows up first in the frontal lobes of the brain, particularly in the sulci -- the deep valleys in the folds of the brain -- and spreads outward from there.

In a study published in the journal Brain late last year, Dr. McKee and her colleagues examined 85 brains of athletes, soldiers and others who had experienced repetitive brain injuries and found CTE in 80 percent of them.

Of the 35 who had played professional football, ranging in age from their 20s to their 90s, all but one had signs of CTE, and seven -- or 20 percent -- had died of suicide, gunshot wounds or overdoses.

Most of the former football players with CTE were in their 40s and older, although three were in their 20s and 30s.

The brains had been donated by families, many of them concerned by psychological changes they had seen in their loved ones, and were not

Mysteries of the Mind: About this series

- Over the course of this year, the Pittsburgh Post-Gazette is looking deeply at five brain disorders that affect millions of people: schizophrenia, athletes' brain injuries, autism, depression and phobias. In this second segment of the series, we examine a disorder that causes mood changes, dementia and may even trigger suicides in some former athletes and soldiers -- chronic traumatic encephalopathy, or CTE. It is the latest of our "Mysteries of the Mind."

Sunday's story: The tragedy of CTE: a brain disease that afflicts athletes

Coming Tuesday: Mike Webster's brain damage was the beginning of a saga that has

part of a randomized study.

"We try to get everybody. We have a very low threshold," she said. "But the fact is you're much more likely to donate if you're concerned."

led to a massive lawsuit against the National Football League.

Looking at CTE after someone has died, however, is less than ideal for understanding how it develops.

"Somebody once said that looking at these pathology endpoints is like walking through a cemetery and looking at the gravestones and trying to figure out what happened in a community," said D. Martin Watterson, a brain researcher at Northwestern University.

Developing new tests

Gary Small, a psychiatrist at the University of California at Los Angeles, hopes to change that with a new test that uses a radioactively tagged tracer to detect tau deposits in living brains.

In a February study of five former National Football League players and five control subjects, the positron emission tomography, or PET, scans showed that the former NFL players had higher levels of deposits in subsurface brain regions and the amygdala, an almond shaped structure that governs emotions like fear and anger.

The UCLA tracer attaches to both tau and beta amyloid proteins, which are found together in Alzheimer's disease, but Dr. Small said the pattern of deposits is different than in Alzheimer's.

The study is too small to draw definitive conclusions, but he hopes to study a much larger group as soon as he can arrange funding.

Even in his small sample, one player who showed significant levels of tau protein, former NFL quarterback Wayne Clark, was not experiencing the mood changes and thinking problems of the other retired players.

So why do some players who get repeated head injuries not develop CTE deposits, or why would others have the damaged protein but not experience symptoms?

One possibility is a genetic vulnerability to the disorder, say several researchers.

Robert Mahley, a scientist at the Gladstone Institutes, affiliated with the University of California at San Francisco, said one candidate is a gene for a certain type of cholesterol transporter, known as APOE4.

Research already has shown that people who inherit the APOE4 gene variant have a much higher risk of

getting Alzheimer's disease, he said, and that those with the variant who suffer a serious head injury have a twentyfold greater risk of getting Alzheimer's later. It's also a risk factor for multiple sclerosis, another neurological ailment.

Dr. Mahley suspects that former athletes who get CTE may have the same vulnerability, although more research is needed to prove that. In the Boston University autopsy studies, for instance, about 40 percent of the former professional football players had at least one version of the APOE4 gene.

Work in the Gladstone labs has shown a direct connection between APOE4 and the damaged tau that shows up in Alzheimer's and CTE. The APOE4 protein has one amino acid that is different than the typical version, out of a string of 299 amino acids. That single change causes the head and tail of the protein to curl toward each other, and the brain, recognizing that isn't normal, produces enzymes that clip off a piece of the protein's tail.

That stray piece can float through brain cells and cause damage, he said, changing tau into the distorted form that clumps together in the brain.

Blast effects

Soldiers who have suffered blast injuries also are vulnerable to CTE, scientists say.

Lee Goldstein, a psychiatrist at Boston University, has shown in experiments with mice that a single blast wave can create tau deposits in the brains of the animals that look just like those in CTE.

The wind that follows an explosion, Dr. Goldstein said, can reach 330 to 350 mph. These blasts end up "whipping the head around like a bobblehead." By analyzing the mice with high-speed photography, his team could show that "it causes shearing forces in the brain, just like if you were to take a bowl of Jell-O and rapidly twist it."

That shearing motion, acting on the spindly axons that carry signals in the brain, causes tau to fall off, "and it damages the surrounding blood vessels, which causes chronic inflammation, which we think leads to the tau around the blood vessels," he said.

In a more recent blast experiment at the University of Pittsburgh, rats whose heads were held still did not show the tau deposits. But even those animals showed subtle changes in gene expression in the brain that mimicked the pattern seen in Alzheimer's disease, said lead investigator Patrick Kochanek, director of Pitt's Safar Center for Resuscitation Research.

Dr. Goldstein said his group is the first one to show a direct mechanical cause of tau deposits in the brain, and he believes the blast effect is equivalent to several smaller blows that athletes would get playing

football, hockey or other contact sports.

While some might question how good a model mice are for human head injuries, another Boston researcher says they have distinct advantages.

William Meehan, a concussion expert and Harvard University pediatrics professor, said one of the arguments that skeptics have made about head injury complaints in football, hockey and other sports is that players may have abused steroids or growth hormones or might be making false complaints.

"But mice don't malinger, they don't take steroids, they're not on growth hormones," Dr. Meehan said, so experimental results aren't confounded by any of that.

His work with mice has shown that a series of mild concussions has profound effects on the rodents when they try to navigate a water maze afterward.

The maze is filled halfway with water and contains hidden platforms underneath, with markers to help the mice remember where the platform is. If the mice can swim to the platform, they are dried off and get a food reward.

The concussed rodents took much longer to find the platform than mice without head injuries. "Mice that sustained five concussions, even a year after the last injury, still had learning and memory problems," he said.

While Dr. Meehan doesn't study CTE directly, it makes sense to him that it could result from a series of milder head injuries.

"I think every single concussion leaves a lasting effect on the brain. But if someone gets one concussion in sport, you're going to recover so much it will not be noticeable," he said. "But if you accumulate them over and over and over again, that small amount will add up and start to have a cumulative effect."

Punch drunk syndrome

CTE was first detected in boxers in the late 1920s by New Jersey pathologist Harrison Martland, who noticed some boxers having balance, memory and speech problems.

He dubbed the condition "punch drunk syndrome."

Dr. Meehan noted that when Martland examined boxers for the syndrome, "he didn't see it in skilled boxers who outscore you with points and dodge your punches. He saw it in sluggers, who kind of wade in, and they don't tend to get a lot of concussions per se, because if you get concussions a lot in boxing, you

lose reaction speed and your career's over."

In a similar way, said Robert Cantu, a neurosurgeon at Boston University, the preliminary evidence suggests that the football players most susceptible to CTE may not be the ones who have spectacular high-speed collisions, but linemen and linebackers, "who on every play are banging their heads and may be experiencing subconcussive blows."

But Robert Harbaugh, chairman of neurosurgery at Penn State University and a member of the NFL's Head, Neck and Spine Committee, said head collisions by themselves may not be enough to cause CTE.

So far, he said, studies haven't shown a "dose-response curve," where players with the most head injuries are the most likely to get dementia. Clouding the issue is the fact that NFL players seem to be at higher risk for getting Alzheimer's disease, he said.

One area he thinks might be relevant to look at is sleep apnea, in which people stop breathing briefly during sleep, often several times a night. People who are heavier have a higher incidence of sleep apnea, and studies have shown it is a risk factor for getting Alzheimer's.

"NFL players tend to be large people, and I suspect there is an increase in sleep apnea" among them, which can raise blood pressure and lower brain oxygen levels, Dr. Harbaugh said.

How to treat it?

While there is no effective treatment for CTE, there are several experimental therapies that show promise.

In Boston, Dr. Meehan is working with Margaret Naeser of the VA Boston Healthcare System on shining red light through the skull as a method of healing brain injuries.

The research, which just received a grant from the American Medical Society for Sports Medicine, is based on studies of mice that received experimental concussions and showed improvement in their brain function after the light therapy.

Experiments are underway now at the Boston VA with soldiers who have had head injuries and at Boston Children's Hospital with children who have had persistent concussion symptoms. Doctors attach several LED clusters to their scalps, and the light shines through the skulls and penetrates about 1 centimeter into the brain.

Dr. Meehan believes the light helps stimulate the production of a vital energy source known as adenosine triphosphate, or ATP, which is needed to restore the chemical balance of brain cells after injury.

In Philadelphia, University of Pennsylvania professor John Trojanowski also has used mice to show that an experimental drug owned by Bristol-Myers Squibb halts the progression of tau degeneration in the rodents' brains and actually improves their thinking ability.

The treatments might hold out hope for both Alzheimer's disease patients and victims of CTE, he said.

"We have shown that preventing this loss of tau function will correct this functional loss and reverse [tau] tangle pathology," Dr. Trojanowski said. "And we're interested in working with others to see if this will be of benefit to football players or soldiers with blast injuries, as well as to develop a better understanding of traumatic brain injury."

In Chicago, University of Chicago neurosurgeon Julian Bailes has suggested that fish oil supplements might be able to lessen damage from brain injuries.

Doctors at nearby Northwestern University have identified an experimental treatment that reduces inflammation in the brain, which some researchers think is an underlying problem in many brain diseases.

Mr. Watterson, the Northwestern brain researcher, said that when the brain is injured, it produces substances called cytokines that create inflammation and can eventually damage the connections between neurons and even kill them. A substance known as MW151 was able to suppress the inflammation in mice subjected to head trauma.

Northwestern sold the rights to the drug to a commercial company for development, he said, but because developing new drugs for human use is so expensive and time-consuming, "companies are risk averse and the government is risk averse and so there is not much funding for this. But the public outcry over sports and military head injuries may increase funding."

Even if treatments are not available for years, though, Boston University's Dr. McKee said she thinks there would be tremendous value in having an effective brain imaging method to pick up signs of CTE early on.

At least that way, she said, athletes could make decisions about whether to keep playing. "If it were me," she said, "I would not go back and play in the NFL if I had those little deposits in my brain."

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SPECT neuroimaging useful for traumatic brain injury: literature review

WEDNESDAY MAR 26, 2014 | REUTERS

Last Updated: 2014-03-26 15:27:03 -0400 (Reuters Health)

By Megan Brooks

NEW YORK (Reuters Health) - Single-photon emission tomography (SPECT) should be part of the clinical workup of patients with traumatic brain injury (TBI), conclude the authors of a comprehensive review of the literature on SPECT neuroimaging in TBI.

There is a "considerable body of literature" establishing a relationship between SPECT and improved lesion detection in TBI (compared to structural CT and MRI), neuropsychological and neurological outcomes, and treatment responses, the reviewers reported in PLoS One online March 19.

"Structural CT and MRI are excellent for identifying acute structural damage to the brain, but functional neuroimaging methods such as SPECT can provide dynamic information about the brain," first author Dr. Cyrus Raji, from the Department of Radiology, UCLA Medical Center in Los Angeles, California, noted in an interview with Reuters Health.

"A rigorous review of 30 years of peer reviewed literature showed that SPECT neuroimaging can reveal functional deficits that can be missed by conventional structural imaging modalities or demonstrate larger brain areas of abnormality compared to structural lesions that are found," he added.

The diagnosis of TBI, particularly mild TBI, remains a clinical challenge. Dr. Raji and colleagues found 1600 articles on SPECT for TBI and included 71 in their review (19 longitudinal studies and 52 cross-sectional studies).

They focused their main analysis on the 19 longitudinal studies (including five intervention studies) involving a total of 903 patients.

Ten studies included comparison modalities to SPECT (structural CT or MRI or both). In all 10, SPECT identified abnormalities not seen on MRI and CT.

Fourteen of the 19 longitudinal studies (77%) had neurological or neuropsychological outcomes and SPECT abnormalities correlated with these outcomes in 13 (93%).

"Specifically, SPECT perfusion changes were statistically significant in their association with neuropsychological or neurological tests," the researchers report. "This included two out of five intervention trials (40%) correlating SPECT perfusion changes with improved neuropsychological or neurological outcomes."

These findings, they say, highlight the "utility of cerebral blood flow on SPECT as a potential biomarker for surrogate endpoints in assessing the effectiveness of new treatments."

Three longitudinal studies examined specific metrics of diagnostic predictive value. One used SPECT to prospectively evaluate 25 patients with mild and 42 with moderate TBI. Each patient had a clinical evaluation and a SPECT scan within four weeks of the initial injury and three months after the first scan.

Among the 33 patients who showed no significant abnormalities on their initial SPECT scan, clinical symptoms resolved within three months in 97%. By contrast, of the 34 patients who had abnormalities on their first SPECT scan, 59% of the patients continued to experience significant clinical symptoms.

The positive predictive value of an abnormal initial scan was only 59% (20 of 34), but if the second scan three months later was also abnormal the sensitivity for the repeat SPECT rose to 95% (19 of 20), the researchers say.

The data also suggest that a negative initial SPECT scan can be a reliable predictor of a favorable clinical outcome. "A negative SPECT scan after TBI is reassuring in showing that that person probably doesn't have permanent neurological damage," Dr. Raji told Reuters Health.

The 52 cross sectional studies, which includes a combined sample of 2,121 persons with TBI, "support the clinical utility of SPECT suggested by longitudinal studies," the researchers report.

They conclude, "The current state of the literature demonstrates both associative and predictive value of SPECT in the setting of TBI. This same literature also demonstrates certain advantages of SPECT compared to structural MRI and CT in multiple studies, particularly in mild TBI. SPECT can therefore be used to provide actionable information in the identification and management of TBI."

SPECT is "reasonably cost-effective and available in outpatient setting," Dr. Raji commented. A SPECT scan costs roughly $1100, MRI ranges between $800 to $1200 and CT costs about $400 to $600 but is the least sensitive for chronic mild TBI, he noted. "Even in the acute setting it's been estimated that a non-contrast head CT scan in the ER will only show up as positive about 10% of the time. SPECT is a good compromise in providing useful functional information at an affordable cost," he said.

"Non-contrast head CT is great in the acute trauma setting, but for chronic repetitive concussions that athletes get, or blast injury that veterans sustain, or sheer force rotational injury, SPECT scans can show larger functional deficits that may be missed on structural imaging," Dr. Raji said.

"With a SPECT scan, you'd be more likely to see abnormalities in brain blood flow and metabolism. That's the big message we are getting out of the review of the literature over the last 30 years - that the SPECT scan can show these abnormalities that can be useful in the assessment and treatment of traumatic brain injury," Dr. Raji said.

Four of the authors have financial interests in entities that provide SPECT services. All of the authors are members of the International Society of Applied Neuroimaging (ISAN), a volunteer organization devoted to the understanding and appropriate clinical use of SPECT brain imaging.

SOURCE: http://bit.ly/1j3cu3Q (http://bit.ly/1j3cu3Q)

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National Trial Lawyers Select Controversial Fort Walton Beach Criminal Defense Lawyer

Florida Criminal Defense Lawyer Routinely Uses Brain Imaging Based Mental Health Evaluations to Eliminate Future Crimes with Effective Treatment and Accountability.

FOR IMMEDIATE RELEASE

PRLog (Press Release) - ***Apr. 22, 2013 - FORT WALTON BEACH, Fla. --*** Each year, the National Trial Lawyers, an exclusive, invitation- only organization, selects the nation's Top 100 Lawyers. This year, Fort Walton Beach criminal defense attorney Stephen G. Cobb, is a controversial selection.

A Florida-based criminal defense attorney, Cobb is certified by the Florida Bar as an expert in criminal law. However, his claim that crime is a medical problem, rather than a moral failure, has been both criticized and praised. Neuroscience research and brain imaging are the foundation of his claim.

1 2 3 4

Florida criminal defense attorney Stephen G. Cobb uses brain imaging routinely.

“Top 100? That's quite flattering. I'm happier when someone stops getting arrested for DUI or domestic violence,” he said, on the steps of the courthouse in south Okaloosa County.

Cobb is passionate about the use of neuroscience and brain imaging in criminal law. Since 2006, he has advocated the elimination of what he calls “blame and punishment based” sentencing laws in favor of a treatment based, long term solution.

University of Pennsylvania professor of law and psychiatry, Stephen J. Morse, takes the opposing view. Professor Morse claims neuroscience research and imaging techniques have no forensic value. In the November 2012 issue of the *Journal of the American Bar Association,* he bluntly stated that, “Neuroscience has added virtually nothing really relevant to criminal law.” Morse is a member of the MacArthur Foundation Research Network on Law and Neuroscience.

“Ridiculous," Cobb counters."If a doctor wanted to repair a broken bone without an x-ray, you would find another doctor. Brain imaging is an important tool in the diagnostic tool box.”

Morse reasons that people, not brains, commit crimes. Cobb bluntly dismisses such criticism as irresponsible since the brain is the organ which controls human behavior.

All criminal defense lawyers use mental health examinations, but Cobb's criminal defense law firm has used SPECT (Single Photon Emission Computed Tomography) brain imaging as part of the diagnostic protocol since 2006.

“SPECT shocked me,” Cobb admits, “Not a single healthy, normal range, patient-defendant brain image in over seven years. Not one.”

Cobb states “only three things are needed to break the pattern of criminal behavior:” an accurate patient-defendant diagnosis, customized treatment plans and patient-defendant accountability. “Government sponsored treatment programs have high failure rates, because they skimp on the diagnostics and use a one-size-fits-all approach,” he argues, “Better psychological testing and brain imaging should be routine.”

The prestigious invitation from the National Trial Lawyers' Organization means the legal community has definitely taken notice, and that the foundation of criminal law is undergoing rapid change.
http://youtu.be/aBbYX2RIwco

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SCIENTIFIC INVESTIGATIONS

Prevalence and Consequences of Sleep Disorders in Traumatic Brain Injury

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Study Objectives: Determine prevalence and consequences of sleepiness and sleep disorders after traumatic brain injury (TBI).

Methods: Prospective evaluation with polysomnography (PSG), multiple sleep latency test (MSLT), Epworth Sleepiness Scale (ESS) and neuropsychological testing including Psychomotor Vigilance Test (PVT), Profile of Mood States (POMS), and Functional Outcome of Sleep Questionnaire (FOSQ).

Setting: Three academic medical centers with level I trauma centers, accredited sleep disorders centers, and rehabilitative medicine programs.

Participants: Eighty-seven (87) adults at least 3 months post TBI.

Measurements And Results: Abnormal sleep studies were found in 40 subjects (46%), including 20 (23%) with obstructive sleep apnea (OSA), 10 (11%) with posttraumatic hypersomnia (PTH), 5 (6%) with narcolepsy, and 6 (7%) with periodic limb movements in sleep (PLMS). Among all subjects, 22 (25%) were found to have objective excessive daytime sleepiness with MSLT score <10 minutes. There was no correlation between ESS score and MSLT (r = 0.10). There were no differences in age, race, sex, or education between the sleepy and non-sleepy subjects. Likewise, there were no differences in severity of injury or time after injury between sleepy and non-sleepy subjects. Sleepy subjects had a greater body mass index (BMI) than those who were not sleepy (p = 0.01). OSA was more common in obese subjects (BMI ≥30, p <0.001). Sleepy subjects demonstrated poorer PVT scores (p <0.05), better self-reported sleep related quality of life (FOSQ scores [p <0.05]), and no differences in POMS.

Conclusions: There is a high prevalence of sleep disorders (46%) and of excessive daytime sleepiness (25%) in subjects with TBI. Sleepy subjects may be more impaired than comparable non-sleepy TBI subjects, yet be unaware of problems. Given the high prevalence of OSA (23%), PTH (11%), and narcolepsy (7%) in this population, there is a clinical indication for NPSG and MSLT.

Keywords: Trauma, brain injury, hypersomnia, sleep apnea, narcolepsy, sleep disorders.

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INTRODUCTION

The increased incidence of sleep disorders after traumatic brain injury (TBI) relative to the general population has become increasingly well recognized.[1-6] Traffic accidents are a common cause of TBI, and there is good evidence that the presence of some sleep disorders is associated with traffic accidents.[7-9] Cognitive dysfunction is a common and well-researched deficit after TBI and is a key factor preventing return to independent living, social re-adaptation, and vocational pursuits.[10-13] Obstructive sleep apnea (OSA) and narcolepsy are associated with some degree of cognitive dysfunction.[14-17] However, there is no literature on cognitive dysfunction in posttraumatic hypersomnia (PTH) or periodic limb movements in sleep (PLMS). The literature is sparse on the relationship of cognitive dysfunction to hypersomnolence in TBI.

The purpose of this study was to: 1) examine the prevalence of sleep disorders in a prospectively sampled group of subjects with TBI; 2) explore the relationship between the presence of sleep disorders, injury characteristics, and subject variables; 3) evaluate the impact of sleep disorders on cognitive functioning, mood state, and quality of life after TBI.

METHODS

Subjects

Subjects over 18 years old who were at least 3 months post TBI were prospectively recruited from rehabilitative services at 3 academic medical centers: Memorial Hermann Hospital (Houston, TX), Transitional Learning Center (Galveston, TX) and Philadelphia Veterans Administration Medical Center (Philadelphia, PA). The study was approved by the Committee for the Protection of Human Subjects/Institutional Review Board of all participating institutions. Each subject underwent a history and physical

Disclosure Statement

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examination, and review of medical records. Exclusion criteria were: 1) presence of circadian rhythm disorder, 2) inability to give informed consent, and 3) use of sedating medications. Each consented subject was scheduled to undergo nocturnal and daytime sleep studies along with neuropsychological testing.

TBI severity was classified by considering both emergency room Glasgow Coma Scale (GCS) and CT scan findings according to traditional criteria.[14] A subject was classified as having a severe injury if his or her GCS score was less than 9 irrespective of CT scan findings. A subject was classified as having had a moderate injury with a GCS of 9-12 irrespective of CT findings, or with a GCS of 13-15 and a positive CT scan.[18,19] A subject was classified as having a moderate/severe injury with a positive CT scan but without available GCS data to make a finer characterization. A subject was classified as having a mild traumatic brain injury with a GCS score of 13-15 and a negative CT scan.

Sleep Studies

An Epworth Sleepiness Scale (ESS) questionnaire[20] was completed by each subject on the night of polysomnography. Nocturnal polysomnograms (NPSG) were performed at least 3 months post injury in sleep laboratories in each center. Using standard techniques,[21,22] a computer data acquisition and analysis system recorded the following signals: electroencephalogram (C_3A_2, C_4A_1, O_1A_2, and O_2A_1), bilateral electroculogram, electrocardiogram, submental and bilateral anterior tibialis electromylogram, thoracic and abdominal excursion by piezocrystals, oral and nasal airflow by thermistor and breath sounds, body position, and oxygen saturation by pulse oximeter. Throughout the studies, subjects were monitored with an infrared video camera and a one-way intercom which connects the bedroom with the monitoring room. All studies were attended by polysomnographic technologists who also scored the studies using 30-second epochs with the Rechtschaffen and Kales criteria,[23] and each study was interpreted by a physician certified by the American Board of Sleep Medicine.

During the day subsequent to the sleep study, a multiple sleep latency test (MSLT) was used to assess objective physiologic sleepiness. The test was performed using standard techniques, and sleep onset was defined as the first epoch with any stage of sleep for >50% of the 30-second epoch.[24] Each subject took 5 naps of 20 minutes duration at 2-hour intervals. The following signals were recorded during the naps: EEG (C_3A_2, C_4A_1, O_1A_2, and O_2A_1), bilateral electrooculograms, submental electromylogram, and electrocardiogram. The average sleep latency over these 5 naps was the **MSLT score**. Those with an MSLT score <10 minutes were termed **sleepy** and those with an MSLT score ≥10 minutes were **non-sleepy**. A urine sample was collected after the NPSG and during the MSLT with analysis for possible opiates, benzodiazepines, cannabinoids, amphetamines, or adrenergic drugs.

Respiratory events were scored as previously described.[5] **Obstructive apnea** was defined by cessation of breathing ≥10 seconds with ≥4% fall in oxygen saturation and/or EEG arousal accompanied by continuous respiratory effort. **Central apnea** was defined by a cessation of breathing ≥10 seconds with ≥4% fall in oxygen saturation and/or EEG arousal without respiratory effort. **Hypopnea** was defined as >50% reduction in airflow for ≥10 seconds accompanied by ≥4% fall in oxygen saturation and/or EEG arousal. The diagnosis of **obstructive sleep apnea (OSA)** was made with ≥ 5 apneas/hour of sleep and/or ≥ 10 apneas+hypopneas/hour of sleep. **Narcolepsy** was defined as an MSLT score (average sleep latency) <5 minutes with ≥2 sleep onset REM periods (SOREMPs) after an unremarkable NPSG with adequate total sleep and REM sleep and negative urine drug screen. **Posttraumatic hypersomnia (PTH)** was defined as an MSLT score ≤10 minutes with <2 SOREMPs after an unremarkable NPSG and no history of hypersomnolence prior to TBI. **Periodic limb movements in sleep (PLMS)** were defined as >5 periodic limb movements (PLMs)/hour of sleep and PLMs were scored according to standard criteria.[25,26]

Neuropsychological Evaluation

Each subject underwent a brief neuropsychological evaluation and completed several self report measures. All subjects were evaluated on 2 occasions. To control for diurnal variations, all evaluations took place beginning at 10:30 between the second and third MSLT nap. The measures used are described below.

Psychomotor Vigilance Test (PVT)

Sustained attention was evaluated with the Psychomotor Vigilance Test (PVT). The PVT was chosen because it is sensitive to the effects of sleepiness on cognitive functioning as well as cognitive problems associated with OSA and its treatment.[27-29] The PVT is administered via a small hand-held computerized device with a 3-digit millisecond LED counter and display window (PVT-192: Ambulatory Monitoring Inc, Ardsley, NY). During the PVT, subjects are presented with a 10-minute trial in which they press a response button as soon as a number counting up from 0 is seen. Once the response button is pressed, the counter stops and feedback is given on their reaction time. The amount of time between stimulus presentations varies between minimum and maximum interstimulus intervals of 2000 and 10,000 ms. Performances are recorded in the PVT device and downloaded into a database after the testing bout.

For the purposes of this study, the average of the fastest 10% of reaction times, the average of the slowest 10% reaction times, and the number of lapses (reaction times ≥ 500 ms) from the Psychomotor Vigilance Test (PVT) were selected for analysis. These variable were selected because they have been shown in prior research to be sensitive to sustained attention under conditions of sleep deprivation and in sleep disorders.[27-29] Normally, the PVT is given in several testing bouts across time. Owing to the time constraints involved in this study, each subject was exposed to the PVT once.

Profile of Mood States (POMS)

The Profile Of Mood States (POMS)[31] is a self-report measure in which subjects rate themselves on each of 65 adjectives using a 1-5 scale. These 65 responses yield 6 mood state scales: Anger-Hostility; Vigor-Activity, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, and Confusion-Bewilderment. This measure enjoys wide use in sleep research and has been shown to be sensitive to mood problems related to sleep disorders.[31,32]

Functional Outcome of Sleep Questionnaire (FOSQ)

The Functional Outcome of Sleep Questionnaire (FOSQ) is a self-report measure designed to assess the impact of sleep disor-

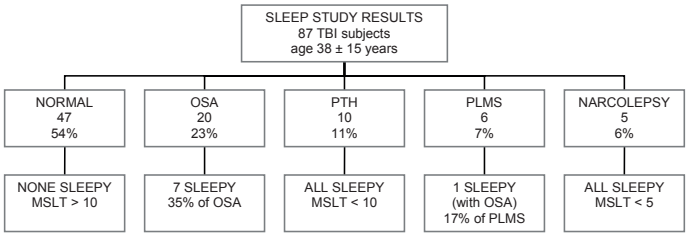

Figure 1—Study subjects by diagnosis and sleepiness status

ders on daily functioning.[33] It has enjoyed use in sleep research and appears to be sensitive to treatment-related change.[34-36] There are 30 items which are divided into 5 scales: Activity, Vigilance, General Productivity, Social Outcome, and Intimacy and Sexual Relationships. These scales are summed to make a total score. Higher scores on the FOSQ indicate better daily functioning. The total score was used for this analysis.

Statistical Analysis

Comparability of demographic and baseline characteristics were summarized by subgroups using means and standard deviations (quantitative data) or frequency of counts (qualitative/categorical data).

Parametric *t* tests for independent samples were used to evaluate group differences when distributions were normal. Because many of the distributions were not normal, nonparametric statistical techniques were employed in the majority of group comparisons. Categorical data was analyzed using chi square tests. Where small cell sizes precluded the use of chi square, Fisher's exact test was employed. For nonparametric independent between group comparisons, the data were subjected to Mann-Whitney U.

RESULTS

There were a total of 87 TBI subjects who underwent sleep studies. The distributions of demographic and severity variables are listed in Table 1. Note that there were 31 subjects who had insufficient clinical data upon which to make severity determinations. Polysomnographic data from these studies are in Table 2. Forty-seven subjects (54%) had a normal NPSG and MSLT. Twenty (23%) were diagnosed with obstructive sleep apnea (OSA), 10 subjects (11%) were diagnosed with posttraumatic hypersomnia (PTH), 5 (6%) were diagnosed with periodic limb movements in sleep (PLMS), and 5 (6%) were diagnosed with narcolepsy. One subject was diagnosed with both OSA and PLMS. For the purpose of group comparisons, this subject was grouped with the OSA subjects, since this was her primary diagnosis. These distributions are depicted in Table 1 and Figure 1. Those diagnosed with OSA had a mean apnea-hypopnea index (AHI) of 26.1 ± 19. Those diagnosed with PLMS had a mean PLM index of 17 ± 7 and a mean PLM-arousal index of 3.9 ± 4.4. Of these PLMS subjects, only one was sleepy (Epworth score of 15 and MSLT score of 5 minutes), and she also had OSA, with an AHI of 13. Although she had 31 PLM-arousals/hour, many of these may have been respiratory-related arousals. The remaining 5 PLMS subjects were asymptomatic, objectively not sleepy, and would not have met criteria for PLMD.

There were 24 females (28%) and 63 males (72%) in the total sample. The racial make up of the sample is included in Table 1. The average age of the entire sample was 38.3 (± SD 15.1) years.

Table 1—Demographic Data for the Sleepy and Non-sleepy TBI Subjects and the Total Sample.

	MSLT > 10 N (%)	MSLT < 10 N (%)	TOTAL SAMPLE N (%)
N	65(74)	22(25)	87
Sex			
Male	47(72)	16(73)	63(72)
Female	18(28)	6(27)	24(28)
Race			
Caucasian	47(72)	14(64)	61(70)
African American	9(14)	4(18)	13(15)
Hispanic	9(14)	3(14)	12(14)
Asian/Pacific Islander	0(0)	1(4)	1(1)
Diagnosis			
Normal	47(72)	0	47(54)
OSA	13(20)	7(32)	20(23)
PTH	0(0)	10(46)	10(11)
PLMS	5(8)	1(8)[a]	6(7)
Narcolepsy	0	5(23)	5(6)
Cause of Injury			
Auto/Vehicle	49(75)	15(68)	64(74)
Fall	7(11)	1(4)	8(9)
Assault	4(6)	2(9)	6(7)
Hit by Falling Object	4(6)	2(9)	6(7)
Construction	1(2)	2(9)	3(3)
CT Scan Findings			
Positive	35(54)	11(50)	46(53)
Not Available	23(35)	9(41)	32(37)
Negative	7(11)	2(9)	9(10)
Brain Injury Severity			
Unknown	22(34)	9(41)	31(36)
Mild	5(8)	2(9)	7(8)
Moderate	13(20)	2(9)	15(17)
Moderate/Severe	5(8)	0	5(6)
Severe	20(31)	9(41)	29(33)
Months Post Injury			
3	10(16)	3(14)	13(15)
4-6	11(17)	1(5)	12(14)
7-12	12(18)	3(14)	15(17)
13-24	8(12)	4(18)	12(14)
25-36	2(3)	1(4)	3(3)
>36	22(34)	10(45)	32(37)

[a]PLMS + OSA

The average education for the sample was 12.7 (± 2.2) years. The average time post injury was 64.3 (± 117.7) months.

Subgroup Analysis by MSLT

When objective sleepiness was measured by MSLT, 10 (11%) had MSLT scores <5 minutes, and 12 (14%) had MSLT scores 5-10 minutes. The subjects were divided into 2 groups based on the results of their initial MSLT. Those subjects with an MSLT score ≥10 minutes were classified as ***not sleepy***. Those with an MSLT score <10 minutes were classified as ***sleepy***. These included all of the narcolepsy and PTH subjects, along with 7 (35%) of the 20 OSA subjects. As noted above, the subject with both OSA and PLMS was in the sleepy group. The descriptive data for these two groups are depicted in Tables 1 and 3 and Figure 1.

There were 22 sleepy subjects and 65 non-sleepy subjects. There were no significant differences ($p > 0.05$) between the 2 groups in terms of age, education, GCS scores, or Epworth

Table 2—Sleep Study Data for the Baseline Studies.

	Normal		OSA[a]		PTH		PLMS[a]		NARCOLEPSY	
	M	SD	M	SD	M	SD	M	SD	M	SD
Total Sleep (h)	5.87	1.41	5.56	1.40	6.77	.96	5.53	1.55	6.42	1.37
Sleep Efficiency	76.07	15.05	69.27	18.56	83.40	9.49	70.42	16.96	86.00	9.00
Sleep Latency	36.25	37.98	47.16	102.80	11.51	25.01	37.10	43.77	17.80	18.57
Percent Stage 1	8.39	6.15	17.84	13.38	11.85	6.12	9.22	2.57	9.40	5.37
Percent Stage 2	68.13	13.11	62.03	14.23	58.46	15.84	71.08	11.60	68.74	16.18
Percent Stage 3 & 4	6.38	9.38	3.66	7.45	11.21	15.22	6.22	7.33	9.24	9.29
Percent REM	16.10	7.35	17.26	9.98	16.81	8.23	13.28	8.80	16.80	2.86
REM Latency	128.28	92.97	141.55	112.19	130.90	64.06	135.63	31.90	62.80	54.04
Total Arousal Index	13.06	8.98	31.63	19.67	12.83	7.67	23.84	12.54	11.24	4.67
MSLT	14.78	2.97	10.86	5.30	5.18	2.38	14.16	3.76	3.44	0.88
PLM Index	2.54	7.94	7.21	14.50	0.80	1.62	16.64	6.62	1.60	3.58
Apnea-Hypopnea Index	2.21	3.80	26.11	19.05	1.77	2.66	1.26	1.48	1.00	1.22

[a]For the purpose of this analysis, the subject with both OSA and PLMS was placed in the OSA group.

scores. There were equivalent numbers of males and females in each group χ^2 *(N* = 87) = 0.01, p >0.05. Race, (Fisher's exact p = 0.40), cause of injury (Fisher's exact p = 0.36), positive CT scan findings (Fisher's exact p = 1.00), and injury severity (Fisher's exact p >0.53), frequencies were similar between the groups. The frequencies of different sleep diagnoses were different between the groups largely due to the fact that the normal subjects were not sleepy (Fisher's exact p <0.01). The time post injury was classified as 3 months, 4-6 months, 7-12 months, 13-24 months, 25-36 months, and greater than 36 months, and the distributions of subjects in each group were compared. Fisher's exact test disclosed no significant difference between the groups (p = 0.64). There was a significant difference between the groups on body mass index (BMI), with the sleepy subjects being heavier (p = 0.01). These distributions are depicted in Table 3.

We next evaluated the relationship between sleepiness, cognitive functioning, mood state, and quality of life. The Functional Outcome of Sleep Questionnaire (FOSQ) total score, the 6 scales from the Profile of Mood States (POMS), the average of the fastest 10% of reaction times, the average of the slowest 10% reaction times, and the number of lapses (reaction times ≥ 500 ms) from the Psychomotor Vigilance Test (PVT) were selected for this analysis. The distributions are depicted in Table 3. Note that there were missing data from some of these neuropsychological tests. PVT analysis was based on 60 non-sleepy subjects and 20 sleepy subjects. The results of these group comparisons disclosed: 1) that the sleepy subjects' fastest reaction times were significantly slower than the non-sleepy subjects (p <0.05); 2) that the sleepy subjects made more lapses (p < 0.05) than the non- sleepy group; 3) that there was a trend toward the sleepy subjects having a slower average slow reaction times (p = 0.05).

The POMS analysis was based on 59 non-sleepy subjects and 23 sleepy subjects and disclosed no significant differences between sleepy and non-sleepy subjects. The FOSQ analysis was based on 48 non-sleepy subjects and 16 sleepy subjects. The sleepy subjects reported significantly higher FOSQ scores than did the non-sleepy group (p <0.05), indicating better self-rated quality of life in the sleepy subjects.

Table 3—Demographic and Performance Data for the Sleepy and Non-sleepy TBI Subjects.

	MSLT > 10		MSLT < 10		
	M	SD	M	SD	p
Age (y)	38.03	15.43	39.23	14.46	0.88[d]
Education (y)	12.74	2.29	12.68	2.10	0.59[e]
Months Post Injury	56.32	100.84	87.73	155.98	0.32[e]
GCS	8.63	4.84	6.69	4.42	0.15[e]
Epworth Sleepiness Scale	8.28	5.31	8.91	5.00	0.94[d]
MSLT	14.57	3.12	4.76	2.06	< 0.01[d]
BMI	26.46	4.29	31.02	8.10	0.01[d]
PVT Number of Lapses[a]	6.55	11.14	10.45	14.64	0.04[5]
PVT Fastest 10% RT[a,f]	221.90	45.61	197.43	262.29	0.03[e]
PVT Slowest 10% RT[a,f]	881.06	1576.76	1515.76	2491.62	0.07[e]
POMS Fatigue[b]	9.35	7.24	8.86	6.62	0.54[e]
POMS Confusion[b]	9.25	5.54	8.68	7.31	0.74[d]
POMS Tension[b]	10.82	7.29	8.55	7.77	0.12[d]
POMS Vigor[b]	12.18	6.35	15.59	7.46	0.07[d]
POMS Depression[b]	12.20	12.16	13.09	15.12	0.72[e]
POMS Anger[b]	9.22	10.66	10.95	12.76	0.94[e]
FOSQ Total Score[c]	9.08	6.47	14.35	6.44	0.01[e]

[a] N= 79 (Not Sleepy=59 and Sleepy = 20). [b] N= 82 (Not Sleepy=59 and Sleepy = 23). [c] N= 64 (Not Sleepy=48 and Sleepy = 16). [d] Analyses conducted using the parametric t tests. [e] Analyses conducted using the nonparametric Mann-Whitney U. [f]Reaction Times (RT) in milliseconds

Table 4—Demographic Data for the Sleep-disordered and Non-sleep-disordered TBI Subjects.

	Non-Sleep-Disordered N (%)	Sleep-Disordered N (%)
N	**47**	**40**
Sex		
Male	32(68)	31(78)
Female	15(32)	9(22)
Race		
Caucasian	34(72)	27(67)
African American	7(15)	6(15)
Hispanic	6(13)	6(15)
Asian/Pacific Islander	0(0)	1(2)
Diagnosis		
Normal	47 (100)	0(0)
Narcolepsy	n/a	5(13)
OSA	n/a	20(50)
PLMS	n/a	5(13)
PTH	n/a	10(25)
Cause of Injury		
Assault	3(6)	3(8)
Auto/Vehicle	38(81)	26(65)
Construction	1(2)	2(5)
Fall	4(9)	4(10)
Hit by Falling Object	1(2)	5(12)
CT Scan Findings		
Not Available	15(32)	17(42)
Negative	6(15)	2(5)
Positive	25(53)	21(53)
Brain Injury Severity		
Unknown	14(30)	17(42)
Mild	5(11)	2 (5)
Moderate	9(19)	6(15)
Moderate/Severe	4(8)	1 (3)
Severe	15(32)	14(35)
Months Post Injury		
3	8(17)	5(12)
4-6	9(19)	3(7)
7-12	8(17)	7(18)
13-24	6(13)	6(15)
25-36	1(2)	2(5)
>36	15(32)	17(43)

Relation Between Sleepiness and Diagnosed Sleep Disorders

All of the PTH and narcolepsy subjects were objectively sleepy by definition. Of the 20 OSA subjects, 7 (35%) had MSLT scores <10 minutes and there was no significant correlation between apnea-hypopnea index (AHI) and MSLT score ($r = -0.18$, $p > 0.05$). Only one of the PLMS subjects had an MSLT <10 minutes. However, this subject was found to have both OSA and PLMS. There was no significant correlation between PLM index and MSLT score ($r = 0.11$, $p > 0.05$).

Data Analysis by Diagnosis

In this analysis TBI subjects who were diagnosed with sleep disorders were compared to non-sleep-disordered subjects on the same variables described in the prior analyses. The descriptive data for these 2 groups are depicted in tables 4 and 5. There were 40 sleep-disordered subjects and 47 non-sleep-disordered subjects. There were no significant differences ($p > 0.05$) between the 2 groups in terms of education or GCS scores. However, the sleep-disordered subjects were significantly older than their non-sleep-disordered peers (43 .5 ± 13 vs 34.3 ± 14.8 years, $p = 0.01$). There were equivalent numbers of males and females in each group χ^2 ($N = 87$) = 0.96, $p > 0.05$. Race, (Fisher's exact $p = 0.86$), cause of injury (Fisher's exact $p = 0.33$), positive CT scan findings (Fisher's exact $p = 0.28$), and injury severity (Fisher's exact $p = 0.53$) frequencies were similar between the groups. The time post injury data was classified as 3, 4-6, 7-12, 13-24, 25-36 and greater than 36 months, and the distributions of subjects in each group were compared. Fisher's exact test disclosed no significant difference between the groups ($p = 0.62$). There was a significant difference between the groups on body mass index (BMI), with the sleep disordered subjects being heavier (29.2 ± 7 vs 26.3 ± 4.1 kg/m^2, $p < 0.05$).

The 2 groups were compared on the same measures as in previous analyses. The distributions are depicted in Table 5. Note that there was incomplete data for some of these analyses. The PVT data analysis was based on 44 non-sleep-disordered subjects and 36 sleep-disordered subjects. The results of these group comparisons disclosed: 1) that the sleep-disordered subjects' fastest reaction times were significantly slower than the non-sleep-disordered subjects ($p < 0.05$); 2) that the sleep-disordered subjects demonstrated significantly slower slow reaction times ($p < 0.05$); and 3) that the sleep-disordered subjects made more lapses ($p < 0.05$) than the non-sleep-disordered group.

The POMS analysis was based on 43 non-sleep-disordered subjects and 39 sleep-disordered subjects. POMS scores did not differ significantly between the groups. The FOSQ analysis was based on 36 non-sleep-disordered subjects and 28 sleep-disordered subjects. There was a trend toward the sleep disordered subjects reporting significantly higher FOSQ scores than the non-sleep-disordered subjects ($p = 0.08$). In order to determine if there was an association between self-reported sleepiness and objectively verified sleepiness, a bivariate correlation was calculated between the MSLT and Epworth Sleepiness Scale (ESS) using all of the subjects with complete data. The resulting correlation was not significant $r(80) = 0.10$, $p > 0.05$.

DISCUSSION

In the present study, we evaluated the presence and impact of sleep disorders in a cohort of prospectively recruited TBI subjects. Forty-seven percent of our sample was found to have a sleep disorder: OSA (23%), PTH (11%), narcolepsy (6%), or PLMS (7%). Twenty-six percent of the sample had EDS as measured by the MSLT score <10. Injury severity, the presence of a positive CT scan, and GCS scores were not associated with the presence of EDS. Subjects with an MSLT <10 objectively demonstrated more problems with vigilance but actually reported better sleep-related quality of life than non-sleepy subjects. There were no significant differences in self-reported mood state between the 2 groups. Comparisons of sleep-disordered versus non-sleep-disordered subjects disclosed no relationship between the presence of a sleep disorder and injury severity, cause of injury, or the presence of positive CT scan findings. Sleep-disordered subjects were more likely to have a higher BMI and demonstrated difficulties with psychomotor vigilance; they showed no differences in mood state and showed a trend toward better self-reported sleep related quality of life.

Table 5—Demographic and Performance Data

	Non-Sleep-Disordered		Sleep-Disordered		
	M	SD	M	SD	p
Age (y)	34.32	13.40	43.05	15.80	0.01[c]
Education (y)	12.53	1.79	12.95	2.67	0.39[d]
Months Post Injury	45.47	81.41	87.56	146.79	0.09[d]
GCS	8.66	4.89	7.45	4.64	0.38[d]
MSLT Score	14.78	2.97	8.93	5.42	<.001
Epworth Sleepiness Scale	7.34	4.87	9.58	5.34	0.04[c]
BMI	26.32	4.08	29.18	7.08	0.03[c]
PVT Number of Lapses[a]	5.84	11.31	9.58	12.92	0.01[d]
PVT Fastest 10% RT[a]	218.53	47.43	213.42	195.77	0.04[d]
PVT Slowest 10% RT[a]	910.73	1812.90	1197.41	1910.35	0.03[d]
POMS Fatigue[b]	8.77	6.80	9.72	7.36	0.54[d]
POMS Confusion[b]	8.58	4.99	9.67	7.01	0.42[c]
POMS Tension[b]	9.98	6.75	10.46	8.22	0.77[c]
POMS Vigor[b]	11.86	6.38	14.46	7.04	0.08[c]
POMS Depression[b]	11.28	11.34	13.72	14.53	0.40[d]
POMS Anger[b]	8.12	9.14	11.41	13.02	0.19[d]
FOSQ Total Score[c]	8.94	6.37	12.27	7.01	0.05[d]

[a]Data analysed using nonparametric Mann-Whitney U. [b]N= 82(Not Sleepy=59 and Sleepy = 23). [c]Analyses conducted using the parametric t tests. [d]Analyses conducted using the nonparametric Mann-Whitney U.

Prior studies[4,5] have shown that in symptomatic (sleepy) TBI subjects, 32%-70% have SDB, 1%-3% have narcolepsy, and 1%-4% have PTH. Lankford et al.[37] reported 8 of 9 sleepy TBI subjects to have posttraumatic narcolepsy, while the 9th met criteria for PTH. Only 2 prior studies have been done on unselected TBI subjects, but these patients were recruited from inpatient rehabilitation facilities, had severe injury, and were often less than 3 months post injury. These studies found that 12%-36% of their samples had SDB. Only one of these studies included MSLTs. This study included only inpatients and found that 47% were objectively sleepy (MSLT score <10 minutes), 3% had narcolepsy, and 28% had PTH. The current study found fewer subjects with objective sleepiness (26%), as would be expected from a prospective study that included predominantly outpatients who were more than 3 months post injury. The prevalence of demonstrable sleep disorders in our study (46%) may be more representative than studies composed of acute or referred samples. The presence of PLMS as a diagnostic finding presents some problems, since most of these subjects were asymptomatic and had less than 5 PLM-arousals/hour. Thus the periodic limb movements (PLMs) noted may constitute an incidental finding of little or no clinical significance in most subjects. There was only one subject with PLMS and an MSLT score <10 minutes, and that subject also had OSA. If we exclude PLMS, then 40% of our TBI subjects had significant sleep disorders. PTH was the second most common sleep disorder (11%) after OSA (23%) in TBI subjects, while 6% had narcolepsy. The MSLT is a necessary part of the sleep evaluation in TBI subjects, since approximately 17% of our TBI subjects had either PTH or narcolepsy, both of which require MSLT for diagnosis.

The fact that narcolepsy is so frequent (6%) in our study sample and in other studies compared to the general population (0.05%) suggests that either some of the subjects had pre-existing narcolepsy, or that TBI may precipitate the onset of narcolepsy symptoms.[2,4,5,37] Since both those subjects with OSA[8] and narcolepsy[9] have a greater chance of MVAs and hence TBI, it is not surprising that both conditions have a higher prevalence in post-TBI subjects. It is very possible that some of our subjects may have had a preexisting undiagnosed sleep disorder, and that the presence of a sleep disorder may actually have contributed to the occurrence of the accident that caused traumatic brain injury. We cannot determine whether TBI or sleep disorder came first, since the purpose of our study was to examine the prevalence and consequences of sleep disorders in patients with TBI, and there was no way to determine how many of these subjects actually had a sleep disorder prior to injury. Pre-TBI symptoms of hypersomnia were not found by Guilleminault et al[2] in any of the 59 TBI patients with SDB, while 3 of 10 subjects in another study[5] had preexisting symptoms. Two of these had SDB and one had narcolepsy. The reliability of the history of preexisting symptoms is very questionable in most cases, given both the medical-legal implications and the dubious reliability of cognitively impaired post-TBI subjects as historians.

We did not find any specific relationship between the presence of sleep disorders and the severity of injury. We did not find significantly different distributions of mildly, moderately, or severely injured subjects in the sleepy and non-sleepy groups or the sleep-disordered and non-sleep-disordered TBI subjects. Similarly, there was no relationship between the presence of CT lesions and sleep disorders or sleepiness. Unfortunately, our study is missing severity data and CT data on a number of subjects, which is a weakness of this study. However, the lack of significant relationships between TBI severity or the presence of CT lesions and sleep disorders has been found previously in a large cohort.[4] Thus, the weight of the evidence would suggest that TBI severity and the presence of CT lesions are independent of sleep disorders and sleepiness.

This is the first study demonstrating that the presence of a sleep disorder adds an additional cognitive burden in TBI subjects. Sleepy subjects showed slower reaction times and made more lapses on the PVT than non-sleepy subjects. The relationship between sleepiness and decreased neurobehavioral functioning has been reported previously in sleep-deprived nonclinical samples.[29] In addition, vigilance problems and EDS appear to commonly co-occur in narcolepsy subjects.[39] TBI has long been associated with significant cognitive impairments.[40] It would

appear from our results that vigilance problems are increased in this population by the presence of a sleep disorder or EDS, and it is possible that these vigilance problems may underlie the cognitive problems of TBI subjects with heretofore unrecognized sleep disorders. Since the sleep-disordered subjects were somewhat older than the non-sleep-disordered subjects, it could be argued that the differences in vigilance might be the result of this age difference. However, correlational analyses disclosed small relationships between PVT variables and age that ranged from r = -0.13 to r = 0.23), which would suggest that age is not responsible for this finding.

In spite of objective evidence of poor vigilance, there was a trend towards sleepy TBI subjects and TBI subjects with a sleep disorder diagnosis to actually report better sleep related quality of life than those that did not carry a diagnosis and/or were not sleepy. TBI is often associated with reduced awareness of problems.[41] Thus, it is highly likely that poor awareness resulted in subjects overreporting self-perceived quality of life and perhaps underreporting mood changes and subjective sleepiness. This conclusion is supported by the low correlation between the MSLT (objective sleepiness) and the ESS (subjective sleepiness) and nonsignificant group differences on POMS measures that would be sensitive to sleep related problems such as Fatigue and Vigor. Future research with this population of sleep disorder subjects as well as clinical evaluations should include objective performance measures as well as collateral report for family and significant others in order to establish a reliable symptom picture and history.

Vigilance problems may make these subjects more prone to have problems in daily functioning. Thus, it is possible that the presence of a sleep disorder causes more functional disability in TBI. The impact of vigilance problems on the day to day functioning of TBI subjects has not been established. This paper could not address the first possibility, because of apparently unreliable reports from our subjects and the lack of data on day to day functioning from collateral informants. This is one of the weaknesses of this study and emphasizes the importance of data from collateral informants in studies on functional outcome. A future paper from this project will begin to address whether optimal treatment improves vigilance problems.

The high prevalence of excessive daytime sleepiness, obstructive sleep apnea, posttraumatic hypersomnia, and narcolepsy after traumatic brain injury leaves us with the conclusion that these subjects should undergo complete sleep evaluations, including NPSG and MSLT. Sleepy TBI subjects have more impaired cognitive function and vigilance performance than other TBI subjects but may be unaware of problems. This may also explain the lack of correlation between MSLT and ESS in these subjects. Hence objective testing should be used in order to assess pathology. Since daytime sleepiness and some neuropsychological deficits of TBI subjects may be due to treatable sleep disorders, their diagnosis and treatment may have a favorable impact on care.

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Review Article Open Access

Sleep Apnea in Traumatic Brain Injury: Understanding Its Impact on Executive Function

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Abstract

Background: Persons who have sustained a traumatic brain injury are at a significantly increased risk for sleep disorders. One of the most commonly diagnosed sleep disorders after traumatic brain injury is sleep apnea, defined as a cessation of breathing accompanied by frequent arousals and hypoxia during sleep. The effects of untreated sleep apnea on a person's cognitive decline and the development of behavioral deficits have only recently been identified. It has been shown that axonal damage can occur because of sleep apnea and numerous neuropsychological studies of sleep apnea patients show deficits in cognitive domains, such as executive function and attention. However, there has been little published discussion regarding the interaction between sleep apnea and executive function among persons with traumatic brain injury.

Objectives: The objectives of this review were to 1) review/synthesize published work relevant to the discussion of sleep apnea influencing executive function; and 2) clarify the nature of the interface between executive function and sleep apnea in persons with traumatic brain injury.

Results: Until now, little attention has been directed to the neurobehavioral consequences of sleep apnea in persons with traumatic brain injury. There is an urgent need for more longitudinal research examining the effects of sleep apnea on executive function after traumatic brain injury and the effectiveness of sleep apnea treatment on executive function after injury.

Keywords: Traumatic brain injury; Executive function; Sleep apnea; Neurobehavior; Risk; Alzheimer's disease; Continuous positive airway pressure

Abbreviations: TBI: Traumatic Brain Injury; EF: Executive Function; SA: Sleep Apnea; CT: Computed Tomography; PET: Positron Emission Tomography; SDB: Sleep-Disordered Breathing; CSA: Central Sleep Apnea; OSA: Obstructive Sleep Apnea; RDI: Respiratory Disturbance Index; CNS: Central Nervous System; CPAP: Continuous Positive Airway Pressure; RCFT: Rey Complex Figure Test

Introduction

Traumatic brain injury (TBI) is a major global health problem. According to the World Health Organization, TBI will surpass many diseases as the major cause of death and disability by the year 2020 [1]. Although the prevalence of TBI, defined as chronic symptoms from an earlier TBI, is not widely studied, it is estimated that in the USA, around 5.3 million people experience long-lasting symptoms caused by TBI [2]. If this statistic is extrapolated to a global scale, an oft-quoted estimate is that approximately 140 million persons are living with a TBI-related disability; however there is a possibility that this number is overestimated or underestimated [3]. Of the various disabilities that are the result of TBI, cognitive and psychological deficits, particularly poor executive function (EF), prevent TBI survivors from reintegrating into the community, returning to school, and re-entering the workplace [4]. Executive function, the cognitive ability that underlies planning, problem-solving, self-monitoring, behavioral control and working memory [5], is therefore a major consideration in the cognitive rehabilitation of patients with brain injury [5]. While a discussion of neurocognitive impairment secondary to TBI would seem to be straightforward, the pathogenesis is likely to be a multifactorial process involving a diverse range of mechanisms. Consequently, it is essential that an examination of post-morbid executive function be done with reference to the other common disorders that can affect the brain. In the current review, we provide an overview of published work that is relevant to the discussion of sleep apnea's (SA) effects on EF and we examine different levels of evidence directed to clarifying the interface of executive function and SA in persons with TBI.

TBI and Cerebral Oxygenation as a Predictor of EF

When the brain is injured, normal pathways for EF performance are disturbed. The organic disruptions as well as cerebral ischemia resulting from post-traumatic hypotension and hypoxia together contribute to the poor cognitive outcomes that often follow TBI [6]. Decreased cerebral blood flow after TBI has been revealed using different diagnostic tools, such as computer tomography (CT) and positron emission tomography (PET) scans [7-8]. The mechanisms by which post-traumatic cerebral ischemia occurs include injury to the vessels as a result of mechanical displacement, hypotension in the presence of auto regulatory failure, inadequate availability of cholinergic neuro transmitters, and potentiation of prostaglandin-induced vasoconstriction. Because of an imbalance between cerebral oxygen consumption requirements and oxygen delivery, the brain

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tissue suffers from hypoxia [9]. It has been reported that the incidence, duration, and extent of tissue hypoxia is associated with poor neuropsychological outcomes post-TBI [10].

The phenomena of increased oxygen demand required for meta cognition and decreased oxygen delivery post-TBI are important concepts in understanding the underlying mechanism of EF decline after trauma to the brain. It is stipulated that persons with TBI who suffer from disorders causing decreased brain tissue oxygenation, constant or intermittent, due to other disorders (e.g.,SA), will demonstrate worse clinical outcomes post-TBI when compared to those who do not.

Defining SA

SA, an intermittent complete cessation of airflow during sleep, is the most frequently reported form of sleep-disordered breathing (SDB) after TBI. SA of at least 10 s is considered clinically important, but in many patients, apneas can last 20–30 s and in some cases as long as 3 min. SA can be central or obstructive in nature. In central sleep apnea (CSA), the neural drive to respiratory muscle is abolished. In obstructive sleep apnea (OSA), airflow ceases because of occlusion of the upper airway in sleep due to the specific anatomical structure of the upper airway or decreased muscle tonus resulting in muscle collapse during sleep. The resulting apnea leads to progression of asphyxia until there is an arousal from sleep, which restores the airway patency. The patient then returns to sleep and the sequence of the events repeats. In the most severe cases, SA occurs up to 500 times per night—resulting in sleep fragmentation and disturbances of sleep architecture. These nocturnal sleep disturbances result in vital exhaustion/daytime sleepiness/ impaired alertness and cognitive dysfunction, especially in the areas of attention and memory [11]. Furthermore, both OSA and CSA, highly prevalent after TBI, result in recurrent episodes of nocturnal asphyxia and decreased oxygenation (hypoxia) of brain tissue. Such brain tissue hypoxia is related to prefrontal lobe dysfunction [12]. Related respiratory events, hypopnea, and respiratory event-related arousals are characterized by a partial reduction in airflow in sleep, and consequent arousals from sleep with or without significant oxygen desaturation. The average number of all respiratory events per hour of sleep is termed the respiratory disturbance index (RDI). An RDI of 5 or greater is of clinical significance and can be an indication of SDB [13].

SA and Oxidative Stress

It is evident that SA may lead to a series of pathophysiologic events [14]. Xu et al. demonstrated that chronic intermittent hypoxia results in cortical neuronal cell apoptosis in mice [15]. Chronic intermittent hypoxia is also shown to be associated with inducible nitric oxide synthesis in the brain [16-17], which plays a role in nerve cell communication, and is associated with neuronal plasma membranes [18]. Other research has shown that free radicals formed as a result of oxidative stress in OSA lead to the up-regulation of transcription factors such as NF-κB [19]. Da Silva et al. reviewed the effects of OSA on homeostasis in the central nervous system (CNS) by examining the levels of biochemical markers of cerebral injury (neuron-specific enolase and the S100B protein derived from astrocytes) in OSA patients. The results of their study showed a significant increase in S100B markers, suggesting a CNS astrocyte reaction in response to cerebral hypoxemia in patients with OSA and supporting the view that OSA causes brain alterations, which can manifest as neuropsychological symptoms [20].

SA as a Predictor of Executive Function

Numerous studies have established a relationship between SA and cognitive deficits, including EF, attention/vigilance, language, memory, and psychomotor speed [21]. Of these various deficits, EF has been a research topic of particular interest. Several tasks, such as the Wisconsin Card Sorting Task, the Tower of Toronto, and the Stroop task, have been used to measure SA sufferers' deficits in EF [22].

Beebe and Gozal [12] studied the involvement of the frontal cortex in OSA patients and its link to EF. These authors reported decreased EF in their patients, which manifested as deficits in behavioral inhibition, self-regulation of affect and arousal, working and contextual memory, and analytical ability. They proposed a model in which sleep fragmentation, hypoxemia, and dysfunction of the frontal lobe cortex are interrelated through the disruption of homeostasis and altered glial viability within primarily frontal regions of the brain cortex. The authors stressed that executive dysfunction in OSA patients leads to reduced social relationships and job tasks; therefore, evaluation of social and work-related skills is crucial and should take precedence over other aspects of cognition (e.g., vocabulary, intelligence).

In one study, abnormal breathing and oxygen desaturation during sleep in heavy snorers were factors associated with obtaining fewer numbers of categories on the Wisconsin Card Sorting Task (i.e., domain of executive function: mental set shifting and abstract behavior). Using a modified version of the task, Naegele et al. [23] reported that poor performance on this task is predictive by the effect of severe hypoxemia in OSA patients. Behavioral manifestations in OSA patients also included difficulties with problem solving and initiation detected by the Tower of Toronto task (i.e., domain of executive function: problem solving). In addition, other researchers have found that persons with OSA require more time to complete EF tasks than do controls. When assessing planning abilities using the Maze task (i.e., domain of executive function: planning and foresight), Bedard et al. found that OSA participants had significant difficulties in completing the task [24].

Halbower et al. [25] studied links between OSA, cognitive deficits, and neuronal brain injury in children. Compared to controls, children with severe OSA had significant deficits in intelligence quotient (IQ) and EF (verbal working memory and verbal fluency), and demonstrated decreased neuronal metabolite ratios in the left hippocampus and the frontal cortex, as measured by proton magnetic resonance spectroscopic imaging. The authors speculated that untreated childhood OSA could permanently alter a developing child's cognitive potential.

Treatment of SA Executive Dysfunction

Several approaches to the treatment of SA have been advocated based on our current understanding of the mechanisms underlying the disorder. Milder OSA can often be managed effectively by weight reduction, avoidance of alcohol, improvement of nasal patency and avoidance of sleeping in a supine position. In more severe OSA cases, nasal continuous positive airway pressure (CPAP), a treatment which delivers positive pressure through a nasal/full-face mask to maintain opening of the upper airway during sleep, is widely used. Patients with CSA, whose apnea arises from instability of respiratory drive, have been shown to respond well to CPAP with or without adding nocturnal supplemental oxygen [26-27].

A current controversy regarding EF and treatment of SA revolves around an important issue: the efficacy of SA treatment in correcting executive dysfunction. Although newer research shows that cognitive deficits are resolved with treatment in the majority of cases, other research suggests some deficits in EF may remain unchanged [28-30]. This raises the possibility of permanent brain changes as a result of OSA.

In their review, Engleman et al. [31] indicated that most research to date has shown trends toward better cognitive performance after CPAP treatment compared to placebo. At least 3 studies comparing neuropsychological test scores of OSA patients before and after 6 months of CPAP treatment with test scores of healthy controls found notable cognitive improvement, including improvement in EF [23,32-33].

A recent randomized double-blind placebo-controlled trial by Ancoli-Israel et al. [34] examined the effect of CPAP on cognitive functioning in patients with Alzheimer's disease (AD). A comparison of pre-and post-treatment neuropsychological test scores (HVLT-R, Trail Making test) in Alzheimer's patients receiving 3 weeks of therapeutic CPAP showed a significant improvement in cognition, especially in episodic verbal learning and memory and in some aspects of EF such as cognitive flexibility and mental processing speed. These data, as well as the data of other researchers [35], seems promising and indicate that OSA may be a reversible cause of cognitive loss in this patient group; moreover, treatment of OSA, especially in the early stages of dementia when patients are still largely independent, may slow the progression of dementia. This reinforces the necessity of identifying and treating SA in individuals with TBI in the early stages post-injury.

Relationship Between TBI, SA, and Executive Dysfunction

Significant correlations have been reported between measures of EFs and regional cerebral glucose metabolism in medial and dorsolateral prefrontal cortical regions and the cingulate gyrus, despite the absence of detectable structural lesions on brain magnetic resonance imaging. These results suggest that impairments of EFs may be related not only to focal traumatic lesions of the prefrontal cortex, but also to lesions of the white matter tracts [36-37]. These effects appear to be non-specific to TBI, as similar results are reported in persons with Alzheimer's disease AD [38]. Interestingly, SA is a risk factor for AD and other neurological diseases [39]. Similarly, the implication of TBI as a contributing factor in the development of AD and dementia has been reported [40]. In some individuals, disruption of axonal transport following TBI can lead to the rapid accumulation of amyloid precursor proteins and other proteins associated with the neurodegenerative disease. The variation observed in the APOE E4 allele in persons with TBI prompted exploration of the role of genetic factors in modulating the risk for AD after TBI [41]. Coincidentally, O'Hara et al. [42] reported the relationship between sleep apnea and dementia through the APOE E4 allele, whose carriers may be at an increased risk for developing dementia. Numerous research studies also report a higher prevalence of SA in the TBI population, ranging from 25% to 35%, compared to 4–9% in the general world population [43].

Although the high numbers of SA in the TBI population can be partly attributed to pre-morbid undetected sleep disorders, which can be a proximate cause of the injury itself, some persons may develop the sleep disorder as a consequence of brain injury. A disturbed coordination of upper airway and diaphragmatic muscles due to damage to the brainstem might favor the appearance of SA. Aggregation of SA can occur with commonly prescribed medications after the injury, such as muscle relaxants, sedatives, or hypnotics. Furthermore, narcotics for pain can cause opioid-induced respiratory depression, defined as a combination of decreased respiratory drive, reduced level of consciousness, and upper-airway obstruction, manifesting as both central and obstructive respiratory events [44].

Theoretical links exist between levels of hypocretins, which play a part in the regulation of various functions, including arousal, muscle tone, locomotion, feeding behavior, and neuroendocrine/autonomic functions, and SA [45-46]. Baumann et al. reported low hypocretin-1 levels in the cerebrospinal fluid from over 90% of 27 patients in the early days post-TBI and in 19% of 21 patients at 6 months post-injury [47-48]. Hypocretin deficiency after TBI may cause the loss of control of respiratory-related activity of hypoglossal motoneurons during rapid eye movement (REM) sleep [49]. Similarly, the presence of motor activity disfacilitation during REM sleep in acute rat preparations, with experimentally induced hypoxia, hypercapnia, and/or reduced airway patency has been reported; many of these conditions are also present in OSA [50]. Therefore, it is possible that due to TBI, disfacilitation of respiratory-related inputs to hypoglossal motoneurons during REM sleep will result in aggravation of SA at the acute stages post-injury, but may resolve with time.

Another relationship relevant to the discussion of executive dysfunction in SA and post-TBI is comorbid psychopathology. Depression after TBI is common, ranging 27–61%, when structural diagnostic criteria are used [51-52]. A nearly twofold increase in the risk for developing major depressive disorders has been reported in persons suffering from SA [53]. Working with acute mild TBI patients, Chaput et al. found that depression and irritability were more frequent in those with sleep complaints [54]. Depression has been reported to be associated with poorer cognitive outcomes, and no published studies have shown that the cognitive effects of depression can be reliably differentiated from the cognitive effects of SA or TBI [55]. Moreover, depression can act as an amplifier of other neurobehavioral changes, including aggression and irritability, and modulate symptom overlap between the post-concussion syndrome and psychopathology [56]. Given the frequent co-occurrence of depression and SA in TBI, recognizing the cumulative evidence for the intertwined processes of mood, sleep, and neuroplasticity post-TBI may have important implications for cognitive rehabilitation.

One of the aims of this review was to determine whether current evidence suggests that SA is causally associated with executive dysfunction after TBI and whether there is any evidence that the treatment of SA is effective in improving EF of these persons. The intent was to shed light on the potential importance of SA screening and treatment post-TBI as a means of halting the progression of executive dysfunction after brain trauma. To directly examine this question, prospective longitudinal studies are required. However, this research design is expensive and demands sustained commitment from participants and investigators. Given the heterogeneity in TBI (e.g., sex, age, injury localization and severity, confounding factors, difference in medication regime, and genetic makeup), the main requirement of an effective prospective study—the recruitment and retention of a sufficiently large sample—is difficult to achieve. An alternative approach has been to focus on comparisons of outcome between groups of persons with TBI of similar age/gender/time since injury/injury localization/severity, but who differ in that some suffer SA and some do not.

Wilde et al. [57] performed such a study on 35 TBI patients, 18 years of age and older and at least 3 months post-TBI. Of these, 19 patients had OSA, as defined by polysomnography, with severity reported by the apnea–hypopnea index. Their EF performance was compared with 16 TBI participants without OSA. Both groups were comparable in terms of age, education, severity of injury, time post-injury, and Glasgow Coma Scale. The main outcome measures were: The Psychomotor Vigilance Test, Rey Complex Figure Test, Rey Auditory

Verbal Learning Test, Digit Span Test from the Wechsler Memory Scale, and finger-taping test. The Rey-Osterrieth Complex Figure Test (RCFT) [58] permits the evaluation of different cognitive functions believed to be EF measures, such as visuospatial abilities, attention, planning, organizational skills and analysis-synthesis. Persons with OSA performed significantly worse on RCFT delayed recall (t_{35}= -2.05, p=0.048), had greater numbers of lapses, and worse retention (i.e., deterioration of thinking ability and memory) compared to those without OSA. Interestingly, the researchers did not find significant differences in OSA vs. non-OSA patients on working memory tests such as the copy administration, total recall list, and the digit span test forward and backward (Table 1). These results are promising, suggesting the possibility of reversibility of executive deficits and the potential of recovery with treatment implementation.

The study has noted limitations. Some data were missing in 10 of 19 participants with OSA and in 8 of 16 non-OSA participants. The localization of brain damage was not reported, even though positive CT scan findings were found in 9 of 19 OSA and 8 non-OSA participants. The authors did not comment on the number of CSA events or whether any hypopneas that were included in the diagnoses were of central origin. Overall, this is valuable information because SA in TBI populations seems to differ from those being described in general. According to reports of Websters et al. [10], the majority of the events in their sample of 28 TBI participants were central in nature rather than obstructive, while in the general population, SA consists of 90% obstructive and only 10% central events [59]. Additional methodological concerns include the great number of variables and the small sample size consisted largely of male participants, which was not allowing definitive conclusions to be drawn.

In summary, executive dysfunction, encompassing impairments in cognitive, behavioral and emotional processes after TBI, presents significant challenges for recovery after injury. Similar process impairments are also found in persons with SA. This review suggests that undetected/untreated SA in persons with TBI may have profound effects on neurobehavioral processes, impacting both structure and function. Different lines of evidence are relevant to the mechanism of EF decline associated with TBI and untreated SA. These include, but are not limited to: 1) evidence from animal studies on hippocampal cell death and apoptosis of the forebrain regions as a result of recurrent SA resulting in secondary neuronal injury, 2) association between white-matter grade and severity of CSA reported, 3) results of CPAP treatment intervention studies showing improvement in EF test performance in SA sufferers, 4) studies on the prevalence of SA in TBI populations, placing affected individuals in a category of greater risk, 5) numerous studies showing the detrimental effects of SA on non-TBI persons' cognitive performance, especially EF, all of which advocate for an association between possible undiscovered and untreated SA and poor cognitive rehabilitation outcomes of TBI survivors. Finally, a recent study by researchers from the University of Pittsburgh School of Medicine retrospectively evaluated diffusion-tensor images from 64 consecutive patients with mild TBI who underwent magnetic resonance imaging. They found that more than half of the patients had sleep and wake disturbances. While researchers did not clarify the category of the sleep disorder, there was a significant reduction in fractional anisotropy in the parahippocampalgyri in patients with sleep and wake disturbances versus those without [36]. This region in the brain plays an important role in memory encoding and retrieval and in identifying social context as well, including paralinguistic elements of verbal communication [60].

Although we have presented a narrative review of published literature relevant to understanding the association between SA and executive function in TBI, a significant challenge in discussing these associations is disentangling the effect of brain injury from the effect of SA on executive function in TBI (Figure 1). It is possible that studies of executive function have been conducted often with TBI survivors who have suffered SA, where untreated pre-existing SA was

Author(s); year	Article Title, journal, pages; Study Objective	Research Design/ Sample Size; Inclusion/Exclusion	Participants	Data Collection Methods/Measures	Findings	Comments
Wilde M, Castriotta R, Lai J, Atanasov S, Masel B, Kuna S; 2007 [57]	Cognitive impairment in patients with traumatic brain injury and obstructive sleep apnea. Arch Phys Med Rehabil. 2007; 88(10):1284-8 To examine the impact of comorbid obstructive sleep apnea on the cognitive functioning of traumatic brain injury patients	Case-control study/35; subjects who were more than 18 years old and at least 3 months post-injury/ Subjects with other sleep disorders	Persons with traumatic brain injury (TBI) from 3 academic medical centers; 2 groups: obstructive sleep apnea (OSA) and non-OSA; n (OSA) =19, n (non-OSA) = 16 Age: mean for OSA, 47.25 y; non-OSA, 51.47 y Time since injury: OSA, 124 mo; non-OSA, 77 mo Male/Female: OSA, 17/2; non-OSA, 12/4 TBI severity (unknown/ moderate/moderate-severe/severe): OSA, 10/3/1/5; non-OSA, 8/2/3/3 Computed tomography (CT) findings (unknown/ negative/positive): OSA, 16/0/9; non-OSA, 8/1/7	Assessments: Clinical interview; Physical examination; Glasgow Coma Score (GSC); CT data; Neurological assessment; Polysomnography (PSG); Multiple Sleep Latency Test (MSLT)	Mean apnea–hypopnea index (AHI) for OSA group: 26.83/h; non-OSA: 4.49/h Mean MSLT score: OSA, 11.19; non-OSA, 5.06 Statistically significant difference in test performance for patients with and without OSA: • memory recall measures: worse in OSA • number of lapses: greater in OSA • retention: worse in OSA No statistically significant difference in performance between groups: • on the copy administration • total recall list • digit span test forward and backward	Definitions: Diagnosis of OSA: 5 or more apneas per hour and/or 10 or more apneas plus hypopneas per hour

Table 1: Literature review on association between traumatic brain injury and sleep apnea.

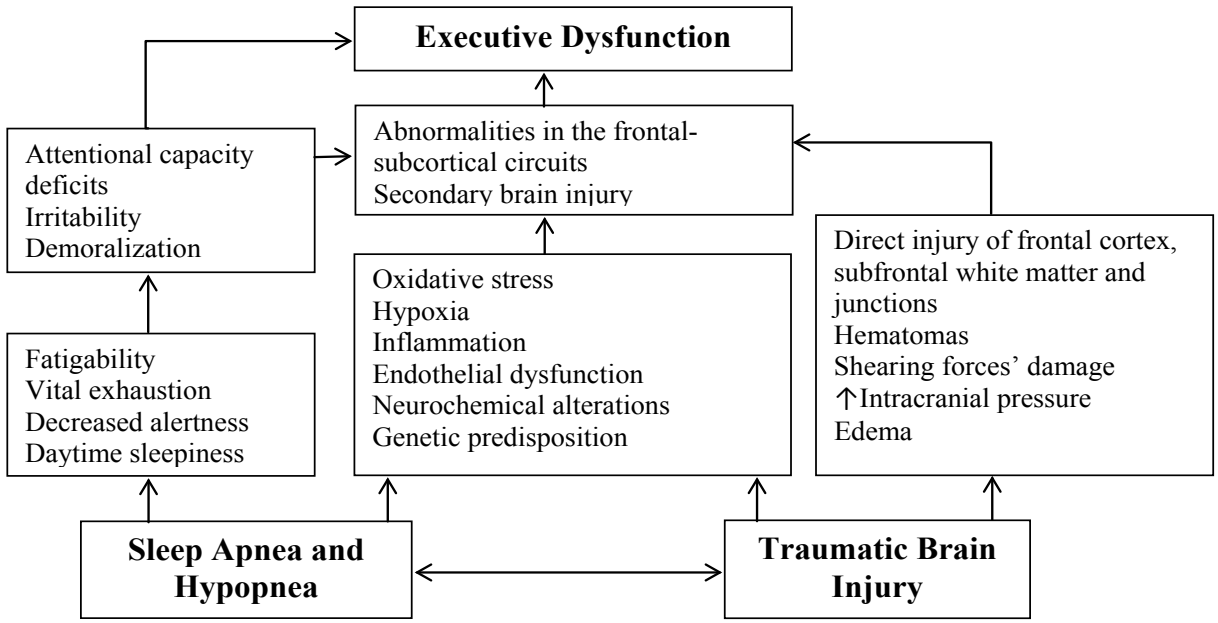

Figure 1: Pathogenesis of development of executive dysfunction among patients with Sleep Apnea and Traumatic Brain Injury.

a proximate cause of the brain injury itself. There is in fact growing evidence supporting an association between sleepiness and fatigue as a result of SA, and the probability of one's involvement in an incident involving injury [60]. As discussed above, non-specific alterations to white and grey matter integrity and aberrant prefrontal activity have been reported in both TBI and SA sufferers' studies. These provocative findings suggest a need for further study of brain connectivity among areas particularly relevant to executive function and vascular risk factors, taking into account the high likelihood of undetected/untreated SA in TBI persons. Given that there is no known cure for brain injury, addressing SA may provide benefits in terms of cognitive function which may be currently overlooked.

To conclude, the findings of this review suggest that limited research that has been done to identify EF outcomes in persons with TBI, and how these outcomes might be related to SA. Considering the impact of brain damage itself on cognitive functioning after TBI, it is still unknown whether executive dysfunction related to SA in the TBI population is a specific entity or whether the presence of SA exaggerates the TBI-related physiological changes in EF. The general processes slowing usually found in patients with brain injuries could explain, to a great extent, the decline in EF observed in persons with TBI, as well as persons with SA [14, 37-40]. More definitive evidence on SA as a cause of poor EF after TBI can be gathered through further research targeting TBI survivors. While it is premature to make strong conclusions regarding the nature of the synergy of SA and executive dysfunction in TBI, this literature review sheds light on the repercussions of SA, if left unrecognized and untreated, to cognitive dysfunction following brain damage. The prospect of improving impaired processes through the treatment of SA cannot be ignored. The current state of evidence indicating a hierarchy of post-morbid cognitive symptom clusters within similar injury severities, as well as sustained executive dysfunction after mild TBI years after injury, further strengthens the need to identify and treat people with TBI who experience SA at the early stages of cognitive rehabilitation.

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Sleep apnea: weaker brain blood flow damages the brain

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Around 10% of adults contend with obstructive sleep apnea, a condition characterized by symptoms of brain dysfunction such as extreme daytime sleepiness, depression, anxiety and memory problems. Now, a new study published in *PLOS One* suggests the damage done in the brains of sleep apnea sufferers is down to weaker brain blood flow.

The study was led by Paul Macey, of the University of California-Los Angeles (UCLA) School of Nursing, and funded by the National Institute of Nursing Research.

People with obstructive sleep apnea (OSA) typically make gasping or snorting noises periodically during sleep, which momentarily interrupts their sleep hundreds of times a night. Every time their breathing stops, their blood oxygen level drops, damaging cells in the body.

If the condition is left untreated, it can lead to high blood pressure, stroke, heart failure, diabetes, depression and other problems.

A CPAP device worn at night is often used to treat sleep apnea.

According to the Centers for Disease Control and Prevention (CDC), if other medical problems such as congestive heart failure or nasal obstruction are present, the condition may resolve with treatment of these problems.

However, gentle air pressure delivered during sleep - usually in the form of a nasal continuous positive airway pressure (CPAP) device - can also serve as an effective treatment.

'Weaker brain blood flow response' in OSA patients

For their latest study, Macey and colleagues measured brain blood flow in sleep apnea patients using a non-invasive MRI procedure called the global blood volume and oxygen dependent (BOLD) signal.

They explain that this method is typically used to examine brain activity, and since previous research showed that sleep apnea sufferers often have poor regulation of blood in the brain, they used the whole-brain BOLD signal to observe blood flow in participants with and without OSA.

"We know there is injury to the brain from sleep apnea," says Macey, "and we also know that the heart has problems pumping blood to the body, and potentially also to the brain." He explains that by using the BOLD method, they were able to observe changes in oxygenated blood amounts throughout the whole brain.

Participants from the study, which included both men and women with and without OSA, had their BOLD signals measured while they were awake during three physical tasks:

- The Valsala maneuver, in which they breathed out forcefully through a small tube that raises the pressure in the chest
- A hand-grip challenge, in which the participants squeezed hard with their hand
- A cold-pressor challenge, in which the participants' right foot was placed in icy water for 1 minute.

Macey says the Valsala maneuver did not yield significant differences between the participants with sleep apnea and without; however, with the hand-grip and cold-pressor challenges, the individuals with OSA had a "much weaker brain blood flow response."

The investigators hypothesize that these differences were due to the signals from the nerves in the arms and legs needing to be processed through high brain areas that control sensation and muscle movement - which was slower because of the brain injury.

They add that because changes from the Valsala maneuver are mainly driven by blood pressure signaling in the chest, it does not require the muscle-controlling parts of the brain.

Study limitations

Another finding from the study reveals that this problem is greater in women with OSA than men, which the researchers say could explain why women have worse apnea-related outcomes. Additionally, other studies from UCLA have previously shown that brain injury from the condition is significantly worse in women than in men.

Though their findings are significant, the researchers note several limitations to their study.

One is that the hand-grip was a subjective, non-isometric challenge; the team says ideally, the test would involve holding a grip pressure at a predetermined maximum, rather than a perceived maximum. As such, this challenge "may not be considered a strictly equivalent challenge across subjects or groups," they say.

Additionally, because the female OSA group only had six subjects, the generalizability of their sex-specific finding is somewhat limited. And at least four of the OSA patients had diabetes and potentially undiagnosed hypertension, which are associated with neural deficits and altered cerebral blood flow, which could be confounding factors.

Still, the researchers conclude their study by noting:

> "These findings, indicative of reduced cerebral blood flow changes to autonomic challenges in [obstructive sleep apnea], complement earlier reports of altered resting blood flow and reduced cerebral artery responsiveness. Females are more affected than males, an outcome which may contribute to the sex-specific brain injury in the syndrome."

They add that they are currently investigating whether OSA treatment can reverse the damaging effects of the brain damage.

Written by Marie Ellis

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Global Brain Blood-Oxygen Level Responses to Autonomic Challenges in Obstructive Sleep Apnea, Paul M. Macey, et al., PLOS One, doi: 10.1371/journal.pone.0105261, published 28 August 2014.

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Spinal Cord Injury without Radiographic Abnormality (SCIWORA) – Clinical and Radiological Aspects

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Summary

The acronym SCIWORA (Spinal Cord Injury Without Radiographic Abnormality) was first developed and introduced by Pang and Wilberger who used it to define "clinical symptoms of traumatic myelopathy with no radiographic or computed tomographic features of spinal fracture or instability''. SCIWORA is a clinical-radiological condition that mostly affects children. SCIWORA lesions are found mainly in the cervical spine but can also be seen, although much less frequently, in the thoracic or lumbar spine. Based on reports from different authors, SCIWORA is responsible for 6 to 19% and 9% to 14% of spinal injuries in children and adults, respectively. Underlying degenerative changes, including spondylosis or spinal canal stenosis, are typically present in adult patients. The level of spinal cord injury corresponds to the location of these changes. With recent advances in neuroimaging techniques, especially in magnetic resonance imaging, and with increasing availability of MRI as a diagnostic tool, the overall detection rate of SCIWORA has significantly improved.

MeSH Keywords: Central Cord Syndrome • Magnetic Resonance Imaging • Spinal Cord Injuries

PDF file: http://www.polradiol.com/abstract/index/idArt/890944

Background

The acronym SCIWORA (Spinal Cord Injury Without Radiographic Abnormality) was first developed and introduced by Pang and Wilberger who used it to define "clinical symptoms of traumatic myelopathy with no radiographic or computed tomographic features of spinal fracture or instability''. The first case of SCIWORA was reported by Burke in 1974 [1]. The definition does not include spinal cord injury from electric current, obstetric complications, congenital spinal anomalies or penetrating injury to the spinal canal [2]. Differential diagnosis of non-traumatic degenerative changes versus acute traumatic injuries in adults is difficult, and sometimes even impossible. Therefore, some authors use the term SCIWORET (Spinal Cord Injury Without Radiographic Evidence of Trauma) as more appropriate [3].

Recent advances in neuroimaging techniques, especially in magnetic resonance imaging, made it possible to detect damages typical of SCIWORA. The aim of the paper was to discuss physiopathology of SCIWORA and current diagnostic options that can be used to investigate this clinical-radiological condition.

Physiopathology

Based on reports from different authors, SCIWORA is responsible for 6 to 19% and 9% to 14% of spinal injuries in children and adults, respectively. The prevalence of this condition is highest among children below 8 years of age who also have the most unfavorable prognosis, which is probably associated with relatively heavy head, weaker neck muscles and greater elasticity of vertebral ligaments in this patient population [4–6]. More horizontal orientation of facet joints further increases susceptibility to these injuries. Specific biomechanics of the vertebral column in children allows the musculoskeletal system to move beyond the normal physiological range of motion without the risk of fracture. The injury to the spinal cord is caused by a contusion or ischemia due to temporary occlusion of vertebral arteries followed by a spontaneous return of vertebrae to their original position [7].

High-energy injuries are often associated with vertebral fractures or instability due to decreased flexibility of the spine in adults. In most cases, SCIWORA occurs as a result of hyperextension forces (e.g., during a rear-end car accident) or from a direct frontal impact to the face. Launay et al. suggested that these injuries are likely to occur during sports such as diving, rugby, wrestling, and baseball. However, they are most often associated with low-energy falls in the elderly. Underlying degenerative changes, including spondylosis or spinal canal stenosis, are typically present in adult patients. The level of spinal cord injury corresponds to the location of these changes which may suggest that degenerative spine conditions predispose to SCIWORA injuries [8]. Even mild hyperextension injury can cause a central cord syndrome in patients with spinal stenosis. Both bone spur growth at the posterior margins of vertebral bodies, and bulging of the yellow ligament from the back side into the spinal canal (due to a decreased height of vertebral bodies), can cause spinal cord compression and impingement (Figure 1). Venous congestion within the compressed spinal cord is an additional pathogenic factor. Neurological deficit, that is usually more severe in the upper extremities than in the lower extremities, is the most typical clinical presentation in patients with SCIWORA [9,10]. The onset of clinical symptoms is delayed from a few minutes to 48 hours after injury in about 50% of patients. This latency is associated with repeated microinsults to the spinal cord from striking against the unstable vertebrae.

Diagnostic Tests

Specific assessments to determine spine injury should include clinical examination, with a special focus on neurological examination. Patients diagnosed with SCIWORA have a broad spectrum of neurological deficits, from mild and transient symptoms such as paresthesia in fingers to quadriplegia. Some patients experience symptoms only at the moment of injury. When performing physical examination it is important to bear in mind that neurological deficits may only become apparent after several days of injury. Since physical examination is limited, clinicians mainly rely on diagnostic imaging when planning treatment for these patients. Conventional x-rays are usually performed as the first-line imaging test. A lateral spine x-ray can identify 75% of fractures with sensitivity of 85%. The sensitivity increases to over 90% when anteroposterior (AP), lateral, oblique and open mouth or odontoid radiographs are taken [11]. The stability of the cervical spine can also be assessed by flexion and extension dynamic radiographs. However, it should be noted that plain x-rays provide inconclusive evidence in patients with post-traumatic cervical dystonia, so they should be postponed until complete resolution of muscle spasm [12].

Computed tomography is most accurate in detecting bony pathology. A CT scan can be used to visualize subtle injuries to the posterior arch or lateral mass of the vertebra, and injuries to the atlas and odontoid process that are poorly visible on standard x-rays. When a diagnosis of spinal fracture can be excluded by x-rays and CT scan, SCIWORA should be suspected and magnetic resonance tomography (MRT) performed in patients with blunt trauma injuries and neurologic deficits.

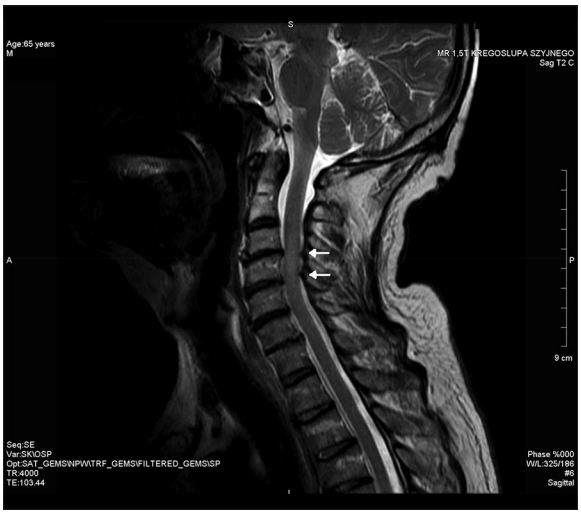

Figure 1. A sagittal T2-weighted spin-echo MR image of the cervical spine in a 65-year-old male patient. Arrows indicate the location of spinal cord compression: anterior impingement from bone spurs at the margin of the vertebral body and posterior impingement from bulging yellow ligament.

Magnetic resonance imaging is the best modality for direct evaluation of the spinal cord. Spin-echo T1 (T1 SE), gradient-echo T2* (T2-weighted GRE*) and STIR-weighted MRI pulse sequences are preferred in patients with spinal injuries. Due to longitudinal anatomy of the spinal cord, its integrity and possible location of changes can be easily determined in sagittal plane. The main symptoms of an acute spinal injury (SCI) include edema, hematoma, anatomic transection (loss of continuity) of the spinal cord and prolapsed nucleus pulposus. T1-weighted spin-echo MR images provide information about morphology and anatomy of the spinal cord and should be performed as first diagnostic step. The bleeding can be best identified on T2-weigted GRE sequences*. An increase in the concentration of deoxyhemoglobin in fresh hematoma causes a decrease in signal intensity on T2-weigted images (Figure 2A, 2B) and, in particular, on T2-weigted GRE images*. One week or more later, with the organization of the hematoma, resulting from the conversion of deoxyhemoglobin into methemoglobin, such lesions are seen as hyperintense on T1- and T2-weighted images. However, hemorrhages will again appear hypointense on T2WI due to the presence of hemosiderin-laden macrophages in the chronic phase. A spinal cord edema is seen as hyperintense signal on T2-weighted images against a background of normal nervous tissue, and is best visible on STIR images (Figure 3). Radiological features of post-traumatic disc herniation are similar to those of non-traumatic. Therefore, it is often virtually impossible to identify the difference between the two forms of disc prolapse. Only the presence of other post-traumatic lesions at the same level may suggest possible diagnosis [13,14]. Magnetic resonance imaging is useful not only for investigating soft tissue abnormalities, it also allows identification of bone marrow edema in injured vertebrae that cannot be seen on CT scans. Short tau inversion recovery (STIR) technique, which is used to suppress the signal from fat, is most valuable in these cases [15]. Differential diagnosis should include embolism from vertebral artery occlusion associated with cardiovascular

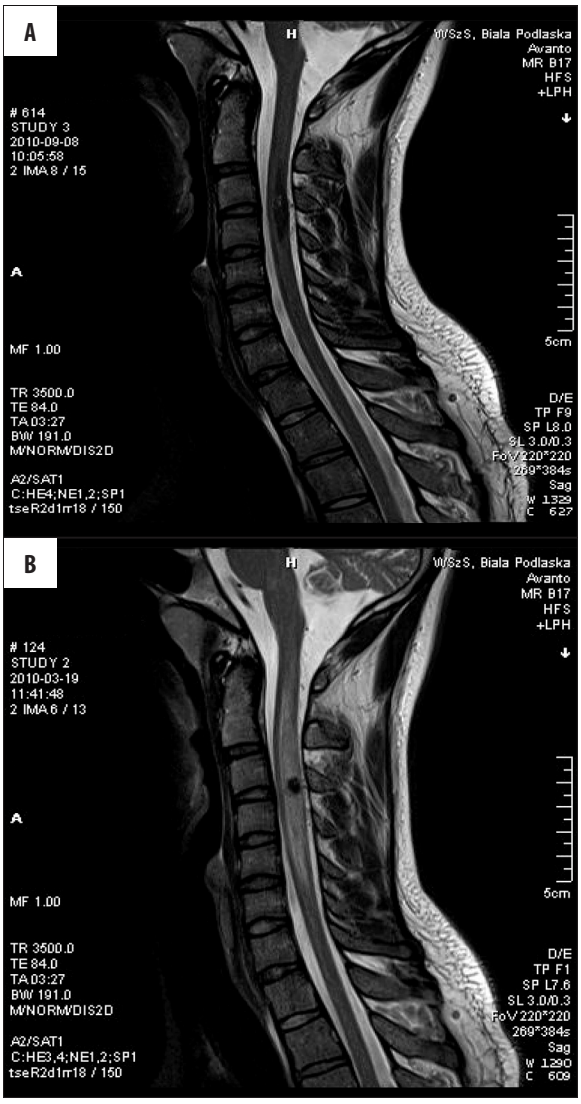

Figure 2. (**A, B**) A 23-year-old patient who suffers from a cervical spine injury due to a fall from a platform. The patient exhibited muscle weakness in the upper extremities and severe neck pain on physical examination. There were no bony abnormalities on x-rays or CT scans. MR images revealed a large hyperintense lesion in the cervical spine corresponding to edema of the cervical spinal cord. A focal signal drop out can be seen in the center of the lesion (a region of hyperacute hematoma). Chronic hematoma would give a similar appearance, except for the presence of spinal edema.

diseases such as endocarditis, cardiac arrhythmia, persistent foramen ovale, arteritis or bleeding disorder. Acute or chronic myelitis should also be excluded [16,17].

Spinal cord lesions revealed by MRI are important prognostic factors in patients with SCIWORA. Small hematomas (measuring up to 1/3 of the spinal cord diameter) or edema have favorable prognosis and resolve over time in most cases. Anatomic transection of the spinal cord or large

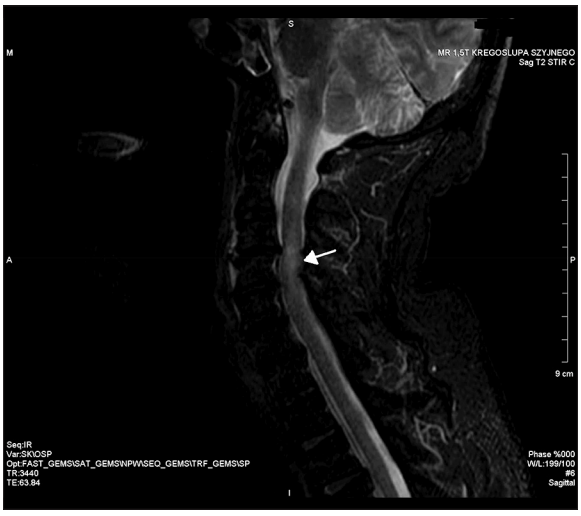

Figure 3. A sagittal STIR-weighted MR image of the spine. A hyperintense area pointed by an arrow represents edema of the spinal cord.

hematomas (greater than 1/2 of the spinal cord diameter) have poor prognosis and are manifested clinically as paresis or paralysis [18].

The increasing use of MRI as the primary imaging study for spinal trauma resulted in increased number of patients diagnosed with SCIWORA who had normal MRI findings. These cases should be classified as SCIWNA or spinal cord injury without neuroimaging abnormality [14]. Shen et al. have demonstrated clinical utility of diffusion weighted imaging (DWI) in evaluation of patients with SCIWNA. Patients with normal MRI findings had hyperintense lesions on DWI [19]. Diffusion tensor magnetic resonance imaging (DTI) also becomes an important diagnostic tool in patients with SCIWORA due to its ability to assess white matter integrity. Due to a small transverse diameter of the spinal cord, DTI requires high spatial resolution and relatively small voxel volume. Moreover, the images may have artifacts introduced by breathing, swallowing or pulsatile flow of the cerebrospinal fluid. The most modern parallel imaging methods, as well as ECG-triggering or ECG-gating scan techniques can improve the image quality [20,21]. Myelography or angiography would have no application as diagnostic tools for SCIWORA.

Treatment

External immobilization of the spine for up to 12 weeks is the main therapeutic option for patients with spinal injury. Patients are also advised to avoid increased-risk activities for 6 months after diagnosis to prevent acute exacerbations of symptoms and reduce the risk of another injury. In asymptomatic patients who obtained stable spine fixation as assessed by flexion and extension dynamic radiographs, external immobilization devices can be removed earlier. Drug treatment includes the use of antihypertensive agents to maintain blood pressure within normal limits [18].

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Regenerating memory with neural stem cells

Date:
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Texas A&M University
Summary:
Although brains -- even adult brains -- are far more malleable than we used to think, they are eventually subject to age-related illnesses, like dementia, and loss of cognitive function. Someday, though, we may actually be able to replace brain cells and restore memory.

Someday scientists may actually be able to replace brain cells and restore memory.
Credit: © Sergey Nivens / Fotolia

Although brains -- even adult brains -- are far more malleable than we used to think, they are eventually subject to age-related illnesses, like dementia, and loss of cognitive function.

Someday, though, we may actually be able to replace brain cells and restore memory. Recent work by Ashok K. Shetty, Ph.D., a professor in the Department of Molecular and Cellular Medicine, associate director of the Institute for Regenerative Medicine, and research career scientist at the Central Texas Veterans Health Care System, and his team at the Texas A&M Health Science Center College of Medicine hints at this possibility with a new technique of preparing donor neural stem cells and grafting them into an aged brain.

Shetty and his team took neural stem cells and implanted them into the hippocampus -- which plays an important role in making new memories and connecting them to emotions -- of an animal model, essentially enabling them to regenerate tissue. Findings were published in the journal *Stem Cells Translational Medicine.*

"We chose the hippocampus because it's so important in learning, memory and mood function," Shetty said. "We're interested in understanding aging in the brain, especially in the hippocampus, which seems particularly vulnerable to age-related changes." The volume of this part of the brain seems to decrease during the aging process, and this decrease may be related to age-related decline in neurogenesis (production of new neurons) and the memory deficits some people experience as they grow older.

The aged hippocampus also exhibits signs of age-related degenerative changes in the brain, such chronic low-grade inflammation and increased reactive oxygen species.

"We're very excited to see that the aged hippocampus can accept grafted neural stem cells as superbly as the young hippocampus does and this has implications for treating age-related neurodegenerative disorders," said Bharathi Hattiangady, assistant professor at the Texas A&M College of Medicine and co-first author of the study. "It's interesting that even neural stem cell niches can be formed in the aged hippocampus."

Shetty's previous research focused on the benefits of resveratrol (an antioxidant that is famously found in red wine and the skin of red grapes, as well as in peanuts and some berries) to the hippocampus. Although the results indicated great benefit for preventing memory loss in aging, his latest work demonstrates a way to affect the function of the hippocampus more directly.

For this latest research, the team found that the neural stem cells engrafted well onto the hippocampus in the young animal models (which was expected) as well as the older ones that would be, in human terms, about 70 years old. Not only did these implanted cells survive, they divided several times to make new cells.

"They had at least three divisions after transplantation," Shetty said. "So the total yield of graft-derived neurons and glia (a type of brain cell that supports neurons) were much higher than the number of implanted cells, and we found that in both the young and aged hippocampus, without much difference between the two."

"What was really exciting is that in both old and young brains, a small percentage of the grafted cells retained their 'stemness' feature and continuously produced new neurons," Hattiangady said. This is called creating a new 'niche' of neural stem cells, and these niches seemed to be functioning well. "They are still producing new neurons at least three months after implantation, and these neurons are capable of migrating to different parts of the brain."

Past efforts to rejuvenate brains using fetal neurons in this way weren't nearly as successful. Immature cells, such as neural stem cells, seem to do a better job because they can tolerate the hypoxia (lack of oxygen) and trauma of the brain grafting procedure better than post-mitotic or relatively mature neurons. When researchers tried in the past to implant these partially

differentiated cells into the aged hippocampus, they didn't do nearly as well. "We have a new technique of preparing the donor neural stem cells," Shetty said. "That's why this result has never been seen before."

The researchers did this work using donor cells from the sub-ventricular zone of the brain, an area called the "brain marrow," because it is analogous to bone marrow in that it holds a number of neural stem cells that persist throughout life and continuously produce new neurons that migrate to the olfactory system. These stem cells also respond to injury signals in conditions such as stroke and traumatic brain injury and replace some of the lost cerebral cortical neurons.

Even a small piece is good enough to expand in culture, so the procedure isn't terribly invasive, but in the future, a skin cell might suffice, as similar neural stem cells can be obtained in large numbers from skin. It's been well known in medical science that a number of cells in the body -- including those of the skin -- can be modified in such a way to create induced pluripotent stem cells. With these cells, scientists can do any number of things, including making neural stem cells that will make both more of themselves and new neurons. "You don't have to get the cells from the brain, you can just take a skin biopsy and push them into neural stem cells," Shetty said.

Although the way the grafted cells thrived is promising, there is still a good deal of work to be done to determine if the extra grey matter actually improves cognition.

"Next, we want to test what impact, if any, the implanted cells have on behavior and determine if implanting neural stem cells can actually reverse age-related learning and memory deficits," Shetty said. "That's an area that we'd like to study in the future. I'm always interested in ways to rejuvenate the aged brain to promote successful aging, which we see when elderly persons exhibit normal cognitive function and the ability to make memories."

Story Source:

The above post is reprinted from materials provided by **Texas A&M University**. *Note: Materials may be edited for content and length.*

Journal Reference:

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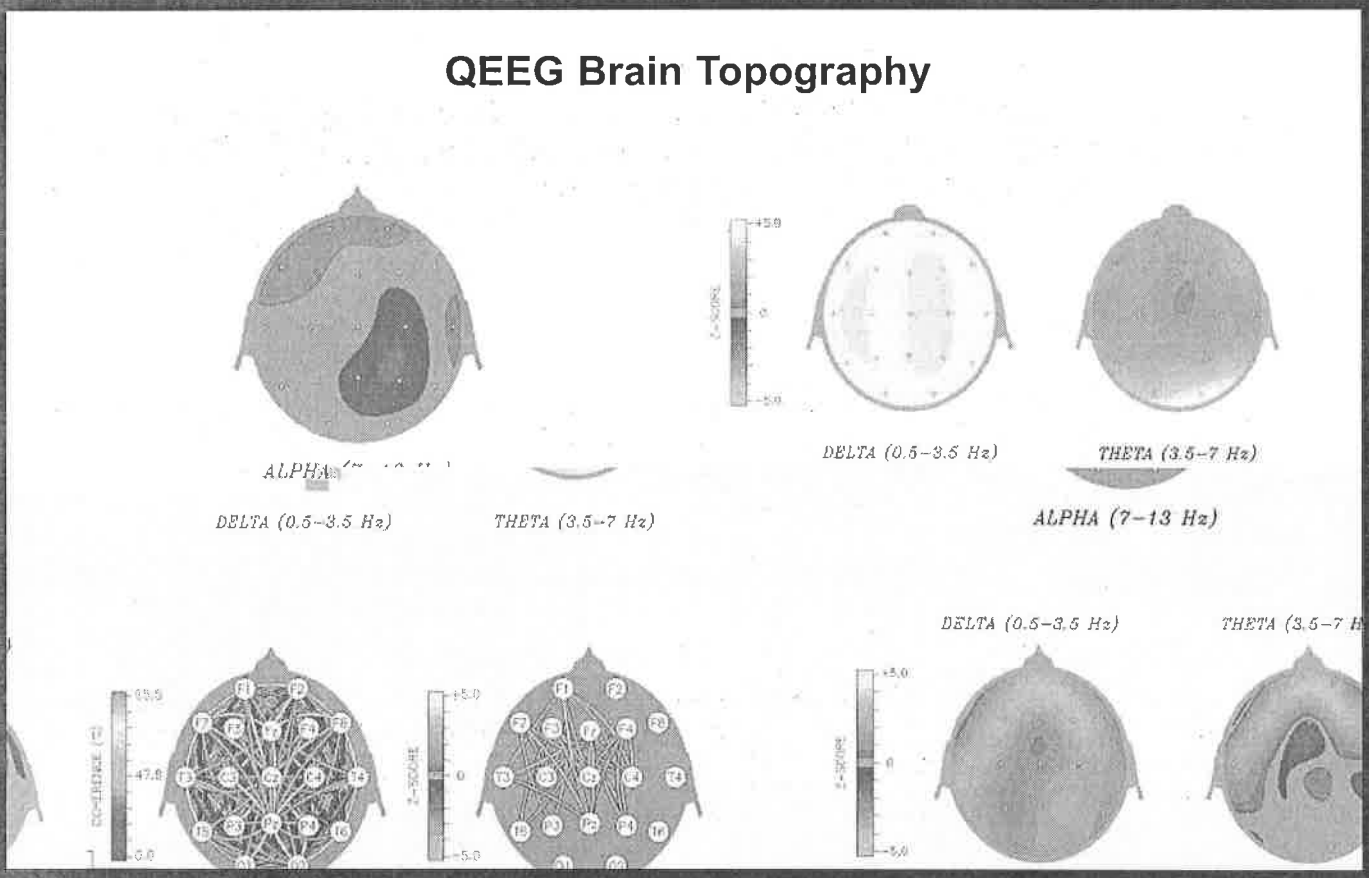
QEEG Testing Can Discern Reason for Cognitive Disorder:

Digital EEG Recordings of Brainwaves Can Determine TBI Etiology

By Gerald Tramontano Ph.D.



Brain mapping works by allowing a neuropsychologist to compare diagnostic and normal databases. Are the QEEG parameters, such as frequency, amplitude, coherence, and morphology, consistent with a traumatic brain injury? Or, are they consistent with a preexisting condition like lupus, dementia, attention deficit disorder, or schizophrenia? We can determine with a high probability—more than 95 percent—whether the disorder is due to one or the other.

A young woman was referred to us by her attorney, who wanted to prove that his client's dysexecutive syndrome—a cognitive disorder marked by a limited ability to problem solve, retrieve, and organize information, which impaired her ability to function both at work and home—was the result of the mild traumatic brain injury (TBI) she suffered in a car accident.

The attorney, a savvy litigator, knew that opposing counsel would readily accept the findings of earlier neuropsychological testing that revealed a brain disorder, i.e., cortical pathology. However, he was convinced that his adversary would challenge whether or not the auto accident was the cause, contending that the woman's confusion was just as likely to be the result of her ongoing battle with systemic lupus erythematosus (SLE) as the head trauma she ostensibly received in the auto accident.

This is exactly where the use of an effective but underemployed test called QEEG, or Quantitative EEG (also known as brain mapping), becomes critical. While hardly a new modality—the observation of electrical signals from the brain first occurred in the mid-nineteenth century and the electroencephalograph (EEG) dates back to the 1920s—it was the advent of digital computers in the late 1960s and early 1970s that first gave experts the ability to detect the subtle and unique patterns in the brainwaves associated with different psychiatric and neurological conditions for the purposes of both treatment and diagnosis.

QEEG is an extremely sensitive measure of the physiological changes of the brain. According to the American Academy of Neurology, it is defined as the "mathematical processing of digitally recorded EEG in order to highlight specific waveform components, transform the EEG into a format or domain that elucidates relevant information, or associate numerical results with the EEG data for subsequent review or comparison." Studies have shown that the very earliest changes associated with Alzheimer's dementia, such as retention and naming deficits, will correlate with a specific QEEG profile unique to the brain pathology due to a dementia of the Alzheimer's type. This is the kind of sensitivity that can help differentiate among neurological disorders such as Alzheimer's disease, lupus, a head injury, or multiple sclerosis.

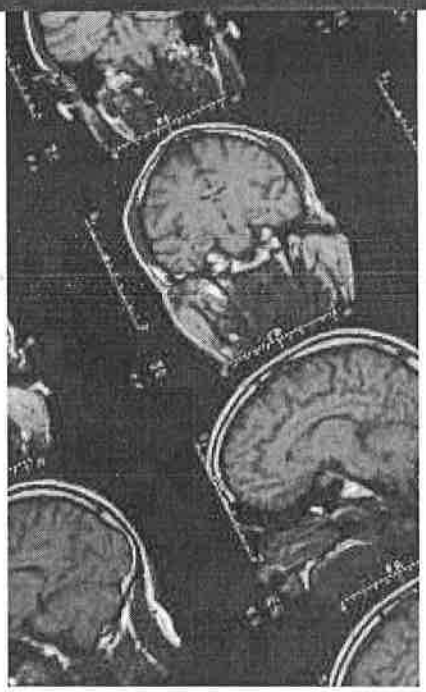
QEEG provides a digital reading from the scalp based on electrical patterns of the cortex, which measures cortical electrical activity or brainwaves. It can help determine whether a cognitive injury is due to trauma or some preexisting neurological or psychiatric illness by taking the EEG information and transforming every little wave and wiggle through a computer program into binary numbers or metrics. These are then run through databases to see what the probability of the overlap is with patients suffering from a specific disorder.

Though easy-to-use, non-invasive, affordable, and hardly an obscure test (with plenty of available literature), QEEG is probably not widely used in forensics for the simple reason that it is not found in every brain injury clinic or neuropsychology practice. In fact, I first came across QEEG quite accidentally ten or twelve years ago while directing the brain injury program at Kessler Rehabilitation Center, a renowned brain injury center that did not offer this kind of testing at the time. We needed to explore baseline metrics for an intervention called "neurofeedback" and, through my research, learned of the benefits of QEEG.

The test is reimbursed by virtually all major insurance companies as part of a comprehensive central nervous system assessment. Clients can be referred by their attorney for a QEEG workup as part of a neuropsychology evaluation. Note that even without insurance coverage the cost of the testing is quite reasonable, on average $450.

QEEG is admissible in court by virtue of the Daubert criteria of the scientific method, which replaced the Frye standards of "general acceptance" in establishing the standards for admissibility of evidence in federal court in a 1993 Supreme Court decision. Since 1923, the Frye test had held that expert testimony that is based upon a scientific testimony is inadmissible unless the technique is "generally accepted in the scientific community."

The Daubert guidelines for scientific validity are 1) hypothesis testing, 2) estimates of error rates, 3) peer-reviewed publication, and 4) general acceptability in the scientific community. The peer-reviewed literature of Quantitative EEG meets all of the Daubert standards of scientific knowledge.



Studies have shown that the very earliest changes associated with Alzheimer's dementia, such as retention and naming deficits, will correlate with a specific QEEG profile unique to the brain pathology due to a dementia of the Alzheimer's type. This is the kind of sensitivity that can help differentiate among neurological disorders such as Alzheimer's disease, lupus, a head injury, or multiple sclerosis.

Furthermore, the science and technical aspects of QEEG in measuring the effects of neurological and psychiatric dysfunction also match the Supreme Court standards of "technical" and "other specialized" knowledge. Finally, it has been shown that QEEG scientific knowledge and "technical" and "other specialized" knowledge meet the standards of Supreme Court rulings in support of QEEG's admissibility as a clinically valid method in the evaluation of the nature and extent of neurological and psychiatric disorders.

Brain mapping works by allowing a neuropsychologist to compare diagnostic and normal databases. Are the QEEG parameters, such as frequency, amplitude, coherence, and morphology, consistent with a traumatic brain injury? Or, are they consistent with a preexisting condi-

(Please see next page)

tion like lupus, dementia, attention deficit disorder, or schizophrenia? We can determine with a high probability—more than 95 percent—whether the disorder is due to one or the other.

Neuropsychological Testing: A Prerequisite for QEEG

In my opinion, a QEEG is to be used as part of a comprehensive neuropsychological assessment. Neuropsychological testing assesses cortical functions largely through computerized and paper-and-pencil tests of various cognitive functions. Although there is overlap with traditional neurological and psychiatric exams, neuropsychological examinations are much more sensitive to cortical pathology, even when there is little if any cognitive impairment or memory loss. For instance, neuropsychological testing may reveal extensive personality, interpersonal, and behavioral changes that are consistent with an injury to certain brain structures or systems, such as the orbital frontal structures of the brain. In fact, this is the part of the brain most responsible for controlling emotion and social functioning, an area where virtually no cognitive networks exist. Since cognition often remains intact, it cannot be diagnosed by traditional cognitive tests.

Attorneys need to be aware that the victim of a mild TBI may suffer not only from cognitive disorders, such as dysexecutive syndrome or memory loss, but also from non-cognitive disorders like "Organic Personality Syndrome," (OPS) which, simply put, means that they don't regulate their emotions or interpersonal world well or make appropriate social judgments like they did before their injury. Depending on the extent of brain damage, OPS can occur with or without cognitive dysfunction. The typical OPS patient post-injury usually experiences a loss or decreased sense of smell, impulsivity, low frustration tolerance, mood swings, and sometimes attention deficits.

In the case of the young woman mentioned above, the results of her neuropsychological testing were consistent with a probable mild TBI from a motor vehicle accident manifesting as a moderate to severe dysexecutive syndrome. However, as previously indicated, she also suffers from SLE. Patients with this condition can present with a dysexecutive syndrome even without any past history of acute encephalopathy from lupus. The question in her case was whether the dysexecutive syndrome was due to the accident, the preexisting condition, or both.

The QEEG Test

In this woman's case, neuropsychological testing had been positive, showing a cognitive disorder. We then administered a QEEG, which takes no more than sixty minutes and involves the patient putting on what looks like a bathing cap with electrodes. We recorded the patient's brain activity with her eyes open and closed and conducted various cognitive-challenging tasks that provided additional information. The computer compared her abnormal activity against databases for different clinical populations. We determined that the probability that the abnormality had been caused or at least significantly exacerbated by a TBI, rather than lupus, to be 99 percent. This made for a very compelling piece of evidence.

Hospitals and clinics offering QEEG testing can be found online. Finding expert witnesses schooled in QEEG will be more difficult.

Documentation of the reliability of QEEG testing is critical in any evidentiary hearing regarding its admissibility. Plaintiff or defense attorney should ask that expert witnesses produce documents showing the reliability of the QEEG samples. According to an April 2003 article in *Clinical Electroencephalography*, "An attorney should ask any expert witness as to his or her familiarity with the peer-reviewed scientific research in support of QEEG and TBI. The expert must be familiar with the peer-reviewed literature, and preferably, also by publishing peer-reviewed papers him/her self and having first-hand experience."[1]

Attorneys can search the National Library of Medicine Web site[2] using the keyword "QEEG" to find a printed listing and determine the expert's knowledge of these articles.

Summary

QEEG and other growing database approaches used to assess cortical functioning together with neuropsychological testing have come a long way and continue to evolve in diagnostic sensitivity and specificity. Together, QEEG and neuropsychological testing permit us to detect subtle changes in central nervous system (CNS) functioning associated with different psychiatric and neurological conditions. Not only have these advances helped clinicians in diagnosing and treating patients, but these cortical assessment tools can also help attorneys litigate and defend for their clients. CL

Dr. Gerald Tramontano, a clinical neuropsychologist, is the clinical director of the NeuroRehab Institute, with offices in Mt. Arlington, Wayne, and Newark, NJ, as well as a clinical assistant professor of psychiatry at UMDNJ-Robert Wood Medical School and an adjunct assistant professor of psychology in neuropsychology at St. John's University. He can be contacted at gtramontano@neurorehabinstitute.com.

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2. The National Library of Medicine Web site search is available at www.ncbi.nlm.nih.gov/entrez/query.fcgi.

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A Case Series

Fluoroscopically Guided Cervical Prolotherapy for Instability with Blinded Pre and Post Radiographic Reading

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Background: Several authors have postulated that cervical instability is a major cause of traumatic spinal pain.

Objective: The purpose of this prospective case series study (n = 6) was to determine if proliferant injections have an effect on cervical translation as measured by a blinded reader.

Design: This study was a prospective case series. Study participants were selected from patients seen for the primary complaint of Motor Vehicle Collision related neck pain in a private sub-specialty pain clinic.

Methods: Flexion and extension views were obtained by standard radiographs taken with a C-Arm fluoroscope under Valium sedation. Patients with more than 2.7 mm of absolute cervical translation and at least 50% reduction of cervical and referred pain with a two day rigid cervical immobilization test were admitted into the study. Participants underwent 3 prolotherapy injections at all sites that demonstrated translation. The difference in means between pre-test and post-test measurements (flexion translation, extension translation, and pain VAS scores) were assessed by a Wilcoxon signed ranks test (alpha = 0.05).

Results: The mean post-test VAS score (M= 3.83, SD=2.3, t=2.889) was significantly less (p=0.04) than the mean pre-test VAS score (M=5.75, SD=1.94). The correlation between difference in mean extension at C2-3 and C5-6 and difference in mean extension was significant (rho=0.89, p=0.02 and rho=0.85, p=0.03 respectively). Difference in mean flexion at C3-4 and C4-5 was significantly correlated with difference in mean flexion (rho=0.88, p=0.02 and rho=0.941, p<0.01 respectively).

Conclusions: The results of this study demonstrate statistically significant correlations between proliferant injections, a reduction of both cervical flexion and extension translation, as well as a reduction in pain VAS score. Since patients with traumatic cervical instability have few viable treatment options other than surgical fusion, cervical proliferant injections under C-Arm fluoroscope may be a viable treatment option.

Keywords: Prolotherapy, cervical instability, flexion, extension, injection, whiplash, neck

Several authors have postulated that instability is a major cause of traumatic spinal pain. Dvorak (1) reported increased upper and mid-cervical hypermobility in a cervical spine trauma group in comparison of trauma versus degenerative pain. In addition, Panjabi et al (2) have reported a biomechanical investigation of increases in the "neutral zone" of the cervical spine as a result of trauma, with significant increases noted in the neutral zone with experimental accelerations of as low as 4.5 g. Most recently, Kristjansson et al (3) have published a report showing that whiplash patients had objectively increased translational and rotational movements when compared with controls.

The idea that instability may be associated with pain and neurologic compromise is not new. Grob (4) performed an experimental protocol on patients with cervical soft tissue injury by applying an external fixator in random patterns. The external fixation applied in a single blinded fashion over presumed unstable segments gave pain relief, while fixation over normal segments provided no relief. Ebraheim et al (5) has determined that lower cervical translation in flexion can have serious negative impacts on spinal canal diameter. In addition, spinal canal volume in normal patients is reduced by both flexion and extension (6). Normal foraminal width in the cervical spine is on the order of millimeters (7). In addition, static foraminal widths decrease significantly with age (8).

The standard for measuring cervical instability is usually considered to be cervical flexion extension radiography. However, Dvorak et al (1) have determined that routine non-stress films may have a significant false-negative rate. This study confirmed that routine active flexion-extension radiographs missed some 39% of levels determined to be unstable on passive examination with over-pressure (9). White et al (10) have produced normal values for flexion-extension radiography. White and Panjabi (10) studied an isolated cervical segment by cutting ligamentous constraints and determining movement. They determined that the segment became unstable at 2.7 mm of absolute movement or 3.5 mm of magnified movement on a 72 inch lateral x-ray. Since that time, normal studies in-vivo have been performed. Knopp et al (11) defined abnormal motion as more than 2 mm of movement at end range flexion. Lin et al (12) also published a series of 100 normals with population norms for patients. If one factors out the "hypermobile" individuals (defined by Lin et al as having significant translation at the C2-C3 level), the amount of normal translation was al-

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ways less than 1 mm.

The purpose of this study was to determine if proliferant injections have an effect on objectively measured cervical translation as measured by a blinded reader.

Methods

This was a prospective case series study of patients seen for the primary complaint of Motor Vehicle Collision related neck pain in a private sub-specialty pain clinic.

Inclusion criteria were:

- Prior history of an motor vehicle collision (MVC)
- Ongoing disability resulting from cervical spine pain for longer than six (6) months related to the MVC
- Cervical flexion extension x-rays that were abnormal either based on the Knopp criteria (2mm or more translation at end range flexion) or the White and Panjabi criteria (2.7mm or more of absolute cervical translation)
- 50% or greater reduction of pain with 48 hour rigid cervical immobilization
- Failure of conservative management (physical therapy and or chiropractic and or alternative care)

Exclusion criteria were:

- History of previous neck pain with a neck injury
- Connective tissue disease
- Rheumatoid arthritis
- Diabetes I or II
- Inflammatory arthritis.

Eligible patients (n=6) were identified from consecutive patients presenting for care who were found to be unstable. The setting was a specialty pain management private practice. The Institutional Review Board (IRB) approval was obtained for the pilot study through a Department of Health and Human Services registered IRB (The Spinal Injury Foundation). Informed consent was obtained.

Flexion and extension views were obtained by standard radiographs taken with a C-Arm fluoroscope with diazepam sedation (10 mg Oral), overpressure into end range flexion and extension, and stabilization of the torso. A radiographic ruler was included in the x-ray field in the same plane as the c-spine for accuracy and to rule out magnification effects between radiographs. Flexion and extension translation were measured by comparing translation to the radiographic ruler and then was recording these measurements in millimeters.

Patients with more than 2.7 mm of absolute cervical translation (3.5 mm of magnified movement on a 72 inch lateral x-ray) and at least 50% reduction of cervical and referred pain with a two day rigid cervical immobilization test were admitted into the study. Six consecutive patients with 11 unstable levels met the inclusion criteria. A blinded reader was used to assess instability before and after proliferant injections. Blinding was accomplished by identifying the films with only a letters and numbers. The reader then recorded the translation in maximum flexion to maximum extension from posterior inferior corner to adjacent posterior superior corner of the cervical vertebra.

Patients underwent 3 prolotherapy series at all sites that demonstrated translation. The number of injections per series were determined by applying the Hackett technique to all unstable levels. The patient was placed prone on an x-ray table and a C-Arm fluoroscope was used to image the c-spine in an AP view. Cephalad tilt was applied to move the skull base out of the field of view. After IV anesthesia was applied, a 25 gauge two or three inch spinal needle (depending on patient body habitus) was used to perform the injections. Injectate consisted of a final concentration of 12.5% dextrose diluted with normal saline and 1-2 cc of lidocaine per 10 cc added for patient comfort. At the unstable levels, several structures were injected when bone was contacted at the unstable level(s) as well as above and below these levels. These structures included: the spinous processes, lamina, and posterior elements according to the technique outlined by Hackett (13). The C-Arm was used to confirm needle position prior to injection

Outcome measures included average neck pain on a modified VAS (1-10) Scale. This was administered 2-4 weeks prior to the injections and one month post injection. Patients refrained from all other types of care for the duration of the study.

Since all variables were not normally distributed, the difference in means between pre-test and post-test measurements were assessed by a Wilcoxon signed ranks test (alpha = 0.05). Bivariate correlations using Spearman's rho were computed among the four outcome measures: mean difference flexion, mean difference in extension, mean difference in overall translation, and mean difference in pain (alpha = 0.05), as well as with all mean translation measures at individual levels of injection for both flexion and extension.

Results

Figure 1 and 2 below show the changes in translation in both flexion and extension for all patients by vertebral level as a result of the treatment. Perhaps the most striking feature is the more dramatic effect of the treatment in flexion ver-

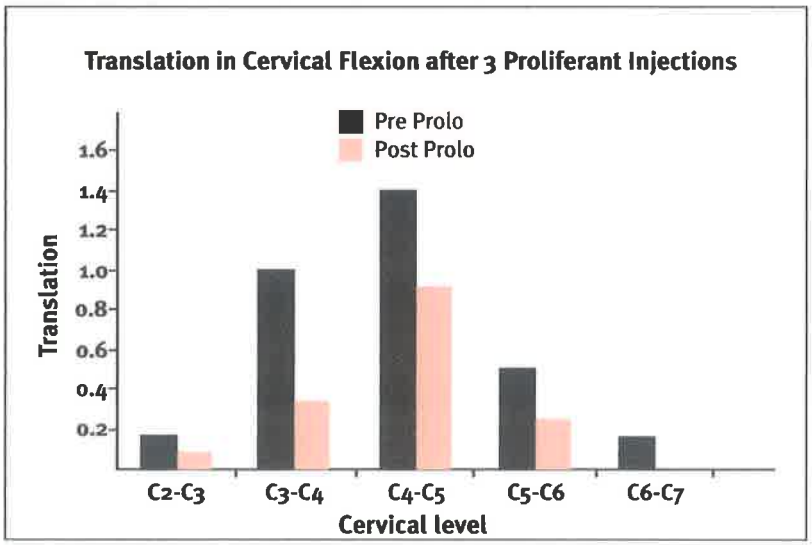

Fig 1. *Translation in cervical flexion after 3 proliferant injections*

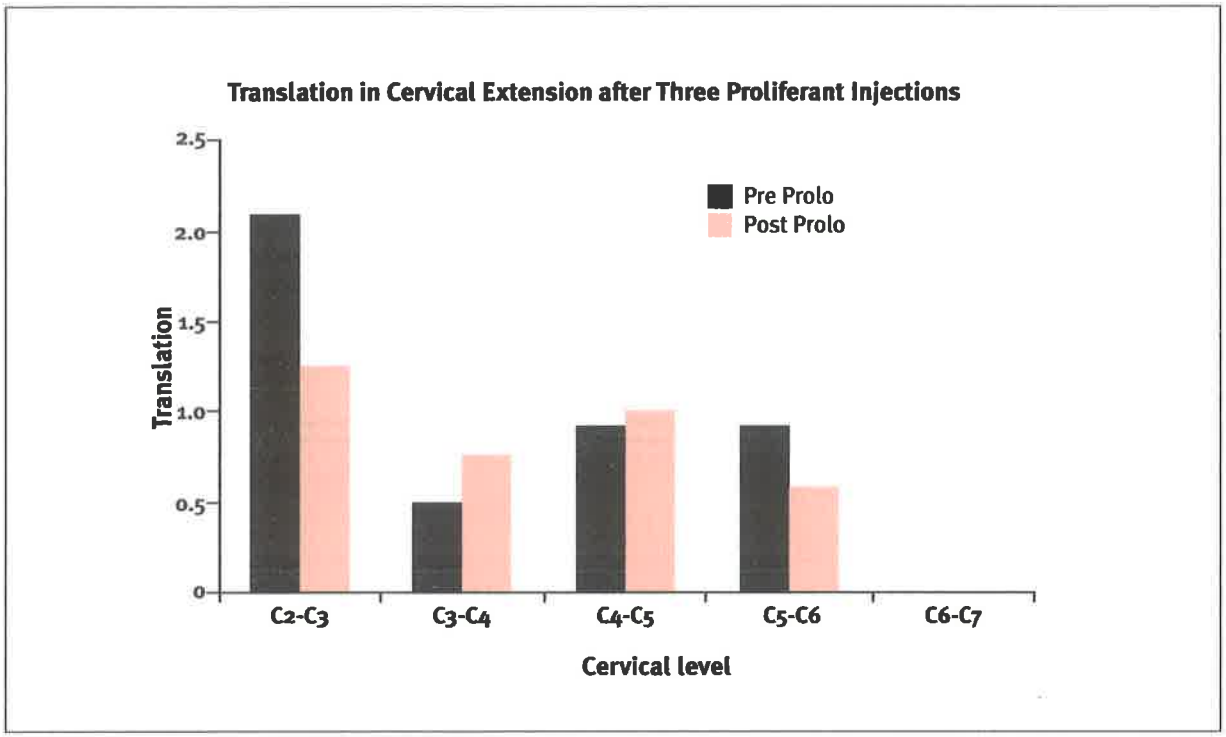

Fig 2. *Translation in Cervical Extension after 3 Proliferant Injections*

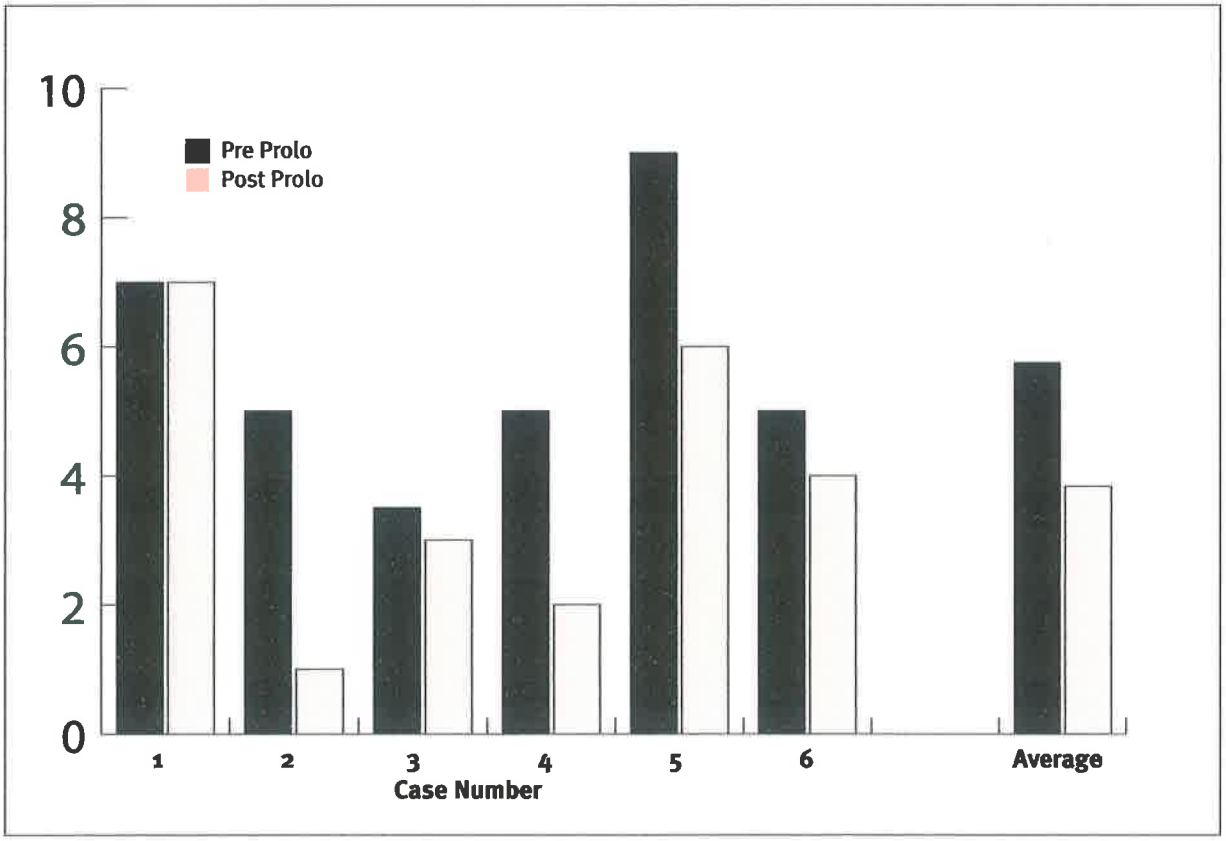

Fig 3. *Average VAS scores after 3 cervical proliferant injections*

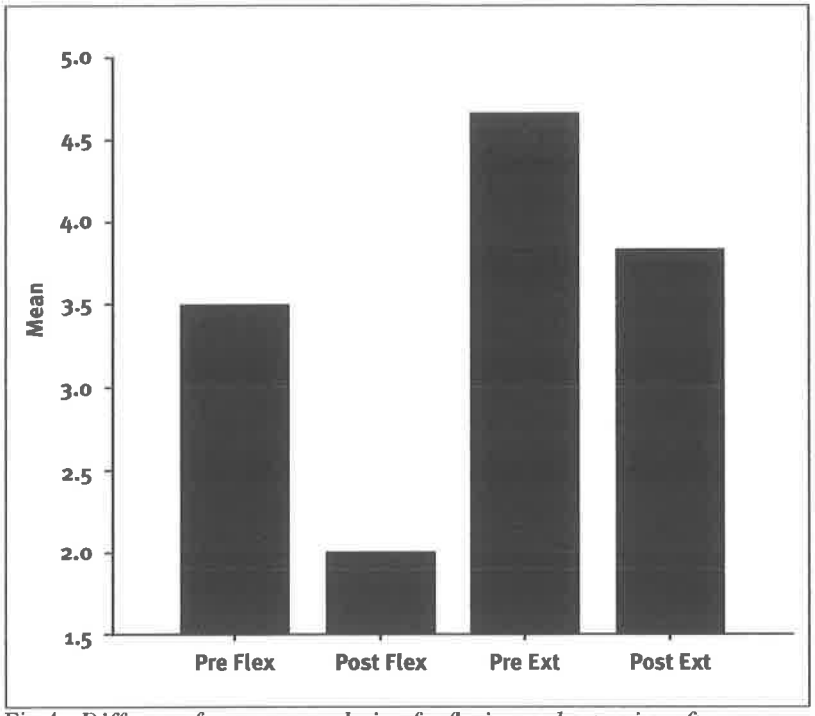

Fig 4. *Difference for mean translation for flexion and extension after 3 cervical proliferant injections*

Table 1. *Correlations of outcome measurements (Spearman's rho Correlation Coefficient)*

	Diff Trans	Diff Flex	Diff Ext	Diff Vas
Diff Trans	1.000	.943(**)	.147	-.883(*)
Diff Flex	.943(**)	1.000	.029	-.794
Diff Ext	.147	.029	1.000	.076
Diff Vas	-.883(*)	-.794	.076	1.000

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 2. *Correlations of outcome measurements with level of extension (Spearman's rho Correlation Coefficient)*

	Diff Ext 2-3	Diff Ext 3-4	Diff Ext 4-5	Diff Ext 5-6	Diff Ext	Diff Trans	Diff Vas
Diff Ext 2-3	1.000	.131	.822(*)	.671	.890(*)	.062	.111
Diff Ext 3-4	.131	1.000	.180	.220	.469	.334	.063
Diff Ext 4-5	.822(*)	.180	1.000	.612	.783	.507	-.348
Diff Ext 5-6	.671	.220	.612	1.000	.853(*)	.000	.000
Diff Ext	.890(*)	.469	.783	.853(*)	1.000	.147	.076
Diff Trans	.062	.334	.507	.000	.147	1.000	-.883(*)
Diff Vas	.111	.063	-.348	.000	.076	-.883(*)	1.000

* Correlation is significant at the 0.05 level (2-tailed).

sus extension. Figure 3 illustrates the decrease in pre-test and post-test VAS scores for individual cases and average scores.

A Wilcoxon signed ranks test was conducted to evaluate whether difference in mean flexion, difference in mean extension, and difference in mean pain VAS scores differed after treatment with cervical prolotherapy. Figure 4 shows the mean decrease in flexion translation (pre-test to post-test) and extension (pre-test to post-test). These findings are not statistically significant due to the small number of test subjects ($p=0.36$ and $p=0.40$ respectively).

However, the results did indicate that the mean post-test VAS score ($M=3.83$, $SD=2.3$, $t=2.889$) was significantly less ($p=0.04$) than the mean pre-test VAS score ($M=5.75$, $SD=1.94$) as illustrated in Figure 3. Furthermore, difference in mean pain VAS correlated significantly with difference in mean translation (Table 1, rho=-0.88, $p=0.02$). Additional correlation coefficients were computed among the four outcome measurements (as presented in Table 1) with difference in mean flexion and difference of mean translation correlating significantly (rho=0.94, $p<0.01$).

Table 2 shows the correlation coefficients between the four outcome measures and difference in mean extension at each cervical level. The correlation between difference in mean extension at C2-3 and C5-6 and difference in mean total extension for all levels was significant (rho=0.89, $p=0.02$ and rho=0.85, $p=0.03$ respectively).

Table 3 shows the correlation coefficients between the four outcome measures and difference in mean flexion at each cervical level. Difference in mean flexion at C3-4 and C4-5 was significantly correlated with difference in mean total flexion for all levels (rho=0.88, $p=0.02$ and rho=0.941, $p<0.01$ respectively).

Discussion

This analysis demonstrated that the treatment decreases flexion translation more than extension translation. In addition, there was a correlation between decrease in translation and change in VAS score (pain relief). The type of effect seen here is important. Since this cervical prolotherapy technique only treats the posterior column of the spine and thus only treats the main ligamentous check to flexion, one would expect that translation

Table 3. *Correlations of outcome measurements with level of flexion (Spearman's rho Correlation Coefficient)*

	Diff Flex 2-3	Diff Flex 3-4	Diff Flex 4-5	Diff Flex 5-6	Diff Flex 6-7	Diff Flex	Diff Trans	Diff Vas
Diff Flex 2-3	1.000	.348	.718	.000	.000	.676	.676	-.348
Diff Flex 3-4	.348	1.000	.719	.674	.674	.883(*)	.794	-.864(*)
Diff Flex 4-5	.718	.719	1.000	.696	.696	.941(**)	.941(**)	-.719
Diff Flex 5-6	.000	.674	.696	1.000	1.000(**)	.655	.655	-.674
Diff Flex 6-7	.000	.674	.696	1.000(**)	1.000	.655	.655	-.674
Diff Flex	.676	.883(*)	.941(**)	.655	.655	1.000	.943(**)	-.794
Diff Trans	.676	.794	.941(**)	.655	.655	.943(**)	1.000	-.883(*)
Diff Vas	-.348	-.864(*)	-.719	-.674	-.674	-.794	-.883(*)	1.000

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

in flexion would be more impacted than translation in extension. Since the anterior column was not treated, it is not surprising extension showed smaller reductions in translation. This agreement between objective experimental data at 11 levels and the areas treated suggests that cervical prolotherapy likely had an impact on segmental translation among our study subjects.

The use of proliferants to treat pain and instability has a long history. In a double blind study, Liu et al (14) injected the medial collateral ligament on rabbits and showed that through repeated injections of 5% sodium morrhuate at the fibroosseous attachments, the bone-ligament-bone junction strength was significantly increased by 28%, ligament mass increased by 44%, and thickness increased by 27% when compared to saline (14). Highly significant increases in the diameter of collagen fibrils in the experimental ligaments vs. controls were demonstrated by morphometric analysis of electron micrographs.

In a double blind clinical study by Ongley et al (15), 81 patients with chronic lower-back pain were injected with proliferants. It was found that significant improvement was seen in more than 50% of patients injected with Dextrose/Phenol/Glycerin vs. saline. In addition, Ongley demonstrated a significant statistical improvement in five patients treated for painful instability of the knees with prolotherapy. Three-dimensional computerized goniometry integrated with force measurements were used to collect ligament stability data. More successful results were seen by Bourdeau (16) who published a 5-year retrospective survey of patients with lower back pain treated with prolotherapy. In the study, 70% (17 patients) reported a successful treatment.

Klein et al (17) was able to histologically document proliferation and regeneration of ligaments in human patients in response to injections of the DPG solution. In addition Klein et al (17) recorded decreased pain and increased range of motion via computerized inclinometry.

In a study of 43 patients with chronic sacroiliac strain, Schwartz et al (18) gave patients a series of three proliferant injections at biweekly intervals. An improvement was seen in all but three patients; 95% improvement was reported in 20 patients 66% improvement was seen in 4 patients, and 10 patients reported recurrence. With this, Schwartz concluded that induced proliferation of collagen and dense connective tissue of the ligament is associated with a reduction of painful subluxations.

Klein et al (19) presented a double blind clinical study of 79 patients who had previously failed to respond positively to conservative treatment for chronic lower back pain. The subjects were randomly assigned to a test group to receive a series of six injections into the posterior sacroiliac and interspinous ligaments, fascia, and facet capsules of the low back from L-4 to the sacrum of either lidocaine/saline or lidocaine/DPG solution in a double blind fashion at weekly intervals. For comparative purposes, all patients underwent pretreatment MRI of CT scans. Following the conclusion of injections patients were evaluated after 6 months using several criteria: visual analog, disability, pain grid scored, and with objective computerized triaxial tests of lumbar function. In the proliferant group, 30 of the 39 patients randomly assigned achieved a 50% or greater decrease in pain or disability scored compared to 21 of 40 in the lidocaine group (p=0.042). In addition, improvements were seen in visual analog (p=0.056), disability (p=0.068), and pain grid scores (p=0.025) for the proliferant group.

A double blind, placebo controlled study demonstrated the benefits of 10% dextrose with lidocaine in knee osteoarthritis with anterior cruciate ligament laxity (20). Goniometric flexion measurements improved by 12.8% (p=0.005) and anterior displacement difference improved by 57% (p=0.025). Dextrose treated knees improved in many measured categories: pain decreased 44%, swelling complaints decreased 63%, knee buckling frequency decreased 85%, and flexion range had an increase of 14° after a 12 month (six injection) treatment. Thus, it was concluded that stimulated growth factors and regeneration occurred after proliferant injection with 10% dextrose solution. This resulted in statistically significant clinical improvements in knee osteoarthritis.

While the small number of patients in this study precludes large scale statistical analysis, the correlational statistics do demonstrate significance in the directions hypothesized. This may prove to be an important correlation, as there are little published data on cervical translation and pain complaints.

Although other authors have published outcome studies on cervical prolotherapy(21,22), this paper represents the first report of image guided cervical prolotherapy with objective changes measured radiographically.

Conclusion

The results of this study demonstrate statistically significant correlations between proliferant injections, a reduc-

tion of both cervical flexion and extension translation, as well as a reduction in pain VAS score. Since patients with traumatic cervical instability have few viable treatment options other than surgical fusion, cervical proliferant injections under C-Arm fluoroscope may be a viable treatment option.

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Original paper

RANDOMIZED PROSPECTIVE DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF DEXTROSE PROLOTHERAPY FOR KNEE OSTEOARTHRITIS WITH OR WITHOUT ACL LAXITY

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Context • *Use of prolotherapy (injection of growth factors or growth factor stimulators).*
Objective • *Determine the effects of dextrose prolotherapy on knee osteoarthritis with or without anterior cruciate ligament (ACL) laxity.*
Design • *Prospective randomized double-blind placebo-controlled trial.*
Setting • *Outpatient physical medicine clinic.*
Patients or other participants • *Six months or more of pain along with either grade 2 or more joint narrowing or grade 2 or more osteophytic change in any knee compartment. A total of 38 knees were completely void of cartilage radiographically in at least 1 compartment.*
Intervention • *Three bimonthly injections of 9 cc of either 10% dextrose and .075% lidocaine in bacteriostatic water (active solution) versus an identical control solution absent 10% dextrose. The dextrose-treated joints then received 3 further bimonthly injections of 10% dextrose in open-label fashion.*
Main Outcome Measures • *Visual analogue scale for pain and swelling, frequency of leg buckling, goniometrically measured flexion, radiographic measures of joint narrowing and osteophytosis, and KT1000-measured anterior displacement difference (ADD).*
Results • *All knees: Hotelling multivariate analysis of paired observations between 0 and 6 months for pain, swelling, buckling episodes, and knee flexion range revealed significantly more benefit from the dextrose injection (*P*=.015). By 12 months (6 injections) the dextrose-treated knees improved in pain (44% decrease), swelling complaints (63% decrease), knee buckling frequency (85% decrease), and in flexion range (14 degree increase). Analysis of blinded radiographic readings of 0- and 12-month films revealed stability of all radiographic variables except for 2 variables which improved with statistical significance. (Lateral patellofemoral cartilage thickness [*P*=.019] and distal femur width in mm [*P*=.021]. Knees with ACL laxity: 6-month (3 injection) data revealed no significant improvement. However, Hotelling multivariate analysis of paired values at 0 and 12 months for pain, swelling, joint flexion, and joint laxity in the dextrose-treated knees, revealed a statistically significant improvement (*P*=.021). Individual paired* t *tests indicated that blinded measurement of goniometric knee flexion range improved by 12.8 degrees (*P*=.005), and ADD improved by 57% (*P*=.025). Eight out of 13 dextrose-treated knees with ACL laxity were no longer lax at the conclusion of 1 year.*
Conclusion • *Prolotherapy injection with 10% dextrose resulted in clinically and statistically significant improvements in knee osteoarthritis. Preliminary blinded radiographic readings (1-year films, with 3-year total follow-up period planned) demonstrated improvement in several measures of osteoarthritic severity. ACL laxity, when present in these osteoarthritic patients, improved. (Altern Ther Health Med. 2000;6(1):68-80)*

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INTRODUCTION

Prolotherapy (*injection of growth factors or growth factor stimulators*) raises growth factor levels or increases growth factor effectiveness to promote tissue repair or growth. The most common solutions used for prolotherapy create a brief inflammatory response. Temporary cellular stress causes a release of cytokines and increased growth factor activity with migration of macrophages (white blood cells), and then multiplication of repair cells specific to the tissue. Unlike repair after an injury, disruption of architecture of tissue from injury does not occur, and new cells and matrix can be deposited in an organized fashion, with maturation of new tissue for 6 to 8 weeks.[1] Two double-blind studies have been performed on prolotherapy in low back pain using inflammatory solutions.[2,3] These studies both showed significant benefit from proliferant injection, but because the solutions were inflammatory there was some potential for impairment of double-blind protocol. The purpose of this investigation was to evaluate effectiveness of prolotherapy without using any inflammatory mechanism so that neither patient, research coordinator

nor primary investigator would have any way to determine patient group. Our specific plan was to study the effect of a non-inflammatory (10%) concentration of dextrose (D-glucose in water) on knee osteoarthritis patients via objective measures of knee cartilage, knee osteophytic status, and knee goniometric range, as well as by subjective measures of knee pain, knee swelling, and knee buckling.

Some patients in the study had anterior cruciate ligament (ACL) laxity, which is known to initiate and worsen knee osteoarthritis. A second purpose for this study was to observe the effect of proliferant injection on laxity of the ACL, as measured by an objective and reproducible measure (an electroarthrometer).

Elevation of extracellular glucose to as little as .5% (normal extracellular and cellular glucose is .1%) has been shown to raise levels of multiple polypeptide growth factors in a variety of human cells.[4-8] Exposure of several human cells to a hypertonic environment will also promptly result in a rise in DNA levels for growth factors within seconds to minutes.[9,10] Therefore, hypertonic dextrose solution has 2 mechanisms by which to increase levels of growth factors, potentially improving the status of critical cells in the joint such as chondrocytes (cartilage producing cells), osteocytes (bone producing cells), and fibroblasts (tendon/ligament/other soft tissue producing cells).

METHODS

Ads were placed for patients with knee arthritis to receive injection of a solution to reduce pain in knee osteoarthritis. Criteria for knee osteoarthritis included 6 months or more of pain in the knee, accompanied by either grade 2 or more joint narrowing or grade 2 or more osteophytic change. Grade 2 joint narrowing can be described as the presence of less than or equal to 3 mm of cartilage (found in only 8% without symptomatic knee osteoarthritis [OA]).[11] A grade 2 osteophyte can be described as a short, fat and obvious bone spur or a moderately long (10 mm or more), thin bone spur (found in only 14% without symptomatic knee OA.)[11] A standard radiographic atlas was used to determine joint narrowing and osteophytic grades, which was designed for that purpose.[12]

The ability to verify ACL laxity by any arthrometer requires testing of both knees for an anterior displacement difference (ADD) side to side. Using this method, the KT1000 (Medmetric Corporation, San Diego, Calif) has been shown to be equal to or more reliable than other arthrometers.[13-16] Based on extensive review of previous studies of the KT1000 an ADD of 2 is estimated to be 85% sensitive and 85% specific for ACL laxity.[15,17-19] Since this study was not funded to allow for magnetic resonance imaging (MRI) studies to rule out complete ACL tear, the number of patients with complete ACL tear could not be determined. Note that the objectivity of this electroarthrometer is found in its use of standard positioning of the knee within the device, audible indications when certain pressures are applied to the knee through the device, a precise readout easily visible for recording, and a routine to perform each reading 3 times to average all 3 readings.

Once the patients were found to meet radiologic and symptomological criteria for knee osteoarthritis, they were assigned serially to group 1 or 2 using a random number table by 1 of 2 data base coordinators always in the office. This group assignment was kept in a database blinded to the chief investigator and research coordinator.

The research coordinator obtained an estimate of arthritis medications taken and then demonstrated the use of a 100-mm visual analogue scale (VAS) and gave 3 examples of its use. The patients then self-scored their pain levels of knee pain at rest, knee pain walking on level surfaces, knee pain with stair use, and subjective swelling, and estimated the number of knee buckling episodes over the previous 2 months. Following this, the research coordinator obtained goniometric readings of joint flexion by the method described in a standard text.[20]

Patients who were taking any medication or oral supplement for osteoarthritis other than calcium, multivitamins, NSAIDS, acetaminophen, or occasional narcotic, were asked to discontinue them. The most common oral supplement discontinued was glucosamine/chondroitin sulfate.

Blood was obtained for sedimentation rate, rheumatoid factor, uric acid, and antinuclear antibody. Significant laboratory abnormalities led to referral to primary physician or rheumatologist for determination of the presence or absence of inflammatory arthritis. No patients required exclusion due to the laboratory battery after the initial phone screening.

Dextrose prolotherapy solutions for maximum safety have typically included bacteriostatic water, a small concentration of lidocaine, and dextrose. Because of the desire to maximize safety and comfort in this study and simulate typical prolotherapy solutions, the control was the usual bacteriostatic water with a very small amount of lidocaine, and the active solution was identical except for the inclusion of 10% dextrose.

At 0, 2, and 4 months solution was drawn up blinded to both chief investigator and research coordinator. Using a 27-gauge needle via an inferomedial approach, tibiofemoral injection was conducted with 9 cc of either 611.4 mOsm (10% dextrose and .075% lidocaine in bacteriostatic water) or 105.4 mOsm (.075% lidocaine in bacteriostatic water) solution. Bacteriostatic water consisted of .9% benzyl alcohol. The small dose of lidocaine was included for postinjection comfort. The solutions were identical in color and viscosity. Dextrose at 10% concentration is very slightly sticky if allowed to dry on the skin but Hibiclenz was used for glove and skin prep which masked any potential of noting any slight stickiness of solution.

Treatment continued beyond 6 months in the dextrose group with additional injections at 6, 8, and 10 months. Subjective variables, goniometric flexion, 2-view radiographs and KT-1000 ADD measurements were repeated at 1 year. Skier's (standing) views of the knee were used to determine tibiofemoral compartment status. Angle of knee flexion on skier's views, angle of radiograph beam to the knee, camera to film distance, power and duration of radiograph beam, and radiograph technician were identical at 0 and 12 months. Magnification on standing films was prevented by ensuring contact of patella with film plate. Skyline views of the patella

were used to determine patellofemoral compartment status, with similar measurements, including camera to knee and knee to film distance, to ensure an identical radiograph method.

Radiographs were read in double-blind fashion in the following way. The study coordinator obscured patients' names and labeled the film with a random patient number. The film date was obscured and a random number table was used to assign a number to the 0- and 12-month films. The 0- and 12-month films were then separated in different packets so that reading 1 film would not influence reading of the next. Osteophytic grade was measured in 6 compartments using a standard atlas with approximately 90% intra-reader agreement.[12] The compartments included medial femoral, medial tibial, lateral femoral, lateral tibial, medial patellofemoral, and lateral patellofemoral. Cartilage thickness was determined in 4 compartments in millimeters: medial tibiofemoral, lateral tibiofemoral, medial patellofemoral, and lateral patellofemoral. General hypertrophic change was evaluated as a width measurement in millimeters: distal femur width proximal to the intercondylar notch, distal femur width distal to the intercondylar notch, and proximal tibial width. Width measurements were made parallel with the film bottom edge through the area of largest width, including any osteophytes present. The x-rays were read by the chief investigator. A database coordinator loaded results onto the database.

Human subject research approval and monitoring was by the Institutional Review Committee of Bethany Medical Center in Kansas City, Kans. Procedures followed were in accordance with ethical standards outlined in the Helsinki Declaration Revision of 1983. The statistical analysis software was SPSS (Statistical Program for Social Science) version 7.5.3.

RESULTS

Blinding method problems were not identified. No treatment complications were noted. Seventy-seven patients had 1 or more knees that met study criteria for symptomatic osteoarthritis (OA). Nine patients dropped out over 12 months of followup, 4 due to lack of efficacy (3 in control group and 1 in active group), and 5 for unrelated medical reasons. This left 111 knees in 68 patients with OA.

At study onset 31 patients met arthrometric criteria for ACL laxity. Two dropped out over 12 months due to lack of efficacy and 4 for unrelated medical issues, leaving 25 for analysis.

Independent sample *t* tests were conducted to compare the active and control groups of OA knees. No significant differences were noted between groups for age, weight, pain levels, range of motion, buckling episodes, or radiographic findings. The same result was noted when *t* tests were conducted to compare active and control groups of knees with ACL laxity. The average knee OA patient in this study was 63 years of age and weighed 195 lb. Males comprised 58% of the study population.

Complications and Safety Issues

Discomfort after injection did not appear to vary between groups, typically lasting a few minutes to several days. Despite use of an allergy-size needle (27 gauge) and a single-insertion technique, some patients had pain with distension of the joint capsule even with this minimal volume (9 cc). The 9 cc volume for injection may be a bit excessive in that some patients were inhibited in flexion for several days. One person had a flare postinjection that appeared substantial, requiring interarticular steroid and then referral to an orthopedic surgeon. When blinding was broken she was found to have received control solution.

No allergic reactions or infections were noted.

Six-Month (Double-Blind Phase) Data Comparing Active and Control Solution for all Osteoarthritic Knees

Figure 1 presents a bar graph depicting improvements in pain (average of improvement in pain at rest, pain with walking, and pain with stair use) and swelling for the active and control groups at 6 months (after 3 injections of 9 cc of solution). Both active and hypotonic control solution administration resulted in considerable gains in VAS scores for pain.

Figure 2 shows improvement in knee flexion for both groups at 6 months. Both active and hypotonic control injections resulted in an improvement in goniometric knee flexion measures.

Hotelling multivariate analysis of paired observations between 0 and 6 months for active and control solution including all nonradiographic variables (pain at rest, pain with walking, pain with stair use, swelling, buckling episodes, and flexion range) demonstrated a statistically superior effect of active solution ($P = .015$). The results of individual paired *t* tests from 0 to 6

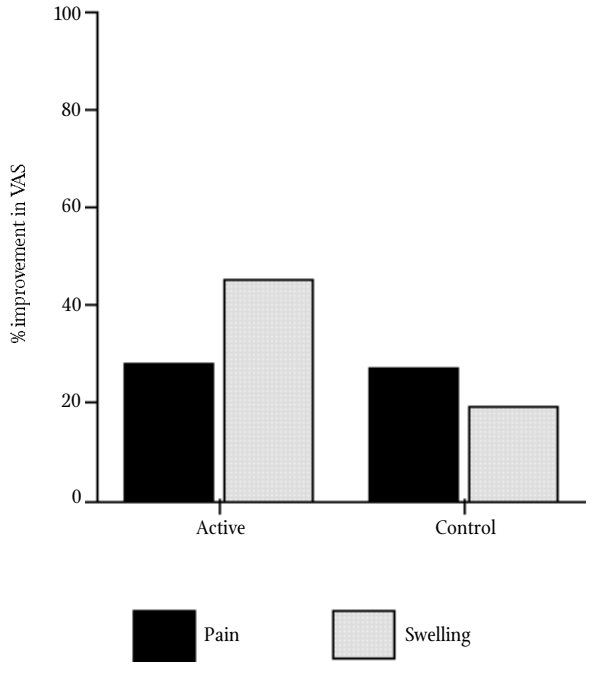

FIGURE 1 Percentage improvement in pain and swelling from study onset to 6 months for active and control solutions.

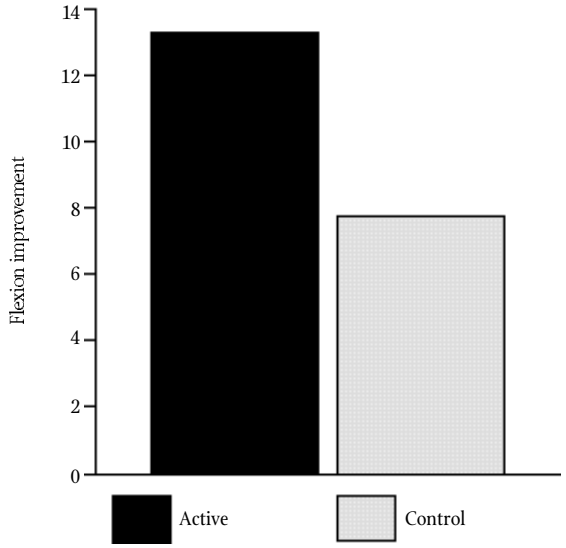

FIGURE 2 Degree improvement in knee flexion range of motion after 3 bimonthly injections of active or control solution.

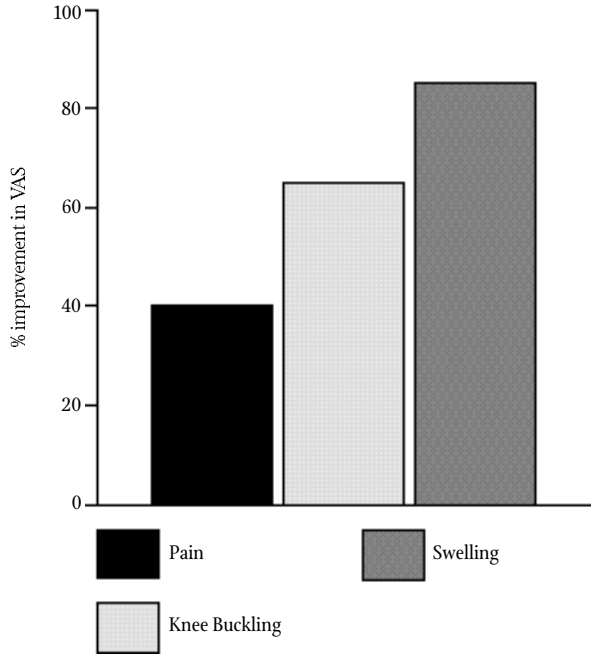

FIGURE 3 Percentage improvement in pain, subjective swelling and number of knee buckling episodes after 6 injections of active solution (at 1-year follow-up).

months for each of the variables are shown in Table 1. Although the active solution was superior statistically, highly significant improvement from 0 to 6 months was seen in pain with walking, pain with stair use, and flexion range of motion in both active and control groups.

The NSAID follow-up question was limited in its ability to determine a degree of change in level of intake, and no significant change between groups was noted. However, neither group had an increase in NSAID intake, which could explain improvement in pain levels or other variables.

One-Year Data (Nonradiographic) for Active Solution for Osteoarthritic Knees

Figure 3 shows percentage improvements in pain and swelling complaints and knee buckling in the dextrose group between 0 and 12 months (with 3 further bimonthly open label injections of dextrose). Pain improved by 40%, swelling by 63%, buckling episodes by 85%, and flexion by 14 degrees as compared with study entry.

Radiographic Data at 1 Year for Active Solution for Osteoarthritic Knees (Table 2)

Thirteen radiographic readings for each knee are shown in Table 2. These variables included medial femoral osteophyte grade (MFOG), medial tibial osteophyte grade (MTOG), lateral femoral osteophyte grade (LFOG), lateral tibial osteophyte grade (LTOG), medial patellofemoral osteophyte grade (MPOG), lateral patellofemoral osteophyte grade (LPOG), medial tibiofemoral cartilage thickness (MTFT), lateral tibiofemoral cartilage thickness (LTFT), medial patellofemoral cartilage thickness (MPFT), lateral patellofemoral cartilage thickness (LPFT), distal femur width proximal to the intercondylar notch (DFWP), distal femur width distal to the intercondylar notch (DFWD), and proximal tibial width (PTW).

Hotelling multivariate analysis of paired observations between 0 and 12 months for the dextrose-treated knees including all 13 radiographic variables revealed a statistically significant change (P=.028). Individual paired t tests showed the means for radiographic variables were all stable except for an improvement (increase) in lateral patellofemoral cartilage thickness (P=.019) and an improvement (decrease) in distal femur width including osteophytes (P=.021).

Data for Knees with ACL Laxity

The 6-month data showed no statistically significant differences between active and control solutions, nor significant changes in ACL laxity measurement. However, the dextrose-treated knees were given 3 additional injections of dextrose and data were collected at 1-year follow-up. Hotelling multivariate analysis of paired observations of the dextrose-treated knees comparing 0 and 12 months for VAS rest pain, VAS walking pain, VAS stair use pain, VAS swelling complaint, flexion range of motion, and KT1000 side-to-side difference showed statistically significant improvement over time (P=.021). The results of individual paired t tests from 0 to 12 months are shown in Table 3. Blinded goniometric range measurement improved by 12.8 degrees with a P value of .005 and KT1000 ADD improved by 57% with a P value of .025. Figure 4 is a bar graph showing the

TABLE 1 Means, standard deviations (SD), and individual paired *t* tests for change in nonradiographic variables from 0 to 6 months in all osteoarthritic knees for active and control solution

	Group	Mean (SD) 0 months	Mean (SD) 6 months	Mean diff 0-6 months	Standard error of mean diff	95% CI for the mean difference	Significance between means at 0 and 6 months
Pain at rest	Active	2.15 (2.24)	1.61 (1.71)	-.54	.24	-1.02 to -.06	.029
	Control	2.73 (2.02)	1.69 (1.73)	-1.04	.25	-1.54 to -.54	.00005
Pain with walking	Active	3.94 (2.82)	2.56 (1.97)	-1.39	.31	-2.01 to -.77	.00002
	Control	3.83 (2.20)	2.85 (2.20)	-.98	.32	-1.62 to -.34	.003
Pain with stair use	Active	5.33 (2.80)	3.96 (2.68)	-1.37	.32	-2.01 to -.73	.00004
	Control	5.83 (2.60)	4.60 (2.91)	-1.23	.32	-1.87 to -.59	.0002
Swelling	Active	2.44 (2.53)	1.35 (1.87)	-1.09	.25	-1.59 to -.59	.00003
	Control	3.12 (2.99)	2.52 (2.80)	-.60	.26	-1.12 to -.08	.022
Buckling episodes per 2 months	Active	7.78 (34.14)	2.54 (11.44)	-5.24	2.23	-9.70 to -.78	.020
	Control	1.00 (2.60)	.21 (.64)	-.79	2.27	-5.33 to +3.75	.729
Flexion range	Active	112.35 (19.54)	125.59 (8.63)	-13.24	2.15	+8.94 to +17.54	.00000001
	Control	117.75 (11.32)	125.44 (7.48)	-7.69	2.19	+3.31 to +12.07	.001

distribution frequency of laxity values (ADD) for dextrose-treated patients at time 0 and 12 months. Note that 8 of the 13 improved to the point that ADD was less than 2, such that they would no longer be considered lax, and this in a group of patients with one or more complete ACL ruptures.

DISCUSSION

Balance of Growth and Disrepair Factors in Bony Cortex, Cartilage, and Synovial Fluid

The balance of disrepair and repair in both bone and cartilage merit examination since degenerative changes in bone occur simultaneously with those in cartilage.[21,22]

Chief repair factors found in osteoarthritic subchondral bone or cartilage include insulin-like growth factor (IGF), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and platelet derived growth factor (PDGF).[21,22] Chief disrepair factors (factors that block growth factor effects or break down tissue or building blocks for tissue) for the bony surface or cartilage include interleukin-1 (IL-1) and tumor necrosis factor (TNF), which lead to a rise as much as 110-fold in metalloproteinases such as collagenase (which breaks down cartilage) in fibrillated cartilage and a rise as much as 24-fold in binding proteins (proteins that bind growth factors to keep them from functioning) in synovial fluid.[23-27]

TABLE 2 Means, standard deviations (SD), and individual paired *t* tests for change in radiographic variables from 0 to 12 months in osteoarthritic knees treated with active solution

Variable	Mean (SD) 0 months	Mean (SD) 6 months	Mean diff 0 - 12 months	Standard error of mean diff	95% CI for the mean difference	Significance between means at 0 and 6 months	Direction of change
MFOG	1.55 (1.07)	1.49 (1.02)	-.06	.11	-.28 to +.16	NS	Stable
MTOG	1.56 (.92)	1.53 (1.05)	-.03	.10	-.23 to +.17	NS	Stable
LFOG	1.65 (.91)	1.76 (.84)	+.11	.13	-.15 to +.37	NS	Stable
LTOG	1.22 (.95)	1.33 (1.00)	+.11	.13	-.15 to +.37	NS	Stable
MPOG	1.24 (.82)	1.25 (.82)	-.01	.12	-.25 to +.23	NS	Stable
LPOG	1.42 (.66)	1.40 (.66)	-.02	.08	-.18 to +.14	NS	Stable
MTFT	2.09 (2.18)	1.94 (2.14)	-.15	.13	-.41 to +.11	NS	Stable
LTFT	5.54 (2.06)	5.58 (2.32)	+.04	.17	-.30 to +.38	NS	Stable
MPFT	4.51 (1.63)	4.59 (1.41)	+.08	.19	-.30 to +.46	NS	Stable
LPFT	4.20 (1.54)	4.59 (1.34)	+.39	.16	+.07 to +.71	.019	Improved
DFWP	93.58 (7.23)	92.96 (7.07)	-.62	.26	-1.14 to -.10	.021	Improved
DFWD	90.18 (8.36)	90.60 (8.14)	+.42	.34	-.26 to +1.10	NS	Stable
PTW	89.18 (7.96)	88.53 (8.08)	-.65	.39	-1.43 to +.13	NS	Stable

Proliferation of Human Chondrocytes by Growth Factors in Culture and Chondrogenesis of Animal Cartilage by Injection of Growth Factors

Bujia[28] and Dunham[29] demonstrated that culturing human chondrocytes (nasal septum chondrocytes) in fluid containing TGF-β,[28] IGF-1,[29] or bFGF[28,29] resulted in proliferation. Injection of animal knees with a single injection of TGF-β,[30] bone metabolic protein-2 (BMP-2),[30] bFGF,[31] or hepatocyte growth factor (HGF)[32] has led to chondrogenesis,[30] enlargement of articular cartilage,[31] and repair of full thickness joint cartilage defects.[32] Implantation of gel or a collagen sponge saturated with growth factor or placement of a surgically placed small pump that delivers growth factors have led to repair of full thickness cartilage lesions in animal models, also.[33-35] However, demonstration of 3 weeks of proteoglycan synthesis after a single injection of TGF-β[30] and healing of full-thickness cartilage lesions with a single injection of growth factor[32] indicates that continuous exposure to growth factor may not be required for a prolonged growth factor effect. In established OA high levels of binding proteins or metalloproteinases may block the effect of a single growth factor

TABLE 3 Means, standard deviations (SD), and individual paired *t* tests for change in pain, swelling, flexion, and laxity variables from 0 to 12 months for active solution in knees with ACL laxity

	Mean (SD) 0 months	Mean (SD) 12 months	Mean diff 0-12 months	Standard error of mean diff	95% CI for the mean difference	Significance between means at 0 and 12 months
Pain at rest	2.31 (2.56)	1.38 (2.06)	-.93	.49	-1.91 to +.06	.082
Pain with walking	3.77 (2.77)	2.31 (2.72)	-1.46	.46	-2.38 to -.92	.008
Pain with stair use	5.54 (3.31)	4.15 (3.29)	-1.39	.47	-2.33 to -.45	.013
Swelling	2.77 (2.71)	1.54 (2.40)	-1.23	.66	-2.55 to +.09	.088
Flexion range	112.69 (16.93)	125.46 (6.89)	+12.77	3.77	+5.23 to +20.31	.005
KT1000 side to side diff	3.08 (1.32)	1.23 (2.24)	-1.85	.72	-3.29 to -.41	.025

injection, and there may be a need in humans to combine growth factors with agents that neutralize disrepair factors for optimum effectiveness in established osteoarthritis.[35]

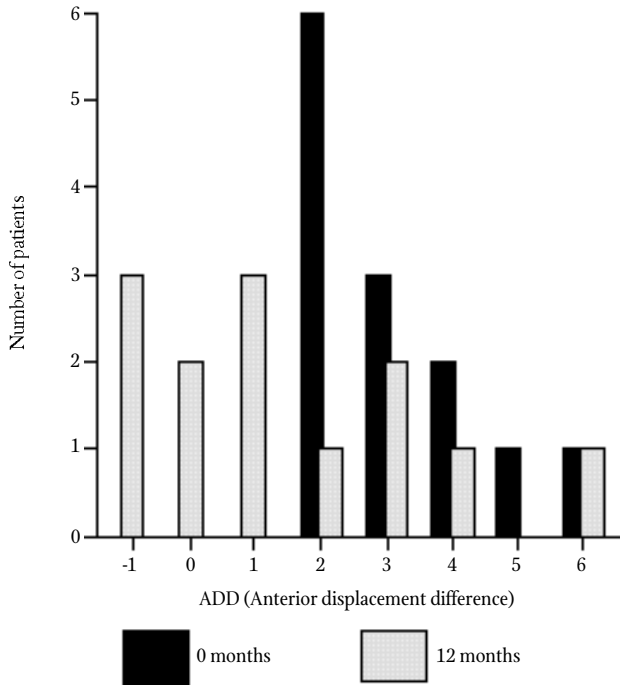

FIGURE 4 Frequency distribution of ADD in dextrose-treated knees. Comparison of 0 and 12 months.

Proliferation of Human Fibroblasts by Growth Factors in Culture

Human ACL ligament growth factors have not been fully elucidated, but Marui et al[36] demonstrated in cell suspension that collagen production by the human ACL ligament cell is increased by transforming growth factor beta (TGF-β) and epidermal growth factor beta (EGF-β), with EGF-β the most potent.

Effect on Human Cells of Exposure to Elevated Glucose

Elevation of extracellular glucose to as little as .5% has been shown to raise levels of IGF-1 in human mesangial (glomerular) cells,[7] IGF-2 in human mesangial cells,[7] TGF-β1 in human mononuclear cells[8] and human mesangial cells,[4,7] PDGF-B (platelet derived growth factor beta) in human mesangial cells[4] and human capillary endothelial cells,[37] bFGF in human gingival fibroblasts,[6] and connective tissue growth factor (CTGF) in human mesangial cells.[5] In addition, glucose in blood mononuclear cells has been found to suppress potential disrepair factors (interleukins such as IL-2, IL-6, and IL-10).[8] Cellular response to elevated extracellular glucose is swift. DNA levels for growth factor production rise within minutes to hours of cellular exposure to elevated glucose concentrations.[38] As many as 15 different genes are induced with exposure to elevated glucose concentration.[5]

Effect on Human Cells of Exposure to Osmolar Changes

Exposure of a cell to an osmolarity change as little as 50 mOsm has also been found to activate enzymes (phosphate donors, also termed kinases) in the cell similar to the growth factors mentioned above.[9,10,39-42] The mechanism appears to be via a

change in cell size, leading to kinase production via natural cellular responses to stress.[43,44] Although the kinases produced by osmolar change are not the same as with glucose elevation, proliferation response to a change in osmolarity has been demonstrated and at least 1 kinase produced is clearly a growth factor related to proliferation (PDGF).[10]

Potential Therapeutic Benefit of Bacteriostatic Water Solution or Anesthetic

The osmolarity of the bacteriostatic water solution used for the control injection was 105 compared to 611 for the active group. Information about the potential efficacy of hypotonic solution came out in the literature after our study began. This raised the question of whether the hypotonic control solution in this study was more than a placebo treatment. Review of placebo responses in recent double-blind studies of knee osteoarthritis revealed a range of pain reduction from 9% to 30%.[45-49] Review of studies on knee OA in which knee flexion measurements were obtained before and after treatment yielded few studies. A search over the last 30 years indicated a range of improvement in knee flexion in placebo groups from a -4.6 degree loss to a 1 degree gain.[50-53] The control group in this study improved by 28% in pain and 8 degrees in flexion range, suggesting more than a placebo effect. Since ligaments in different locations in animals respond to different growth factors there may be dissimilar findings for different joints.[54-56] Thus it is of interest that a concurrent finger OA study did show similar benefit with dextrose solution but the control solution did not show an appreciable benefit.[57]

It is possible that there was some therapeutic effect from inclusion of anesthetic in the solution as well, and if so this may explain some benefit in both groups. However, the concentration of lidocaine at .075% was quite low and was identical in both treatment solutions.

Magnitude of Clinical Benefit from Dextrose Solution Use Compared to Active Groups in Other Recent Studies

Pain improvement in the active treatment group by 40% through 1 year after 6 injections of 9 cc of simple dextrose solution approximated that of the active treatment group in recent studies on avocado soybean unsaponifiables,[48,58] chondroitin sulfate,[59] glucosamine,[47] and NSAIDs.[45,53,60,61] Range of motion improvement in flexion in the dextrose-treated knees (14 degrees) exceeded the range of flexion improvement (-2.6 to +12.5) in active treatment groups found in double-blind knee arthritis studies over the past 30 years.[50-53] No past studies could be found that quantified subjective swelling complaints or knee buckling frequency to compare with the 63% and 85% reductions demonstrated in the current study. Only 2 other studies indicated potential stabilization of radiograph findings similar to the current study.[62,63]

Previous Prolotherapy Injection Trials on Knee Ligament Laxity

Double-blind studies of injection prolotherapy with non-inflammatory solutions for knee osteoarthritis or knee ligament laxity have not been previously reported. However, stimulation of the inflammatory cascade produces growth factors, and temporary inflammation induction by sodium morrhuate has been shown in a double-blind study in rabbits to thicken and strengthen knee collateral ligaments.[64] The only human study on knee-ligament strengthening by inflammatory induction (using a 1.25% phenol 12.5% dextrose and 12.5% glycerine solution) had few patients and was unblinded.[65] However, despite the low patient numbers, highly significant improvement of laxity measurements by a Genucom knee arthrometer was noted.

Potential Applications and Future Study Implications

This study is 1 of 2 concurrent double-blind studies (along with a concomitant finger arthritis study)[57] to demonstrate that 10% dextrose alone is capable of a beneficial effect upon introduction into OA joints and that a treatment frequency of every 2 months is effective. Potential applications include patients too large or too young for total knee replacement, any patient in a third world country without replacement availability, patients who are symptomatic despite prescribed exercises or physical therapy or NSAIDs, or patients who are intolerant of NSAIDs.

This is the first study to demonstrate in double-blind fashion that simple 10% dextrose will correct ACL ligament laxity in an objectively-measurable fashion. Potential applications may include patients with laxity without rupture, post surgical repair to prevent the typical post-surgical gradual loosening, and large total joint patients with dislocation tendency.[66] The ability to intervene in a simple way for ACL laxity to limit the known complications of secondary arthritis should be of much interest. The broadness of application of dextrose injection in ligament/tendon treatment will depend on the cost of alternative treatments such as growth-factor-impregnated implants, direct stem cell injection, or injection of ACL ligament cells transfected with viruses whose genome has been altered to produce growth factors or to block growth factor inhibitors.[67-70] The safety and low cost of dextrose injection may make it suitable for study in prophylactic use for knee injection in athletes prone to ACL injuries or in those with injuries but intact ligament.

These study results with 10% dextrose use are intriguing in that clinical experience indicates that dextrose 25% is superior to 10% dextrose in the treatment of knee OA and ACL laxity. This author is currently investigating the ability of patients to tell the difference between 10% and 25% dextrose upon injection into the knee in preparation for direct study of 25% dextrose, to be certain that double-blind protocols would not be affected by the brief inflammatory effect of 25% dextrose. Future study protocols using dextrose for prolotherapy should consider different volumes of dextrose injection, as some have suggested that smaller volumes are equally effective and may allow 25% dextrose to be used without patient awareness. Other applications of injection prolotherapy and areas of past and current study are covered in 2 recent publications.[71,72]

If growth factor production results in more inexpensive and safe solutions for injection, this may be an alternative to stimulating growth factors by either brief inflammation or by dextrose

or by osmotic effects, and yet a likely outcome is that oral supplements, growth factor stimulant injection (prolotherapy), and direct growth factor provision by injection or other method will be complementary.

Frequency of treatment necessary for dextrose injection needs further evaluation, with current studies not designed to answer all questions about this. Clinical experience with 25% dextrose suggests that 2 to 3 bimonthly treatments are necessary prior to treatment taper.

For future studies on the ACL ligament, MRI availability to rule out complete ACL rupture and arthroscopy to confirm changes in cartilaginous surfaces would be ideal.

Now that the safety of dextrose in bacteriostatic water has been demonstrated in this study and a concomitant finger osteoarthritis study, future studies with dextrose should perhaps have dextrose in sterile water or saline versus an isotonic saline placebo.

Long-term radiograph follow-up data from the current study patients will be helpful to note net effect on cartilage and osteophytic change over a prolonged period, and patients are being followed for long-term radiographic findings.

CONCLUSIONS

Dextrose injection is clinically and statistically superior to bacteriostatic water in treatment of OA of the knee, with substantial improvements in joint pain, subjective joint swelling, flexion range of motion, and tendency for knee buckling. Anterior cruciate ligament tightening by objective measures was demonstrated with use of interarticular dextrose. Preliminary (1-year) radiographic findings show positive effects but 30- to 36-month followup radiography is planned for a clearer idea of the effect of proliferant injection on radiographic findings of OA. The inclusion of 38 knees in this study that were completely void of cartilage in at least 1 compartment, the long history of pain (8 years) in these knee OA patients, and their average size (195 lbs) strengthen the significance of the clinical outcomes demonstrated.

This study is remarkable in part because it represents an effective intervention with injection of as little as 9 cc of simple dextrose injection on 3 separate occasions. This study result, coupled with findings of a double-blind study on small joint (finger) OA, indicates that dextrose injection may have broad effectiveness in the treatment of joint and soft tissue.[57] Future studies using isotonic saline as placebo and using a higher concentration of dextrose solution will be important, although blinding may be more difficult for such studies. In the meantime prolotherapy with dextrose should be considered as one of the treatments for OA of knee and ACL laxity.

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Hypertonic Dextrose Injections (Prolotherapy) for Knee Osteoarthritis: Results of a Single-Arm Uncontrolled Study with 1-Year Follow-Up

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Abstract

Objective: The objective of this study was to determine whether prolotherapy, an injection-based complementary treatment for chronic musculoskeletal conditions, improves pain, stiffness, and function in adults with symptomatic knee osteoarthritis (KOA) compared to baseline status.
Design: This was a prospective, uncontrolled study with 1-year follow-up.
Setting: The study was conducted in an outpatient setting.
Participants: Adults with at least 3 months of symptomatic KOA, recruited from clinical and community settings, participated in the study.
Interventions: Participants received extra-articular injections of 15% dextrose and intra-articular prolotherapy injections of 25% dextrose at 1, 5, and 9 weeks, with as-needed treatments at weeks 13 and 17.
Outcome measures: Primary outcome measure was the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC). Secondary outcome measure was the validated Knee Pain Scale (KPS). Tertiary outcome measure was procedure-related pain severity and participant satisfaction.
Results: Thirty-six (36) participants (60 ± 8.7 years old, 21 female) with moderate-to-severe KOA received an average of 4.3 ± 0.7 prolotherapy injection sessions over a 17-week treatment period and reported progressively improved scores during the 52-week study on WOMAC and KPS measures. Participants reported overall WOMAC score improvement 4 weeks after the first injection session (7.6 ± 2.4 points, 17.2%), and continued to improve through the 52-week follow-up (15.9 ± 2.5 points, $p < 0.001$, 36.1%). KPS scores improved in both injected ($p < 0.001$) and uninjected knees ($p < 0.05$). Prescribed low-dose opioid analgesia effectively treated procedure-related pain. Satisfaction was high and there were no adverse events. Female gender, age 46–65 years old, and body–mass index of 25 kg/m^2 or less were associated with greater improvement on the WOMAC instrument.
Conclusions: In adults with moderate to severe KOA, dextrose prolotherapy may result in safe, significant, sustained improvement of knee pain, function, and stiffness scores. Randomized multidisciplinary effectiveness trials including evaluation of potential disease modification are warranted to further assess the effects of prolotherapy for KOA.

Introduction

Knee osteoarthritis (KOA) is a degenerative disease causing joint pain, stiffness, and decreased function.[1] It is common, expensive,[2] and age-related[3]; by age 65, the majority of the population has radiographic evidence of osteoarthritis and 11% have symptomatic KOA.[4] The etiology of pain and disability in KOA is not well understood. Sources of pain likely include the joint capsule, ligaments, synovium, bone, and in the knee, the outer edge of the menisci as well as supportive extra-articular ligaments and tendons.[5,6] Standard-of-care is multidisciplinary, often including physical therapy, anti-inflammatory medication, intra-articular viscosupplementation, and arthroscopic surgery. However, a recent systematic review reported no clear benefit of any one therapy.[4] Other conservative therapies[7] and oral supplements[8,9] have also been reviewed. While some support exists for their use, definitive evidence is lacking. Acupuncture was reported as efficacious in

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a rigorous randomized controlled trial (RCT), though results were limited by substantial missing data and short follow-up period.[10] In light of high prevalence and substantial impact on individuals and society, and lack of effective treatment, the Agency for Healthcare Research and Quality has called for new approaches to prevent and treat KOA.[4]

Prolotherapy is a complementary injection therapy for chronic musculoskeletal pain, including knee osteoarthritis (KOA),[11,12] that has been hypothesized to stimulate healing of chronic soft-tissue injury. Hypertonic dextrose is a commonly used prolotherapy injectant.[11] A single randomized controlled trial (RCT) reported significant improvement in KOA pain scores when treated with prolotherapy[13]; however, the effectiveness of prolotherapy for KOA using validated measures has not been assessed. Therefore, a prospective uncontrolled pilot study was conducted to test the hypothesis that dextrose prolotherapy improves knee pain, function, and stiffness compared to baseline status in participants with symptomatic moderate to severe KOA.

Methods

The study protocol was approved by the University of Wisconsin Institutional Review Board.

Eligibility criteria and participant recruitment

Adults 40–76 years old were enrolled and followed from July 2004 to July 2008. They were recruited from University of Wisconsin Sports, Rehabilitation and Family Medicine clinics, prior control groups of an ongoing RCT assessing prolotherapy for KOA and the community. Inclusion criteria were a diagnosis of KOA based on clinical criteria for KOA defined by the American Rheumatological Association,[14] identification by a radiologist of KOA on an existing knee radiograph within 5 years, tenderness of one or more anterior knee structures on physical examination conducted by the lead physician (DR), and moderate-to-severe knee pain for at least 3 prior months, defined by scoring "3" or more on the question "What is the average level of your left/right knee pain over the last week?" using a 0–6 ordinal response scale. Exclusion criteria included the following: pregnancy, significant comorbidity (including uncontrolled diabetes mellitus defined as glycosylated hemoglobin >7.5%), anticoagulation therapy, history of, or planned, total knee replacement, prolotherapy or any other knee injection within the past three months, inflammatory or postinfectious knee arthritis, daily use of opioid pain medication, allergy or intolerance to study medication, lack of x-ray report of the affected knee or body–mass index (BMI) > 45 kg/m^2. Each knee was assessed separately for eligibility. Interested, eligible persons attended an informational meeting and gave informed consent.

Outcome measures

The primary outcome measure was change in the total score of Western Ontario McMaster University Osteoarthritis Index (WOMAC), a validated quality-of-life instrument designed to evaluate KOA severity using pain, stiffness, and function subscales.[15] The WOMAC total score, constructed as the average of the three subscale scores, ranges from 0 to 100, with 100 indicating maximum (best) knee-related quality of life, and has been shown to be responsive to change. Minimal clinical important differences on the WOMAC for KOA have been reported as 12%[16]–25%.[17] Secondary outcomes included the Knee Pain Scale (KPS),[18] a validated questionnaire assessing pain and function of the individual knee. KPS assesses pain frequency using a 0–4 Likert scale, and pain severity using a 0–5 Likert scale, with higher values indicating worse pain frequency/severity. KPS data were collected separately for each treated knee as well as for untreated knees to evaluate whether unilateral prolotherapy could have bilateral effects on knee pain scores. To the authors' knowledge, the minimal clinical important difference has not been published for the KPS. The WOMAC and KPS were collected in person and prior to any procedure at baseline, 5, 9, and 12 weeks, and by phone at 26 and 52 weeks postentry.

Tertiary outcomes included procedure-related pain severity and patient satisfaction. Participants reported pain levels on a 1–7 ordinal response scale immediately following and 2 days after a given injection session. Opioid medication use was recorded (yes/no). Participant satisfaction was assessed by the question "Would you recommend the therapy you received in this study to others with KOA like yours?" (yes/no). Participants were able to make brief qualitative comments about their treatment and clinical response.

Demographics, self-reported weight and height and severity of KOA-related findings on knee radiographs were collected at baseline to characterize the sample and to evaluate as covariates (age, gender, BMI, and x-ray-based KOA severity score) for statistical analysis. A fellowship-trained musculoskeletal radiologist (RK) using the 1–4 Kellgren-Lawrence KOA scoring system[19] evaluated existing, available knee radiographs. Among participants for whom existing radiographs were available and who also received injections on both knees, the more severe of the two radiographs was obtained.

Intervention

Injections were performed at 1, 5, and 9 weeks postentry, with optional sessions at weeks 13 and 17, per physician (JJP) recommendations and participant preference. Participants were offered an optional single 5-mg oxycodone tablet for analgesia 30 minutes prior to injection. The injector (JJP) examined the knee, marked tender anterior points, placed anesthetic skin wheals of 1% lidocaine and performed injections according to an existing protocol (Fig. 1).[20] Extra-articular injections were done "on bone" at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique and placing a possible total 22.5 mL of solution. The single intra-articular injection was 6 mL of 25% dextrose using an inferomedial approach. Postinjection, participants were offered acetaminophen and eight 5-mg oxycodone tablets to use as needed for up to 1 week and were advised to have relative rest for 2–3 days, with progressive resumption of routine activity over 1 month. They were discouraged from using nonsteroidal anti-inflammatory medications and from starting new therapies for knee pain during the study period.

Analysis

Data were analyzed using SAS® 9.1 statistical software (SAS Institute Inc., Cary, NC). Distributional data characteristics were assessed; primary and secondary continuous variables were normally distributed. Descriptive statistics

A

Injection type	Solution	Injection Technique
Intra-articular	25% Dextrose: 5 mL 50% Dextrose 5 mL Lidocaine 1%	6.0 mL of 25% dextrose in a single injection was performed using an inferomedial approach.
Extra-articular	15% Dextrose: 6.75 mL 50% Dextrose 4.5 mL 1% Lidocaine 11.25 mL 0.9% Saline	Up to 15 sub-dermal injections were placed and 0.5 mL of 15% dextrose solution was injected using a peppering technique with a 25-gauge needle at each ligament-bone insertion. Each puncture site allowed for placement of solution at as many as 3 ligament-bone insertions using the technique of skin sliding (withdrawing the needle to just below the skin and reinserting into an adjacent area without removing from the initial puncture site) allowing for the peri-articular placement of up to 22.5 mL of dextrose solution.

B

1. Medial Collateral Ligament
2. Pes Anserine attachment
3. Tibial Tuberosity
4. Coronary Ligaments
5. Patella
6. Lateral Collateral Ligament
7. Intra-articular injection

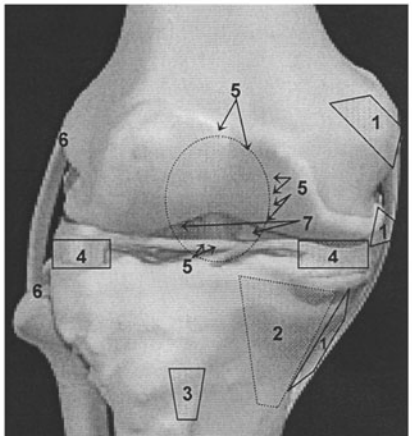

FIG. 1. **A.** Prolotherapy solutions and injection techniques. **B.** Injection locations (anterior right knee). Images © and courtesy of Primal Pictures Ltd.

were applied to describe outcomes at each time point; mean value ± standard deviation (SD) was reported at baseline unless otherwise specified.

Repeated-measures analysis of variance compared baseline to follow-up WOMAC total and subscale scores and the subscales of the KPS (five time points over the 52-week follow-up period). Mean values ± standard error was reported for this analysis. The unit of analysis in the WOMAC model was the participant. Because WOMAC evaluates participant's KOA-specific quality of life regardless of the number of knees (one or two) affected, the analysis of the WOMAC scores was on a "per participant" basis, regardless of whether one or both knees were injected. In addition to the unadjusted repeated-measures analysis, covariate analyses were also conducted, based on interaction of the covariates with the time-related trend in the model. Separate covariate analyses were conducted for participant age, gender, BMI, race, education, income, tobacco use, diabetes, prior knee surgery, Kellgren-Lawrence severity, and duration of knee pain. Percent improvement in WOMAC scores was calculated as the percentage change in total WOMAC score from baseline to 52 weeks relative to the potential improvement obtainable (100 minus the baseline). The number needed to treat (NNT) to achieve a minimal clinical important difference of 12% on the WOMAC total score,[16] and to achieve overall improvement of 25% and 50% were calculated.

The unit of analysis for the KPS model was the individual knee. Because KPS assesses each knee separately (that is, each participant completes two KPS questionnaires at each time point: one per knee), the KPS scores for each knee were analyzed individually. If a participant had both knees treated, that participant accounted for two knees in the treated-knees model. A hierarchical repeated-measures model corrected the standard errors for the interaction between the reports on two knees by the same individual.

A separate repeated-measures model analyzed KPS scores for knees that were not treated during the study. The model included untreated knees for individuals who only received treatment on a single knee. The significance test for change from baseline is reported for WOMAC scores and for KPS-assessed scores of treated and untreated knees. Two-tailed p-value < 0.05 was established as a statistical significance level.

Results

The recruitment and participation scheme is given in Figure 2. Thirty-eight (38) participants were enrolled. Two (2) participants withdrew consent after enrollment: 1 prior to injection due to scheduling difficulties and 1 after a single treatment session due to a herniated spinal disc unrelated to the study. Therefore, 36 participants were included in the analysis. Of these, 30 were recruited from community or outpatient clinics, and 6 from the former control groups of a

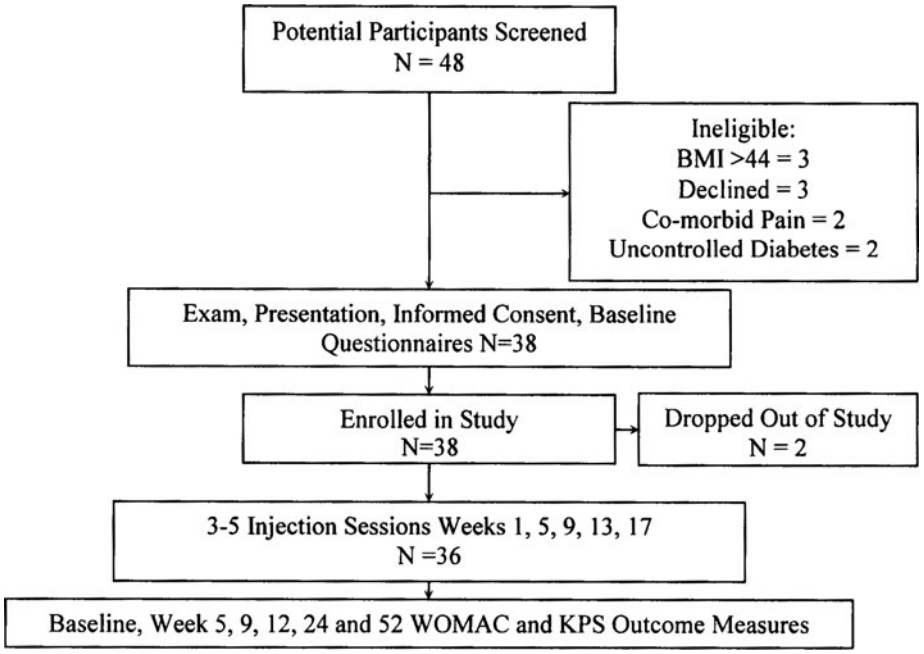

FIG. 2. Enrollment of participants and completion of the study. BMI, body–mass index; WOMAC, Western Ontario McMaster University Osteoarthritis Index; KPS, Knee Pain Scale.

prior prolotherapy RCT. The study sample ($N=36$; Table 1) consisted of white adults (60 ± SD 8.7 years old, range 46–71 years), the majority of whom were women ($N=21$) and who reported BMI over 25 kg/m^2. The reported duration of knee pain was 81.2 ± SD 72.9 months (range: 3–360). Most participants had tried and failed one or more conservative measures. Thirty-one (31) radiographs were available for evaluation; 0 radiographs were available for 5 participants, and 1 for each of the remaining 31 participants.

Prolotherapy intervention

Thirty-six (36) participants received an average of 4.3 ± 0.78 prolotherapy sessions; 22 participants had both knees treated, contributing 44 knees to the KPS analysis. Fourteen (14) participants had only one knee treated. The total sample size for the WOMAC and KPS analyses of treated knees was therefore 36 participants and 58 knees, respectively. The sample size of the KPS analysis of untreated knees was 14.

WOMAC

Repeated-measures analysis showed overall improvement in the total and subscale WOMAC scores (Table 2) during the study compared to baseline ($p<0.001$). The WOMAC scores progressively improved from baseline through 5, 9, and 12 weeks. Although a slight dip in the scores was noted at 24 weeks, they recovered by 52 weeks by which time participants reported a 36.1% (15.9 ± 2.5 points) improvement in the overall WOMAC score ($p<0.001$). Covariate analysis showed that female gender ($p=0.05$), age (46–65 years old, $p=0.04$), and a BMI ≤ 25 kg/m^2 ($p=0.04$) were associated with greater improvement in WOMAC scores. Improvement in the WOMAC scores was not related to the participant recruitment source, number of received injection sessions, injection of one or both knees, duration of KOA pain, prior KOA therapies, tobacco

Table 1. Baseline Subject ($N=36$) Characteristics

Variable	*Number (%)*	
Female, *n* (%)	21 (58%)	
Age, years, mean (SD)	60 (8.7)	
Income, *n* (%)		
<$50,000	7 (20%)	
$50,000– $79,000	11 (31%)	
$80,000+	17 (49%)	
Duration of knee pain, months, mean (SD)	81.2 (72.9)	
BMI, kg/m, *n* (%)		
≤25	8 (22%)	
26–30	15 (42%)	
31+	13 (36%)	
Prior knee intervention, *n* (%)[a]		
Arthroscopic surgery	15 (43%)	
Physical therapy	20 (61%)	
Hyaluronic acid injection	4 (12%)	
Corticosteroid injection	7 (21%)	
Diabetes, *n* (%)	2 (6%)	
WOMAC total score, points (SD)	55.9 (3.1)	
Pain	57.9 (17.5)	
Stiffness	51.7 (23.0)	
Function	58.1 (17.0)	
KPS score, points (SD)	Treated knees	Untreated knees
Pain frequency (0–4)	2.60 (0.90)	1.64 (1.24)
Pain severity (0–5)	2.08 (0.92)	1.19 (1.10)
X-ray Kellgren-Lawrence OA severity score (0–4) of treated knees[b]		
1–2 score (mild OA)	8 (22%)	
3–4 (moderate to severe OA)	23 (64%)	

[a]Percentage does not add up to 100 due to participants' varied use of conventional therapies.

[b]Existing knee radiographs were obtained for the more severely affected injected knee in each participant. Percentage does not add up to 100 due to missing data on five baseline knee radiographs.

SD, standard deviation; BMI, body–mass index; WOMAC, Western Ontario McMaster University Osteoarthritis Index; KPS, knee pain scale; OA, osteoarthritis.

Table 2. Change in WOMAC Scores Compared to Baseline Status

Measure	Score	Change in score compared to baseline					
	Baseline (n = *36*)	*Wk 5* (n = *36*)	*Wk 9* (n = *36*)	*Wk 12* (*n* = *33*)	*Wk 24* (*n* = *35*)	*Wk 52* (n = *34*)	p-*Value*[a]
Total and change in WOMAC score (SE)	55.9 (3.1)	+7.6 (2.4)	+11.6 (2.4)	+15.9 (2.5)	+13.9 (2.5)	+15.9 (2.5)	< 0.001
% Total score improvement	NA	17.2%	26.3%	36.1%	31.5%	36.1%	
WOMAC subscale scores (SE)							
Pain	57.9 (3.0)	+8.1 (2.6)	+10.8 (2.6)	+15.3 (2.6)	+14.6 (2.6)	+14.0 (2.6)	< 0.001
% Pain score improvement	NA	19.2%	25.7%	36.3%	34.7%	33.3%	
Stiffness	51.7 (3.3)	+5.6 (3.4)	+10.4 (3.4)	+15.6 (3.5)	+11.8 (3.4)	+16.5 (3.4)	< 0.001
% Stiffness score improvement	NA	11.6%	21.5%	32.3%	24.4%	34.2%	
Function	58.1 (2.9)	+9.3 (2.3)	+13.6 (2.3)	+16.9 (2.4)	+15.4 (2.4)	+17.1 (2.4)	< 0.001
% Function score improvement	NA	22.2%	32.5%	40.3%	36.8%	40.8%	

[a]Significance (*p*-value) is reported for overall treatment effect (repeated-measures model).
WOMAC, Western Ontario McMaster University Osteoarthritis Index; Wk, week; SE, standard error; NA, not applicable.

use, or diabetes. Improvement in WOMAC scores at 52 weeks was also not associated with pretreatment Kellgren-Lawrence scores (18.7 point improvement for participants with Kellgren-Lawrence scores of 1–2 and 11.7-point improvement for participants with Kellgren-Lawrence scores of 3–4; $p = 0.09$). The NNT to achieve the minimal clinical important difference of 12%[16] was 1.3; the NNT to achieve more robust overall improvements of 25% and 50% were 1.7 and 3.9, respectively. Thirty-eight percent (38%) of the participants achieved a 50% or greater improvement in the total WOMAC score at 52 weeks. The WOMAC score of 4 participants worsened over the 52-week study period, with no covariates being predictive. Qualitative comments revealed that three of these participants engaged in early strenuous physical activity after two or more prolotherapy treatment sessions. Overall, 15 participants reported engaging in strenuous physical activity earlier than recommended after clinical improvement at one or more points during the study.

KPS

Similar to the WOMAC, KPS scores improved progressively through the 52-week study period (Table 3; $p < 0.001$) in injected knees ($n = 58$), regardless of the number of knees injected. Participants reported less severe baseline KOA pathology in uninjected knees ($n = 14$) but interestingly, reported a statistically significant improvement in KPS scores even in the uninjected knees for both pain frequency (50%, $p < 0.001$) and severity (43%, $p = 0.001$) at 52 weeks (Table 3).

Procedure-related pain, satisfaction, and safety

As expected, all participants experienced self-limited postinjection pain, with 68% reporting oxycodone use prior to injections ("premedication") and 45% reporting oxycodone use after the injections. Ninety percent (90%) of those using oxycodone reported that it substantially decreased procedure-related pain. Participants reported that procedural pain waned by the second day after injection, from 3.8 ± 1.4 points to 3.1 ± 1.4 points on the 1–7 ordinal response pain severity scale. One (1) participant experienced local numbness distal to the knee that spontaneously resolved in 2 hours. Twenty-nine (83%) participants reported that they would recommend prolotherapy to patients with similar KOA. There were no adverse events.

Table 3. Change in KPS Scores Compared to Baseline for Treated and Untreated Knees[a]

	Treated knees (N = *58*)[b]		*Untreated knees* (N = *14*)[b]	
	Pain frequency	*Pain severity*	*Pain frequency*	*Pain severity*
Baseline score	2.60 (0.13)	2.09 (0.13)	1.64 (0.2)	1.19 (0.22)
Score change compared to baseline:				
Wk 5	−0.38 (0.12)	−0.39 (0.12)	−0.23 (0.23)	−0.08 (0.25)
Wk 9	−0.59 (0.12)	−0.56 (0.13)	−0.78 (0.23)	−0.54 (0.25)
Wk 12	−0.85 (0.12)	−0.78 (0.13)	−0.74 (0.25)	−0.66 (0.26)
Wk 24	−0.78 (0.12)	−0.70 (0.13)	−0.94 (0.24)	−0.67 (0.25)
Wk 52	−0.91 (0.12)	−0.76 (0.13)	−0.82 (0.23)	−0.51 (0.25)
% Improvement	35%	36%	50%	43%
p-Values[c]	< 0.001	< 0.001	0.001	0.028

[a]Results are presented as mean score (baseline) or mean score change (weeks 5–52) (standard error).
[b]Twenty-two (22) participants had both knees treated (44 knees) and 14 participants had one knee treated (14 knees) for a total of 58 knees treated and 14 knees untreated.
[c]Significance (*p*-value) is reported for overall treatment effect (repeated-measures model).
KPS, knee pain scale; Wk, week.

Discussion

This uncontrolled pilot study of participants with KOA found substantial, consistent improvement in knee pain, function, and stiffness at 52 weeks after treatment with prolotherapy. The 36% improvement on the validated WOMAC measure exceeded reported minimal clinical important difference of 12%[16]–25%[17] on the WOMAC; 38% of participants exceeded 50% improvement at 52 weeks.[21] While improvement was generally progressive over 52 weeks, there was a slight dip in scores in both the WOMAC and the KPS at 24 weeks, perhaps because some participants overused their knees following substantial improvement in knee pain at one or more time points in the study. These results may therefore underestimate the potential effect of prolotherapy in patients who adhere to recommendations for a gentle return to activity or sport following prolotherapy. These results provide level 3B evidence[22] that prolotherapy may be an effective treatment for pain and disability related to KOA.

Participants also reported significantly improved KPS scores on *uninjected* knees. This may represent a reduction in compensatory mechanisms of the uninjected side. Individuals with KOA have reduced knee and hip motion (i.e., angular velocity in the sagittal plane) on the affected side relative to controls,[23,24] thus placing additional burden on the unaffected limb when trying to maintain a given walking speed.[25,26] This may result in overuse, pain, and disability of the contralateral knee. Participants may have needed to compensate less on the uninjected side as a result of post-injection improvement of the primarily affected knee, sparing it from overuse and improving bilateral knee function. Overall, WOMAC and KPS data suggest that prolotherapy may improve upon standard of care for KOA, given that most participants were refractory to prior therapeutic measures. Such positive change may improve quality of life in the near term and delay progression of KOA in the long term. Clinical improvement may accrue preferentially to those who are of normal weight, female, and middle-aged.

These effects are consistent with another prolotherapy study, though comparison is limited by different injection protocols and outcome measures.[12] Direct comparison of these data to those in studies of hyaluronic acid injection and other conventional therapies is also difficult given the heterogeneity of reporting methods in many trials, but improvements of 20%–40% compared to baseline have been reported for conventional therapies and acupuncture.[4,8]

Prolotherapy is an evolving modality gaining popularity in sport and family medicine,[11,27] though its mechanism of action is unclear. Dextrose injections have been hypothesized to stimulate healing of chronically injured extra-articular and intra-articular tissue[28]; animal model studies reported increased inflammatory markers[29] and significantly enlarged cross-sectional area in medial collateral ligaments.[30] The potential of prolotherapy to stimulate release of growth factors favoring soft-tissue healing[12,31] and a positive neural effect have also been suggested.[32] Needle trauma and volume expansion of local tissue may also produce a tissue-level effect.[33] The combined effect of dextrose-specific effects, needle trauma, and volume expansion may explain positive results in this study. The source of pain in KOA is multifactorial. Prolotherapy injections target multiple potential nociceptors, including the relatively avascular articular cartilage and richly innervated intra-articular and extra-articular tissue including periosteum, periarticular ligaments, periarticular muscle, synovium, and joint capsule[6,34] and have been hypothesized to have intra-articular and extra-articular effects.[11,12,27]

Limitations and Strengths

Limitations of this study include small sample size and lack of comparison group. The assessment of participant satisfaction was indirect and subject to bias. Radiographs were not available for all participants, and the use of Kellgren-Lawrence criteria for baseline radiological assessment of KOA severity is controversial, given that scores have not been uniformly correlated to patient-centered outcomes. The Kellgren-Lawrence score, however, is likely to remain an important measure for gauging disease severity in symptomatic patients.[35] The enrollment of 6 participants who had completed a prior prolotherapy trial may have introduced bias, though participant recruitment source was not a significant covariate. Strengths include pragmatic assessment using validated, patient-oriented outcomes and robust, consistent results with minimal missing data.

Directions for Future Research

Determination of clinical utility of prolotherapy for KOA will require assessment in a larger randomized multidisciplinary effectiveness trial that includes biomechanical and imaging outcome measures to assess for potential disease modification.[36,37]

Conclusions

Prolotherapy resulted in safe, significant, and sustained improvement on validated pain, function, and stiffness measures in participants with KOA. Prolotherapy performed by an experienced operator may be an appropriate therapy for selected patients with moderate-to-severe KOA who are refractory to conservative care.

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Disclosure Statement

No competing financial interests exist.

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Dextrose Prolotherapy for Knee Osteoarthritis: A Randomized Controlled Trial

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ABSTRACT

PURPOSE Knee osteoarthritis is a common, debilitating chronic disease. Prolotherapy is an injection therapy for chronic musculoskeletal pain. We conducted a 3-arm, blinded (injector, assessor, injection group participants), randomized controlled trial to assess the efficacy of prolotherapy for knee osteoarthritis.

METHODS Ninety adults with at least 3 months of painful knee osteoarthritis were randomized to blinded injection (dextrose prolotherapy or saline) or at-home exercise. Extra- and intra-articular injections were done at 1, 5, and 9 weeks with as-needed additional treatments at weeks 13 and 17. Exercise participants received an exercise manual and in-person instruction. Outcome measures included a composite score on the Western Ontario McMaster University Osteoarthritis Index (WOMAC; 100 points); knee pain scale (KPS; individual knee), postprocedure opioid medication use, and participant satisfaction. Intention-to-treat analysis using analysis of variance was used.

RESULTS No baseline differences existed between groups. All groups reported improved composite WOMAC scores compared with baseline status ($P < .01$) at 52 weeks. Adjusted for sex, age, and body mass index, WOMAC scores for patients receiving dextrose prolotherapy improved more ($P < .05$) at 52 weeks than did scores for patients receiving saline and exercise (score change: 15.3 ± 3.5 vs 7.6 ± 3.4, and 8.2 ± 3.3 points, respectively) and exceeded the WOMAC-based minimal clinically important difference. Individual knee pain scores also improved more in the prolotherapy group ($P = .05$). Use of prescribed postprocedure opioid medication resulted in rapid diminution of injection-related pain. Satisfaction with prolotherapy was high. There were no adverse events.

CONCLUSIONS Prolotherapy resulted in clinically meaningful sustained improvement of pain, function, and stiffness scores for knee osteoarthritis compared with blinded saline injections and at-home exercises.

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INTRODUCTION

Knee osteoarthritis is a chronic disease resulting in joint pain, stiffness, and decreased function.[1] It is common, expensive for patients[2] and society, and age-related[3]; by age 65 years, most of the population has radiographic evidence of osteoarthritis.[4] Sources of pain include intra-articular and supportive extra-articular structures.[5,6] Standard-of-care is multidisciplinary; however, a recent systematic review reported no clear benefit of any one therapy.[4] Conservative therapies[7] and oral supplements[8,9] have been evaluated but are without clear efficacy. The Agency for Healthcare Research and Quality has called for the development of new therapies to prevent and treat knee osteoarthritis.[4]

Prolotherapy is an injection therapy for chronic musculoskeletal injury, including knee osteoarthritis.[10-12] A core principle is the injection of small volumes of an irritant solution at multiple painful ligament and tendon insertions and in adjacent joint spaces over several treatment sessions.[10] Prolotherapy has been used in a form recognizable to contemporary prac-

titioners for at least 75 years; the earliest substantive report appeared in the allopathic literature when the technique was referred to as sclerotherapy as a result of the scar-forming properties of early injectants.[13] Contemporary injection techniques were formalized in the 1950s, when the more commonly used term *prolotherapy* (from *proliferant* therapy) was adopted based on the observation that a larger cross-sectional area of ligamentous tissue was seen after prolotherapy injection in animal models.[14] Literature of generally low methodological rigor from the 1930s to the early 2000s reported positive clinical outcomes.[15] The mechanism of action is unclear. Contemporary hypotheses suggest that prolotherapy stimulates local healing of chronically injured extra- and intra-articular tissue, though definitive evidence is lacking.[10] Hypertonic dextrose is a commonly used injectant.[10] Prolotherapy injections target multiple potential pain generators in and around the knee joint; it may be well-suited to address the multifactorial cause of knee pain from osteoarthritis. A single randomized controlled trial (RCT)[11] and 1 open-label study[16] reported improvement in outcomes in response to prolotherapy but were not methodologically rigorous. We therefore conducted a 3-arm RCT to assess the hypothesis that adults with symptomatic knee pain receiving prolotherapy will report greater improvement in knee-related quality-of-life than those receiving saline injections or at-home knee exercises.

METHODS

The study was approved by the University of Wisconsin (UW) Health Sciences Institutional Review Board. Adults aged 40 to 76 years were recruited from 2004 to 2009 from the community and University of Wisconsin family medicine, sports medicine, and rehabilitation clinics; each was then observed for 1 year. Inclusion criteria were a diagnosis of knee osteoarthritis based on clinical criteria (American College of Rheumatology),[17] identification of knee osteoarthritis by a radiologist on an existing knee radiograph obtained within 5 years of enrollment, tenderness of 1 or more anterior knee structures on physical examination, and self-reported moderate-to-severe knee pain for at least 3 months, defined as a score of 3 or more (0 to 6 ordinal response scale) on the question, "What is the average level of your left/right knee pain over the last week?" Exclusion criteria included pregnancy, diabetes, anticoagulation therapy, history of total knee replacement, prior knee prolotherapy, any knee injection within 3 months, inflammatory or postinfectious knee arthritis, daily use of opioid medication, allergy or intolerance to study medication, body mass index (BMI) greater than 40 kg/m^2, and comorbidity severe enough to prevent participation in the study protocol, including at-home exercise or attendance at scheduled injection appointments. Each knee was assessed separately for eligibility. Interested, eligible persons attended an informational meeting, gave consent for participation, and were enrolled.

Study Design

Participants were randomly assigned to 1 of 2 injection groups (dextrose or saline) or exercise using a computer-generated randomization scheme in forced blocks of 6 prepared by the UW Pharmacy Research Center. The injector, outcome assessor, principal investigator, and participants were blinded to injection group status.

Injection Intervention

Injections were performed at 1, 5, and 9 weeks with optional additional sessions at 13 and 17 weeks per the physician's (J.J.P.) recommendations and the participant's preference. Before the procedures the off-site UW Pharmacy Research Center prepared dextrose and saline syringes that were blinded using an opaque paper sleeve. Participants were offered an optional single 5-mg oxycodone tablet 30 minutes before injection. The injector (J.J.P.) examined the knee, marked tender anterior knee locations, placed anesthetic skin wheals of 1% lidocaine, and performed extra- and intra-articular injections according to a published protocol (Table 1).[16] Extra-articular injections were done on bone by palpation at major tender tendon and ligament insertions through up to 15 skin punctures using a peppering technique, placing a possible total 22.5 mL of solution; ultrasound guidance was not used. The 6-mL intra-articular injection was then delivered using an inferomedial approach. After the injection, participants were offered acetaminophen and 8, 5-mg oxycodone tablets to use as needed for up to 1 week and were advised on relative knee rest for 2 to 3 days with progressive resumption of routine activity over 1 month. They were discouraged from using nonsteroidal anti-inflammatory medications (NSAIDs) and from starting new therapies for their osteoarthritis during the study period.

At-home Exercise Intervention

Exercise group participants received an informational pamphlet about knee osteoarthritis (Visual Health Information, at http://www.vhikits.com/Default.aspx) depicting 10 at-home knee exercises demonstrated by the study coordinator at baseline. Participants were advised to begin exercises (3 sessions per week, 1 session daily, 10 repetitions per exercise), to gradually increase therapy as tolerated over 20 weeks (5 sessions per week, 3 times daily, 15 repetitions per exercise), and to continue them thereafter if desired.

Adherence and Precautions

Exercise group adherence was encouraged and assessed during telephone call reminders at the same interval that injection sessions occurred. Members of all groups were cautioned at each contact against knee overuse.

Outcome Measures

The primary outcome measure was change in knee-related quality-of-life as assessed by the composite score of Western Ontario McMaster University Osteoarthritis Index (WOMAC), a validated questionnaire evaluating osteoarthritis severity using pain, stiffness, and function subscales.[18] The WOMAC composite score, constructed as the weighted average of the 3 subscale scores, ranges from 0 (worst) to 100 (best) knee-related quality-of-life[19] and has been shown to be responsive to change.[18] The minimal clinical important difference (MCID) on the WOMAC for knee osteoarthritis has been reported as 12 points of change on a 0- to 100-mm visual analog scale.[20,21] Secondary outcomes included the knee pain scale (KPS),[22] a validated questionnaire assessing knee pain frequency (0 to 4 ordinal scale) and severity (0 to 5 ordinal scale), with higher values indicating worse symptoms. KPS data were collected separately for each treated knee and for untreated knees. The WOMAC and KPS scores were collected in person and before any procedure at baseline, 5, 9, and 12 weeks, and by telephone at 26 and 52 weeks.

Tertiary outcomes for injection participants included (1) ratings of procedure-related pain severity, using a 1 to 7 ordinal scale, obtained immediately after and 2 days after each injection session; and (2) daily logs of opioid medication use (yes/no) during the 7 days after each injection. Treatment satisfaction was assessed among all participants at 52 weeks with the question, "Would you recommend the therapy you received in this study to others with knee osteoarthritis like yours? (yes/no)." All participants were able to make brief qualitative comments about their experiences.

Demographics, self-reported weight and height, and severity of knee osteoarthritis seen on knee radiographs were collected at baseline to characterize the sample and to evaluate as covariates for statistical analysis. A fellowship-trained musculoskeletal radiologist (R.K.), using the 1- to 4-point Kellgren-Lawrence knee osteoarthritis scoring system,[23] evaluated existing, available knee radiographs. Attendance at injection sessions was tracked. Adherence to at-home exercises was assessed by the question, "In the past month, did you perform home exercises as directed? (yes/no)," administered by monthly mail-in logs for the first 20 weeks of the study. Blinding of the injector and injection participants was assessed at each injection session by asking each to identify the participant's group assignment using the items "dextrose," "saline," or "don't know."

Analysis

Two RCTs and clinical experience guided a priori sample size calculations. One RCT assessing prolotherapy for knee osteoarthritis reported a 44% effect size compared with baseline status on a visual analog scale.[11] A well-designed RCT reported a 20% to 40% effect size of prolotherapy for low back pain.[24] Assuming minimal change in the control groups and minimal loss to follow-up, 32 participants per arm would provide 80%

Table 1. Injection Solutions and Injection Techniques

Injection Type	Solution	Injection Technique
Dextrose		
Intra-articular 25% dextrose	In a 10-mL syringe: 5 mL 50% dextrose 5 mL lidocaine 1% saline	6.0 mL was injected using an inferomedial approach
Extra-articular 15% dextrose	22.5 mL distributed in 3, 10-mL syringes (7.5 mL each) using the following recipe: 6.75 mL 50% dextrose 4.5 mL 1% lidocaine 11.25 mL 0.9% saline	Up to 15 subdermal injections were placed, and 0.5 mL of 15% solution was injected using a peppering technique with a 25-gauge needle at each ligament-bone insertion. Each puncture site allowed for placement of solution at up to 3 ligament-bone insertions using a skin-sliding technique (withdrawing the needle to just below the skin and reinserting into an adjacent area without removing from the initial puncture site), allowing for the placement of up to 22.5 mL of solution
Saline control		
Intra-articular	5 mL 0.9% sodium chloride 5 mL 1% lidocaine	Injection technique identical to intra-articular injections above
Extra-articular	22.5 mL distributed in 3, 10-mL syringes (7.5 mL each) using the following recipe: 18 mL 0.9% sodium chloride 4.5 mL 1% lidocaine	Injection technique identical to extra-articular above

power to detect a 20% difference in mean composite WOMAC scores between control and dextrose participants at a significance level of 5%.

Data were analyzed using SAS 9.1 statistical software (SAS Institute Inc). Descriptive statistics describe outcomes at each time point; mean value and standard deviation (SD) were reported at baseline.

Analysis was by intention-to-treat. Repeated measures analysis of variance compared treatment groups on follow-up WOMAC total and subscale scores and KPS subscales after adjusting for baseline scores, age, sex, and BMI. Statistical significance between treatment groups was assessed at each time point (group × time interaction) and comprehensively for the entire time frame (main time effect). Because the WOMAC evaluates participant's knee-specific quality-of-life not considering the number of knees affected, the unit of analysis of the WOMAC scores was the participant regardless of the number of knees injected. Percentage improvement in WOMAC scores was calculated as the percentage change in total WOMAC score from baseline to 52 weeks relative to baseline score.[25,26] The proportion of participants in each group who met the MCID benchmark of 12 points on the 0- to 100-point composite WOMAC was calculated.

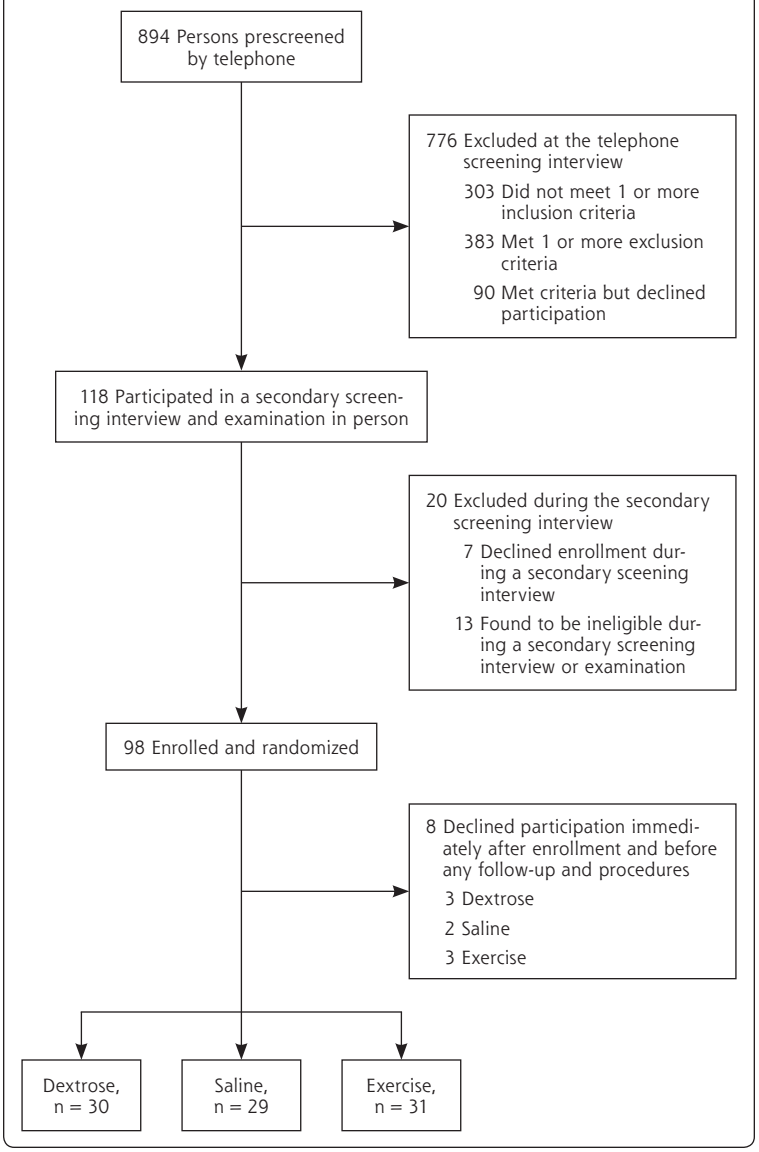
The unit of analysis for the KPS model was the individual knee. Because each participant completed 2 KPS questionnaires at each time point—1 per knee, the KPS scores for each knee were analyzed individually. If a participant had both knees treated, that participant accounted for 2 knees in the treated knees model. A hierarchical repeated measures model corrected the standard errors for the interaction between the reports on 2 knees by the same individual. A separate repeated measures model analyzed KPS scores for single untreated knees. The significance test for change from baseline is reported for WOMAC and KPS scores. A 2-tailed P value <.05 was established as a statistical significance level.

RESULTS

Of the 894 persons screened by telephone, 118 met initial eligibility criteria; 98 persons were enrolled and randomized. Eight enrollees dropped out before completion of any procedures or follow-up data collection. Ninety participants were therefore included in the analysis (Figure 1).

There were no significant baseline differences between groups (Table 2). The 8 enrollees who withdrew before the follow-up procedures were women; there were no other differences between the 8 women and the analyzed sample. The study sample consisted of 66% women with a mean age of 56.7 years (SD = 7.2 years); 74% were either overweight (BMI ≥25-29.9 kg/m^2) or obese (BMI ≥30 kg/m^2). Participants reported more than 5 years of knee pain, and most had failed at least 1 conservative therapy. Although radiograph reports identifying osteoarthritis were available for all included knees, administra-

Figure 1. Screening, enrollment, and randomization.



tive difficulties resulted in procurement of only 68 prestudy radiographs. The Kellgren-Lawrence scores ranged from mild to severe, and overall inclusion criteria, x-ray reports, and baseline WOMAC scores[19] suggest that on average, this cohort had moderate severity of knee osteoarthritis (Table 3).

Dextrose participants received 3.95 ± 1.0 injection sessions; 13 participants had both knees treated (26 knees), and 17 participants had 1 knee treated (total 43 knees). Saline participants received 3.71 ± 1.1 injection sessions; 13 participants had both knees treated and 15 participants had 1 knee treated (total 41 knees). Exercise participants returned an average of 22 (77.4%), self-assessments during the 20-week treatment period; 77% of participants reporting doing their at-home exercises as directed; 16 participants had both knees treated and 15 participants had 1 knee treated (total 47 knees). Fourteen participants reported using NSAIDS in the dextrose and saline groups, whereas 15 exercise participants reported NSAID use.

Between-group comparisons showed that dextrose participants at 52 weeks reported improved composite WOMAC scores (15.32 points, a 24% improvement compared with baseline status) compared with participants in the saline (7.59 points; $P = .022$) and exercise groups (8.24 points; $P = .034$). Fifty percent (15 of 30) of the dextrose participants improved by 12 or more points on the composite WOMAC score at 52 weeks compared with 30% (10 of 29) of saline participants and 24% (8 of 31) of exercise participants. Significant differences were also found at 9 weeks for dextrose compared with saline and exercise groups, 13.91 points compared with 6.75 points ($P = .020$) and 2.51 points ($P = .001$), respectively; and at 24 weeks, changes of 15.85 points compared with 8.12 points ($P = .021$) and 8.48 points ($P = .024$), respectively (Table 4, Figure 2).

Evaluation of the WOMAC subscale scores showed that dextrose participants generally reported consistent improvement across the subscales, achieved near-maximum improvement by 26

Table 2. Baseline Participant Characteristics by Treatment Group

Characteristic	Dextrose	Saline	Exercise	*P* Value
No.	30	29	31	
Female, No. (%)	19 (63)	20 (69)	21 (68)	0.82
Age, mean (SD), y	56.8 (7.9)	56.8 (6.7)	56.4 (7.0)	0.97
Duration of knee pain, No. (SD), mo	79.8 (62.9)	108.0 (99.5)	60.4 (71.6)	0.08
Body mass index, No. (%)				
≤25	10 (33)	8 (28)	6 (19)	
25-30	6 (20)	11 (38)	12 (39)	0.44
≥30	14 (47)	10 (34)	13 (42)	
Prior knee intervention, No. (%)				
History of arthroscopic surgery	7 (23)	5 (17)	7 (23)	0.84
Physical therapy	6 (20)	3 (27)	16 (52)	0.08
Hyaluronic acid injection	3 (10)	0 (0)	2 (6)	0.62
Corticosteroid injection	4 (13)	1 (9)	2 (6)	0.79
Glucosamine	7 (23)	5 (17)	8 (26)	0.82

Table 3. Baseline Participant Knee Osteoarthritis Severity Scores by Treatment Group

Characteristic	Dextrose		Saline		Exercise		*P* Value	
X-ray Kellgren-Lawrence osteoarthritis severity score[a]								
1-2 (mild osteoarthritis)	11		12		9		.35	
3-4 (moderate to severe osteoarthritis)	14		9		14			
WOMAC total score (SD) [range][b]	63.1 (15.0) [34.6-93.1]		62.7 (14.3) [34.3- 90.8]		60.5 (11.3) [35.7-77.0]		.73	
Pain score (SD) [range]	66.8 (14.9) [35.0-95.0]		66.7 (16.1) [30.0-95.0]		63.2 (13.1) [35.0-90.0]		.49	
Stiffness score (SD) [range]	57.1 (19.9) [25.0-87.5]		53.9 (14.2) [25.0-87.5]		55.3 (18.0) [12.5-100.0]		.73	
Function score (SD) [range]	65.2 (15.8) [39.7- 96.9]		67.6 (17.5) [35.3-100.0]		61.9 (12.7) [36.8-86.8]		.36	
Knee pain scale[c]	Treated Knee n = 43	Untreated Knee n = 17	Treated Knee n = 41	Untreated Knee n = 17	Treated Knee n = 47	Untreated Knee n = 15	Treated *P* Value	Untreated *P* Value
Pain frequency score (SD)	2.5 (0.9)	0.6 (1.1)	2.4 (0.9)	0.9 (0.9)	2.5(0.9)	0.7 (1.0)	.52	.69
Pain severity score (SD)	1.8 (0.8)	0.5 (1.1)	1.7 (0.7)	0.6 (0.8)	1.7(0.8)	0.4 (0.7)	.42	.74

WOMAC = Western Ontario McMaster University Osteoarthritis Index.

[a] Kellgren-Lawrence scores range from 1 to 4.

[b] The theoretical range in this study is 0 to 100, with higher values indicating better knee-related quality of life.

[c] The theoretical range of scores for knee pain frequency is 0 to 4 and for knee pain severity is 0 to 5, with higher values indicating worse symptoms.

Table 4. Change in the WOMAC Composite and Subscale Scores Over Time

Score	Week 5	Week 9	Week 12	Week 24	Week 52
WOMAC composite score change, mean (SE)					
Dextrose	7.94 (3.21)	13.91 (3.23)[a]	13.31 (3.32)[b]	15.85 (3.26)[a]	15.32 (3.32)[a]
Saline	5.22 (3.21)	6.75 (3.27)[a]	8.19 (3.37)[b]	8.12 (3.33)[a]	7.59 (3.36)[a]
Exercise	4.42 (3.21)	2.51 (3.26)[a]	4.26 (3.36)[b]	8.48 (3.28)[a]	8.24 (3.33)[a]
Subscale score change, mean (SE)					
Pain					
Dextrose	8.17 (3.49)	14.00 (3.52)[a]	11.78 (3.62)[b]	15.50 (3.56)[a]	14.18 (3.62)
Saline	3.28 (3.50)	5.29 (3.56)[a]	5.79 (3.67)[b]	6.40 (3.63)[a]	7.38 (3.67)
Exercise	4.53 (3.51)	3.44 (3.55)[a]	4.89 (3.66)[b]	8.07 (3.60)[a]	9.24 (3.63)
Stiffness					
Dextrose	7.08 (4.50)	14.17 (4.53)[c]	13.49 (4.67)[b]	14.85 (4.58)	15.55 (4.66)
Saline	8.62 (4.51)	9.12 (4.59)[c]	12.22 (4.73)[b]	10.40 (4.67)	9.97 (4.72)
Exercise	3.63 (4.51)	0.14 (4.58)[c]	3.13 (4.71)[b]	8.18 (4.61)	8.31 (4.68)
Function					
Dextrose	8.57 (3.27)	13.58 (3.30)[a]	14.61 (3.40)[a]	17.19 (3.33)[a]	16.25 (3.39)[a]
Saline	3.77 (3.28)	5.85 (3.34)[a]	6.63 (3.44)[a]	7.62 (3.40)[a]	5.46 (3.44)[a]
Exercise	5.10 (3.28)	4.00 (3.33)[a]	4.89 (3.43)[a]	9.30 (3.35)[a]	7.31 (3.40)[a]

WOMAC = Western Ontario McMaster University Osteoarthritis Index.

Notes: Numbers of participants for measurement points are as follows. Week 5: n = 30 dextrose, n = 29 saline, n = 28 exercise. Week 9: n = 30 dextrose, n = 26 saline, n = 27 exercise. Week 12: n = 27 dextrose, n = 24 saline, n = 25 exercise. Week 24: n = 28 dextrose, n = 25 saline, n = 27 exercise. Week 52: n = 26 dextrose, n = 25 saline, n = 26 exercise. Repeated measures analysis of variance compared between-group total and subscale WOMAC scores after adjusting for baseline scores, age, sex, and body mass index.

[a] Dextrose outperformed saline (P <.05) and exercise (P <.05); no statistically significant differences between saline and exercise.

[b] Dextrose outperformed exercise (P <.05); no statistically significant differences between dextrose and saline, and between saline and exercise.

[c] Dextrose outperformed exercise (P <.05); saline outperformed exercise (P <.05); no statistically significant differences between dextrose and saline.

weeks, and remained stable through 52 weeks. The most dramatic improvements were on the function subscale; dextrose participants reported significantly better function than both saline and exercise participants for a change of 16.25 compared with 5.46 (P = <.001) and 7.31 points (P = .009), respectively, at 52 weeks.

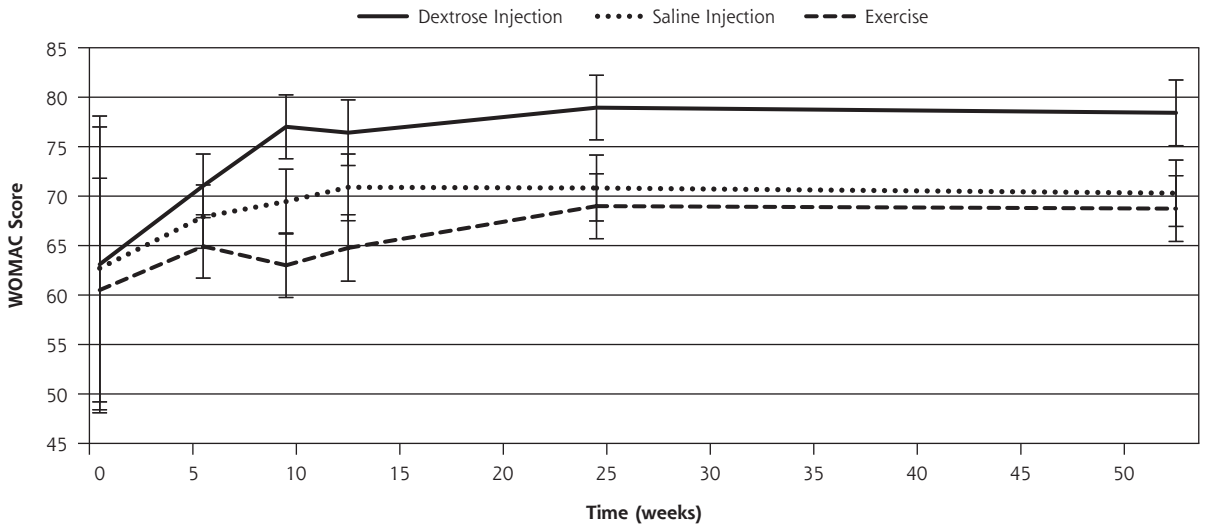
At 9 weeks, dextrose participants reported significantly better function than both saline and exercise, with a change of 13.58 compared with 5.85 points (P = .021) and 4.00 points (P = .004), respectively.

At 24 weeks, dextrose participants also reported significantly better functional change than both saline and exercise, with a change of 17.19 points compared with 7.62 points (P = .005) and 9.30 points (P = .018), respectively.

There was no correlation between exercise compliance in the exercise group and WOMAC composite improvements at 52 weeks (r = –0.11, P = .625).

Overall, the WOMAC scores of saline participants did not significantly differ from those of the exer-

Figure 2. Change in WOMAC composite scores over 52 weeks (± standard error).



WOMAC = Western Ontario McMaster University Osteoarthritis Index.

Note: WOMAC is scored on a range of 0 to 100 points, with higher scores indicating better knee-related quality of life. Nonoverlapping confidence intervals indicate significance of change in dextrose scores compared with change in scores of both saline (P <.05) and exercise (P <.05) groups.

Table 5. Change in Knee Pain Scale Pain Frequency and Pain Severity Scores in Individual Treated Knees Over Time

Measure	Week 5	Week 9	Week 12	Week 24	Week 52
KPS pain frequency score, mean (SE) [No.]					
Dextrose	−0.55 (0.26) [43]	−0.84[a] (0.25) [42]	−0.87[a] (0.27) [38]	−1.19[a] (0.25) [40]	−1.20[a] (0.21) [37]
Saline	−0.26 (0.26) [40]	−0.32 (0.25) [37]	−0.31 (0.27) [36]	−0.48 (0.25) [37]	−0.60 (0.21) [38]
Exercise	−0.15 (0.25) [38]	−0.22 (0.24) [40]	−0.12 (0.26) [37]	−0.49 (0.24) [39]	−0.40 (0.21) [38]
KPS pain severity score, mean (SE)					
Dextrose	−0.25 (0.26)	−0.48 (0.25)	−0.51 (0.27)	−0.92[a] (0.25)	−0.92[a] (0.21)
Saline	−0.07 (0.26)	−0.19 (0.25)	−0.16 (0.27)	−0.26 (0.25)	−0.32 (0.21)
Exercise	−0.07 (0.25)	−0.15 (0.24)	−0.06 (0.26)	−0.33 (0.24)	−0.11 (0.21)

KPS = knee pain scale.

Repeated measures analysis of variance compared between-group KPS scores after adjusting for baseline scores, age, sex, and body mass index.

[a] Change in dextrose score was greater than change in saline (P <.05) and exercise (P <.05) scores, and there were no statistically significant differences between saline and exercise scores.

cise group except for the stiffness scores at 9 (P = .047) and 12 weeks (P = .049), when the saline group fared better. Regardless of the number of knees injected, KPS-based knee pain frequency (9 through 52 weeks, P <.05) and severity (24 and 52 weeks, P <.05) were significantly reduced in the dextrose group compared with both comparison groups (Table 5). KPS scores of untreated knees improved slightly in all 3 groups compared with baseline but were not different between groups.

All injection group participants experienced expected mild to moderate postinjection pain; 3 participants in the dextrose group and 5 in the saline group experienced self-limited bruising. There were no other side effects or adverse events. The use of periprocedural analgesics was not different between injection groups. Sixty-three percent of saline participants used acetaminophen before or after injection compared with 74% of dextrose participants. Oxycodone was used before (63%) and after (47%) dextrose sessions and before (57%) and after (43%) saline injection sessions. Ninety-one percent of dextrose participants, 82% of saline participants, and 89% of home exercise participants reported they would recommend their respective interventions to other patients with knee osteoarthritis. Blinding was intact; the injector indicated "don't know" 93% of the time, and participants indicated "don't know" 91% (dextrose) and 93% (saline) of the time, with the remaining selections evenly divided between correct and incorrect answers (P = .77).

DISCUSSION

This RCT of adults with symptomatic knee osteoarthritis found substantial, consistent, and significant improvements in composite WOMAC scores at 26 and 52 weeks for the dextrose group compared with saline injections and at-home exercise groups. At 52 weeks, the average improvement on the WOMAC score was 15.32 ± 3.3 points or 24% compared with the baseline score; 50% (15 of 30) of the dextrose group reported improvement in the composite WOMAC score for the dextrose-treated participants, which exceeded the MCID of 12 points. Improvement in the dextrose group was consistent across the 3 WOMAC subscales, was nearly maximum by 26 weeks, and remained stable through 52 weeks. KPS-based results on a per knee basis were consistent with WOMAC findings.

These effects are consistent with findings of a single-arm prospective study (N = 36) using an identical injection protocol and similar eligibility criteria.[16] Participants in that study were slightly more symptomatic at baseline but reported similar overall effects at 52 weeks on WOMAC and KPS outcome measures; uninjected contralateral knees also showed significant improvement, suggesting that dextrose prolotherapy for more symptomatic knee osteoarthritis may also result in improvement of the uninjected side, likely through reduction in compensatory mechanisms. Our current findings are also consistent with a second prolotherapy RCT for knee osteoarthritis, though comparison is limited by methodological heterogeneity.[11] Direct comparison with studies of hyaluronic acid injection or other therapies is also limited given the heterogeneity of study eligibility criteria, overall health status, patient expectation, baseline osteoarthritis severity,[21] and WOMAC scoring methodology,[27] but improvements of 20% to 40% compared with baseline have been reported.[4,28]

The mechanism of action for dextrose is unclear. Hypertonic dextrose has been hypothesized to stimulate healing of chronically injured extra- and intra-articular tissue[29]; animal model studies reported

increased inflammatory markers[30] and significantly enlarged cross-sectional area in medial collateral ligaments.[31] The potential of prolotherapy to stimulate release of growth factors favoring soft tissue healing[11,32] and a positive neural effect[33] have also been suggested. In addition to dextrose-specific effects, needle trauma and volume expansion of local tissue may also produce tissue-level effects.[34]

Limitations of this study include a relatively small sample size, though the effect size of prolotherapy proved adequate to detect between-group differences. The study was not large enough to detect uncommon adverse events, such as intolerance to study medication or rare injection-related sequelae. Generalizability may be limited by numerous exclusion criteria, the relative youth of the cohort compared with those in some knee osteoarthritis studies,[35] and the relative lack of participants with very severe baseline WOMAC scores. The assessment of participant satisfaction was indirect and subject to bias. Radiographs were not available for all participants, and the use of Kellgren-Lawrence criteria for baseline radiological assessment of knee osteoarthritis severity is controversial. The Kellgren-Lawrence score, however, is likely to remain an important measure for gauging disease severity in symptomatic patients.[36] The exclusion of patients taking chronic opioids limits the generalizability of the results. Although clinical experience suggests that such patients may still benefit from prolotherapy, long-term (greater than 1 year) effectiveness and side effects are unknown. Strengths include pragmatic assessment using validated, patient-oriented outcomes and robust, consistent results.

These findings suggest that dextrose prolotherapy may improve upon standard care of knee osteoarthritis for certain patients. Its use in clinical practice is relatively uncomplicated; prolotherapy is performed in the outpatient setting without ultrasound guidance using inexpensive solutions. The knee protocol is easy to learn and requires less than 15 minutes to perform; continuing medical education is provided in major university and national physician organizations settings.[10] A prior study suggested that clinical improvement may accrue preferentially to those who are middle-aged, of normal BMI, and female.[16] For responders, whether prolotherapy results in sustained effect past 52 weeks, disease modification, or delayed definitive care, such as knee replacement, is not known. Clinical experience suggests that repeated sessions and tune-up sessions after 52 weeks improve outcomes and do not pose additional risk. The described procedure costs $218 per session in our clinic. Some third-party payers cover prolotherapy with authorization, but most patients pay out-of-pocket. Interest in prolotherapy among physicians and patients in the United States appears to be high based on attendance at continuing medical education conferences and physician listings on relevant websites.[10] Although the number of practitioners who perform prolotherapy in the United States is likely in the hundreds, no formal survey has been done since 1993.[37]

Prolotherapy for knee osteoarthritis has not been compared with other current therapy, including intra-articular corticosteroid and hyaluronic acid injections. Determination of clinical utility of prolotherapy will require confirmation in a larger effectiveness trial that includes biomechanical and imaging outcome measures to assess potential disease modification.[38,39] Clinical trials designed to optimize dose and assess biological mechanism of action are also warranted.

Prolotherapy performed by a trained operator resulted in safe, significant, and sustained improvements on validated, quality-of-life, pain, function, and stiffness measures compared with blinded (saline injections) and nonblinded (at-home exercise) comparison interventions. Prolotherapy may be an appropriate therapy for patients with knee osteoarthritis refractory to conservative care.

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Rabago D, Zgierska A, Mundt M, Kijowski R, Belling J, Patterson, JJ; *Dextrose prolotherapy for knee osteoarthritis: Results of a randomized controlled trial* (Oral presentation); North American Primary Care Research Group (NAPCRG) 39th annual conference; Banff, Canada; November 12-14, 2011.

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American Association of Orthopaedic Medicine Position Statement

Prolotherapy for the Treatment of Back Pain

This pronouncement was written for the American Association of Orthopaedic Medicine by Robert G. Klein, M.D., Jeffrey Patterson, D.O., Bjorn Eek, M.D. and David Zeiger, D.O.

Summary

It is the position of the American Association of Orthopaedic Medicine that prolotherapy is a safe efficacious therapy for the treatment of selected cases of low back pain and other chronic myofascial pain syndromes. This is based upon basic science data showing the effects of prolotherapy in animal models, clinical studies, a lengthy history of clinical use and efficacy, and increasingly widespread acceptance within the medical community. While we recognize that further basic science and clinical studies need to be done and are currently in process, we believe that prolotherapy is a safe, cost effective and efficacious therapy that can provide pain relief and return of function for many patients.

Introduction

Prolotherapy is an injection therapy used to treat chronic ligament, joint capsule, fascial and tendinous injuries of the low back. The goal of this treatment is to stimulate proliferation of collagen at fibro-osseous junctions to promote non-surgical soft tissue repair and to relieve pain. [1] Animal studies by Liu and others have shown proliferation of collagen with strengthening of ligaments with prolotherapy.[2] Further animal research is currently underway at the University of Wisconsin Medical School. Prolotherapy is commonly used in veterinary medicine.

The mechanism of action of ligament proliferation was supported by a pilot study in human volunteers that demonstrated an average increase of 65% in cross-sectional diameter of posterior sacroiliac ligaments 3 months after treatment. Computerized measurements of range of lumbar motion before and after treatment have also demonstrated improvements in motion that are consistent with soft tissue healing. [3, 4]

Scientific Evidence

There have now been 5 randomized clinical trials (RCT'S) of prolotherapy [5-9]for chronic low back pain; their methodology has varied considerably. Two of the trials [6, 7]used similar protocols with well defined injection sites, using dextrose-glycerine-phenol-xylocaine as the solution injected, and 6 weekly injection treatments of 20-30mL each. Both trials used multiple standardized and validated outcome measures to capture changes in pain, disability, and function over a minimum of 6 months, and both trials reported statistically significant improvements in pain and disability in the treatment groups.

The 3 other trials differed considerably. The study by Mathews et al [9] enrolled only 22 patients (16 treatment and 6 controls) and was unlikely to have the statistical power needed to detect a reasonable difference between treatment and placebo. The study by Dechow et al [8] had only 3 weekly injection treatments of 10mL each (total volume 30mL vs. 120-180mL in the two successful trials) of dextrose-glycerine-phenol solution. In addition, the authors attempted to inject all low back ligaments from only 2 injection sites rather than lifting and reinserting the needle at multiple sites as is commonly practiced. This technical difference may have impacted where the solution was injected. Patient selection was also an impediment in this trial, and the authors concluded that: "Many patients were not considered ideal candidates for sclerosing injections by the operator at the time of the treatment for a variety of reasons relating to technical difficulties, deconditioning, patients relying on invalidity benefit, excessive psychological stress, etc. even though they technically fulfilled the inclusion criteria. Therefore, the group of patients recruited into our study was likely to respond poorly to any single intervention in keeping with the relatively poor prognosis in the group of patients today in the UK."

The most recent study by Yelland from Australia [5] used a 20% dextrose solution that was injected at only 20% of the usual sites and did not include facet joint capsules included in the 2 positive RCT's. Not surprisingly, the study failed to show an advantage of plain dextrose, which is a weak prolotherapy solution, compared to a placebo injection of saline. Despite the shortcomings of this study the results obtained in terms of pain relief and increased function are quite striking. In both the group of prolotherapy patients (mean duration of pain was 14.8 years) and in the saline injection group (mean duration was 13.8 years), there was a statistically significant decrease in pain and disability scores at both 12 and 24 months' follow-up. In fact, just a fraction less than half of the patients in the prolotherapy group (46%) achieved a greater than 50% reduction of pain and 42% achieved a greater than 50% reduction in disability score. The authors stated that "participants exhibited marked and sustained improvements in their pain and disability, even with saline injections and normal activity." It should be appreciated that the bleeding and tissue disruption associated with needling and saline injections also has a mild proliferant effect so in fact there was no true placebo treatment. There may also be neurological effects of prolotherapy in relieving pain. The authors also admitted that "this trial's success rates in reducing pain and improving disability are at least as good as those reported for spinal cord stimulation, surgery or multidisciplinary treatment for patients with low back pain of shorter duration."

Although there is disagreement among the studies regarding the use of prolotherapy for chronic low back pain, this situation is hardly unique to this specific injection treatment. A recent systematic review of the literature by Nelemans in Spine ([10]attached) demonstrates how little evidence there is for the efficacy of a variety of commonly utilized and reimbursed low back treatments including facet injections, trigger point injections, and epidural injections. One of the prolotherapy trials discussed above [6]was included in this review and ranked fourth out of twenty-one randomized trials in terms of study design and is mentioned as the only one with significant follow-up. This study was

one of the few that they cited as showing definite statistical efficacy when compared to a control treatment using placebo saline injections.

The literature also indicates that prolotherapy appears to be very safe. None of the clinical trials have reported any serious adverse events with this treatment. In addition, a survey of adverse events related to prolotherapy reported that a group of almost 100 physicians had collectively almost 500,000 patients with this treatment approach and experienced only 66 complications, none of which were life-threatening. This is supported by the low number of serious or adverse reactions documented in the Florida review.

Although additional studies regarding the use of prolotherapy for chronic low back pain are necessary to address methodological issues of the previous trials, the same is true for all other low back treatment approaches, many of which are commonly utilized and covered by insurers with less documentation than prolotherapy. The reality is that despite the enormous impact of low back pain to our society there are no clearly effective treatments for chronic back pain, at least not in the sense that they are supported by multiple, high-quality randomized clinical trials using multiple validated outcome measures and an appropriate follow-up period. Nevertheless, patients continue to receive care for their chronic low back pain and insurers routinely pay for such care despite a lack of convincing efficacy for all chronic low back pain treatments. In fact, because of multiple pain generators that may come into play in low back pain, it is quite likely that multiple therapies will be necessary in any one patient or group of patients.

Recommendations

Prolotherapy should be considered a valid treatment option in a selected group of chronic low back pain patients. As such, it should not be held to a higher standard than other treatments with the same lack of efficacy that are nevertheless covered by insurers, such as epidural injections, steroid injections, and IDET, not to mention surgery for cases in which instability or progressive neurological deficit is absent. The goal of providing access only to the highest quality of treatments supported by the scientific literature is laudable. However, if insurers were to adopt a universal policy of denying payment for chronic low back pain treatments based on lack of definitive evidence, no one with chronic back pain would be able to obtain any treatment. Since this is clearly unacceptable, an alternative is to provide coverage for those treatments that are biologically plausible, supported in the literature by a number of cohort and randomized clinical trials, and have a reasonable safety profile.

Prolotherpy should be performed by well trained providers utilizing selected solutions and techniques. A number of different solutions are used in prolotherapy. The most common ingredients in these solutions are hyperosmolar dextrose and/or glycerine, combined with local anesthetics such as lidocaine or marcaine. A more detailed description of prolotherapy is available in the appended position paper by the Florida Academy of Pain Management and the review in Musculoskeletal Medicine that is also appended.

Conclusions

Vert Mooney, M.D., a prominent orthopedic surgeon and former chairman of orthopedics at the University of California, San Diego, wrote a recent editorial in The Spine Journal concerning prolotherapy ([11], see attached). He concluded that "this fringe treatment (prolotherapy) is no longer at the periphery and seems to be at the frontier of a justifiable, rational treatment with a significant potential to avoid destructive procedures."

We therefore urge the California Technical Assessment Forum to provide coverage for prolotherapy for chronic low back pain.

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Dec. 2, 2013

The Link Between Traumatic Brain Injury and Obstructive Sleep Apnea

In the cartoons, if someone slams you on the head with a frying pan, all you'll get is a few stars, or maybe birds, floating around your head – à la the rings of Saturn – and in the next scene you're back to normal. In real life, though, your brain would be much more scrambled. Our brains are protected from only so much velocity. Take for instance a major car collision, the blast of a mortar shell, or the stampede of a 250 pound backer – a traumatic brain injury can change the course of your life. Now, research is suggesting that traumatic brain injury and obstructive sleep apnea may go hand in hand, and that a causal relationship may be stronger than ever.

Approximately 1.7 million people sustain a traumatic brain injury (TBI) every year in the United States, with 1.4 million seeking treatment, 250,000 hospitalizations, and 50,000 deaths.

- Christopher J. Lettieri, MD

Every year, 1.7 million people suffer from a traumatic brain injury, which results in nearly 50,000 deaths. Not to mention, there are countless hospitalizations. When it comes to traumatic brain injuries, many people have no idea how severe the damage is until they actually get to the hospital – or they simply go home, curl up on the couch and fall asleep…never to wake up again. In a series of retrospective clinical observances, doctor Christopher J. Lettieri – a program director at the Walter Reed National Military Medical Center – explored a number of cases that hint to the conclusion that sleep apnea is prevalent in patients who recently suffered a traumatic brain injury.

In one study, conducted at the B.G.Tricounty Neurology and Sleep Clinic in Warren, Michigan, researchers took a look at 60 adults with traumatic brain injury. Out of those 60 – 30% were said to have developed obstructive sleep apnea. In another study, that was conducted at the University of Texas-Houston Medical School, researchers observed 87 patients, just three months after they sustained a traumatic brain injury. Researchers found that polysomnography was irregular in 46% of patients and 23% of patients were diagnosed with sleep apnea. When it comes to traumatic brain injury and obstructive sleep apnea, these studies suggest a stronger relationship than originally thought.

In another interesting study, researchers at Walter Reed National Military Medical Center analyzed 116 soldiers who recently saw combat in Iraq and Afghanistan and who suffered a traumatic brain injury. All of the soldiers went through extensive studies and sleep evaluations to determine if they had some kind of sleep disordered breathing. Not surprisingly, almost all of the patients reported having difficulty sleeping, but a striking 34.5% were diagnosed with obstructive sleep apnea. Perhaps more interestingly, the type of brain injury sustained determined the severity and predominance of the sleep disorder. For instance, soldiers with blunt trauma were much more likely to have obstructive sleep apnea and the risk for the sleep disorder skyrocketed.

Why are these studies so important? These studies are pertinent because they show how direct a link there is between traumatic brain injury and obstructive sleep apnea. Also, not diagnosing obstructive sleep apnea in someone who has just sustained a brain injury could impede recovery and rehabilitation. And as more and more soldiers are coming back from a war – a war that has turned young men and women into mere glimpses of their former selves – and as more and more professional athletes, especially football players, are suffering from the lingering effects of the sport, this link is becoming increasingly more important. When it comes down to it, understanding the link is just the half the battle, because it is also critical for these traumatic brain injury sufferers to undergo CPAP treatment right away. Perhaps with CPAP treatment, people who have become lost because of their injury can finally find themselves again. If you've sustained a serious injury and are seeing stars – or birds for that matter – you may want to get tested for sleep apnea.

Original study: "Recognizing Obstructive Sleep Apnea in Patients With Traumatic Brain Injury"

NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

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The Comorbidity of Sleep Apnea and Mood, Anxiety, and Substance Use Disorders among Obese Military Veterans within the Veterans Health Administration

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SCIENTIFIC INVESTIGATIONS

Objectives: To determine the relations between obstructive sleep apnea (OSA) diagnosis, the likelihood of being diagnosed with a psychological condition, among obese veterans, after accounting for severity of obesity and the correlated nature of patients within facility. We hypothesized that (1) individuals with a diagnosis of OSA would be more likely to receive a diagnosis of a (a) mood disorder and (b) anxiety disorder, but not (c) substance use disorder.

Design: Cross-sectional retrospective database review of outpatient medical records between October 2009 and September 2010, conducted across all 140 Veterans Health Administration (VHA) facilities.

Setting: The entire VA Health Care System.

Patients or Participants: Population-based sample of veterans with obesity (N = 2,485,658).

Main Outcome Measures: Physician- or psychologist-determined diagnosis of psychological conditions including mood, anxiety, and substance use disorders.

Results: Using generalized linear mixed modeling, after accounting for the correlated nature of patients within facility and the severity of obesity, individuals with a diagnosis of sleep apnea had increased odds of receiving a mood disorder diagnosis (OR = 1.85; CI = 1.71-1.72; $p < 0.001$), anxiety disorder diagnosis (OR = 1.82; CI = 1.77-1.84; $p < 0.001$), but not a diagnosis of substance use disorder.

Conclusions: Among obese veterans within VA, OSA is associated with increased risk for having a mood and anxiety disorder, but not substance use disorder, with the strongest associations observed for posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). In addition, this relation remained after accounting for severity of BMI.

Keywords: Sleep apnea, depression, anxiety, veterans

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Obstructive sleep apnea (OSA), defined as impaired patency of the upper airway during sleep, resulting in apneas (complete cessation of airflow for at least 10 seconds) and/or hypopneas (50% reduction in airflow), is one of the most common forms of sleep disordered breathing (SDB). OSA can result in hundreds of brief arousals from sleep in a single night and affects approximately 2% of women and 4% of men nationwide,[1] with higher rates documented among military veterans (6.5%).[2] Indeed, OSA is one of the most common, yet underdiagnosed, causes of sleep disturbances among veterans, showing no remittance without treatment or lifestyle changes (loss of weight).[3] The nearly twofold difference in prevalence of OSA among veterans, compared to community samples, is thought to be due, at least in part, to two risk factors which are common among veterans: male gender and obesity.[4]

In addition to direct effects (e.g., daytime fatigue, disturbed sleep, irritability, memory problems, and decreased quality of life),[5,6] OSA is associated with a number of indirect physical and psychological complications. Such complications include hypertension, heart disease and heart failure, stroke, insulin resistance and impairments in neurocognitive functioning, workplace and driving accidents, and elevated psychological symptoms.[7-11] While the associations between OSA and physiological conditions are well established, research is starting to expand our knowledge of the relation between OSA and psychopathology.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Previous work has documented a relation between sleep apnea and psychopathology, however, limited work has examined this among veterans, a sample of individuals at elevated risk for both sleep apnea and psychopathology. The current study examines the relations between sleep apnea and the likelihood of being diagnosed with a psychological condition among veterans throughout the VA Health Care System.

Study Impact: Results indicate a strong association between mood and anxiety disorders and sleep apnea among obese veterans. This highlights the importance of conducting sleep apnea assessments among obese veterans with mood and anxiety disorders (especially MDD and PTSD), as well as conducting anxiety and mood assessments among obese veterans with sleep apnea; such information could aid in the allocation of resources in order to optimize treatments for psychopathology and sleep apnea.

OSA and Mood Disorders

To date the majority of studies investigating the association between OSA and psychopathology have focused on mood disorders, specifically major depressive disorder (MDD). While a few studies have demonstrated a lack of an association between OSA and MDD,[12,13] a majority have pointed, instead, to a strong relation between OSA and MDD.[14,15] For example, community-based epidemiological work has suggested that individuals with MDD are at a five-fold greater risk for having OSA than healthy controls,[16] with between 44.6% and 56% of patients with OSA meeting criteria for MDD.[17,18] Providing further support for the relation between OSA and MDD, intervention studies have demonstrated that treatment of OSA (via continuous positive airway pressure [CPAP] or surgery) results in improvements in depressive symptoms.[19]

OSA and Anxiety Disorders

Relatively less research has investigated the relation between OSA and anxiety disorders. The work that has been done in this area has demonstrated that 16.7% of military veterans with OSA also had an anxiety disorder.[20] Though the comorbidity between OSA and anxiety is striking, the majority of work conducted on this association has specifically focused on the relation between OSA and posttraumatic stress disorder (PTSD), and to a lesser extent, panic disorder (PD). Indeed, 12.86% of veterans with OSA have a diagnosis of PTSD[20]; and OSA has been associated with nocturnal panic attacks and aggravation of panic symptoms.[21,22] Intervention research further supports this association. Similar to findings with MDD, the treatment of OSA through the use of CPAP reduces symptoms of PTSD and panic.[22-24] Unfortunately, over 50% of veterans with PTSD are non-adherent to CPAP, a significantly lower adherence rate than veterans without PTSD,[25] suggesting that PTSD itself may interfere with successful treatment of OSA.

OSA and Substance Use Disorders

A relative dearth of research has investigated the relation between OSA and substance use disorders (SUDs), with generally mixed results among existing empirical investigations. Cross-sectional work has suggested a relation between OSA and SUDs, particularly alcohol use disorders.[26] However, epidemiological work among military veterans has found no differences in SUD diagnosis (or alcohol use disorders, specifically) between those with and without OSA.[20] While this finding may have been influenced by differential rates of diagnosis across Veterans Affairs (VA) facilities, further research is clearly needed to better understand the relation between OSA and SUDs.

Summary

Taken together, previous work has documented a relation between OSA and psychopathology,[27] with the strongest associations being observed for MDD,[16-18] anxiety disorders,[20] and PTSD, specifically.[28] To date, there has been only one study investigating the relation between OSA and psychopathology within the VA Health Care System, which is surprising given the heightened prevalence of OSA among veterans.[2,22] This study was a cross-sectional retrospective review of a centralized VA database between the years 1998 and 2001. The sample included 4,060,504 military veterans with and without sleep apnea. ICD-9-CM codes were extracted to identify diagnostic status of sleep apnea and psychological conditions. Results from logistic regressions demonstrated that OSA was associated with increased risk for psychological diagnosis including MDD (21.8%), anxiety (16.7%), PTSD (11.9%), and bipolar disorder (3.3%). Two main extensions to this prior work are needed in order to inform our understanding of the relations between OSA and psychopathology among veterans. First, the study by Sharafkhaneh and colleagues[20] did not account for differential diagnosis rates across VA facilities, which may explain the observed associations between OSA and psychological diagnosis. Second, relatively little work has accounted for third factors that may influence the observed associations. For example, it is possible that a common risk factor for both OSA and psychopathology may be driving these relations (e.g., severity of obesity[14]).

The Role of Severity of Obesity

Obesity is associated with mood, anxiety, and somatoform disorders as well as elevations in psychological distress.[29-31] In addition, obesity is one of the leading risk-factors for OSA.[32] The relation between obesity and OSA is thought to be due to anatomical modifications that result in either upper airway constriction or reduction in lung volume, leading to a loss of caudal traction of the upper airway and pharyngeal collapse.[33] In fact, a one standard deviation increase in body mass index (BMI) has been associated with a 4-fold increase in the prevalence of OSA.[34] Indeed, of those with severe obesity (BMI > 40), the prevalence of OSA ranges between 40% and 90%.[35] Given these associations, there is clearly a need to account for the severity of obesity when assessing relations between OSA and psychological diagnoses.

Current Study

We sought to replicate and extend the work of Sharafkhaneh[20] by examining the association between OSA and the likelihood of being diagnosed with a psychological condition. We aimed to test these associations among obese veterans across all 140 Veterans Health Administration (VHA) facilities, after accounting statistically for the potentially correlated nature of both patients and diagnostic conventions within each facility as well as severity of obesity (i.e., BMI). We examined these relations among obese veterans only, as we wanted to investigate if the pattern of these relations remained consistent with findings from Sharafkhaneh when examining a population at significant risk for both psychological conditions and OSA.[32] Based on prior research,[20] we hypothesized that individuals with a diagnosis of OSA would be more likely to be diagnosed with (a) mood disorders, and (b) anxiety disorders, but not (c) substance use disorders. In addition, we expected these relations would hold after accounting for severity of obesity (i.e., BMI).

METHODS

The current study is a retrospective cross-sectional database review of all outpatient medical records collected across each of the 140 VHA facilities for fiscal year (FY) 2010 (October 2009-September 2010). Study procedures were approved by the

VA Palo Alto Health Care System's research office and Stanford University's Human Research Protection program.

Information Collected

Data Extraction

Data were obtained from the outpatient VHA Decision Support System (DSS) database. The DSS is a national clinical centralized relational database that includes encounter data from VHA clinical information systems. Patient information, including but not limited to, demographics, diagnoses, procedures, and services provided are updated on a daily basis. In order to construct a database appropriate for the current analyses, SAS v9.2 was used to extract demographic variables, body mass index (BMI), obesity-related physical conditions (ICD-9-CM codes), psychological diagnoses (ICD-9-CM codes), and diagnosis of sleep apnea. A unique identifier (scrambled social security number) was used to obtain complete patient records within the DSS.

Selection of Participants

Within the DSS we sought to identify veterans at-risk for sleep apnea as a function of obesity. From the 5,576,858 total VHA outpatients seen in FY2010 across the 140 facilities, 64% (N = 3,574,765) had at least one record entry of height and weight available to calculate BMI. Previous research using this database has indicated that 90% of within-person repeated measures demonstrated < 1-inch differences in height and < 2% had different values for weight.[36] Based on this work, we included individuals with ≥ 1 measurement for height and weight in order to optimize our potential sample size. In the case of multiple values per patient, the largest biologically plausible (i.e., height < 84 inches and weight < 700 pounds), value was used to calculate BMI. The largest weight value was chosen because those fluctuating throughout the year in meeting obesity criteria were considered higher risk than those not meeting criteria at any point during the year. Patients were retained in the final sample (n = 2,485,658) if they had a (a) BMI ≥ 30, or (b) 25 ≤ BMI < 30 and at least one obesity associated comorbidity (e.g., diabetes, hypertension, hyperlipidemia, heart disease, congestive heart failure, cholelithiasis, osteoarthritis, low back pain, gastroesophageal reflux disease, and obstructive sleep apnea).

Measures

Outcome Variables

The primary outcomes of this study included psychological diagnostic status. All diagnoses were made by outpatient health care providers and are based on diagnostic criteria consistent with ICD-9-CM diagnoses. Previous work has vetted the accuracy of diagnoses within VA administrative databases.[37] First, we investigated psychological diagnostic status across broad classifications including (a) mood disorders, (b) anxiety disorders, and (c) substance use disorders (SUDs; see **Table 1** for corresponding ICD-9-CM codes). Second, in the event of a clinically significant finding within a classification, subsidiary analyses were then conducted for each specific disorder (e.g., PTSD, MDD, alcohol use disorder; see **Table 1** for corresponding ICD-9-CM codes) comprising that classification. All outcomes were binary (0 = absence of diagnosis, 1 = presence of diagnosis).

Table 1—ICD-9-CM Diagnostic Codes

Condition	*ICD-9-CM* diagnosis code
Obesity	278.00, 278.01, 259.9, V778
Sleep Apnea	780.57, 786.03, 327.2, 327.20, 327.21, 327.23, 327.29
Diabetes	250, 357.2, 362.0, 366.41
Hypertension	401, 402, 403, 404, 405
Hyperlipidemia	272
Coronary Heart Disease/Ischemic Heart Disease (includes CAD, MI)	429.1, 429.0, 429.2, 429.9, 410, 411, 412, 413, 414, 440
Congestive heart failure	402, 404.0, 414.19, 425.4, 428, 429.1, 429.4, 997.1
Cholelithiasis	574
Osteoarthritis	715
Low back pain	722, 724, 846, 847
Gastroesophageal reflux disease	530.11, 530.81, 530.2, 787.1
Bipolar Disorders	296.00-296.06, 296.10-296.16, 296.40-296.46, 296.50-296.56, 296.60-296.66, 296.70, 296.80-296.81, 296.89
Major Depressive Disorder	296.20-296.26, 296.30-296.36
Panic Disorder	300.01
Generalized Anxiety Disorder	300.02
Phobic Disorders	300.20
Agoraphobia	200.21, 300.22
Social Phobia	300.23
Obsessive Compulsive Disorder	300.30
Posttraumatic Stress Disorder	309.81
Alcohol Use Disorders	303.00, 303.90, 305.00-305.03
Cannabis Use Disorders	304.30-304.33, 305.20-305.23

Mood Disorder comprised codes for major depressive disorder and bipolar disorders. Anxiety Disorders comprised codes representing panic disorder, generalized anxiety disorder, phobic disorders, agoraphobia, social phobia, obsessive compulsive disorder, and posttraumatic stress disorder. Substance use disorders comprised alcohol and cannabis use disorders.

Explanatory Variables

To determine patient characteristics associated with psychological diagnostic status, data on patient variables were obtained including: (a) BMI (defined as [703 × weight in pounds]/height in inches squared), (b) obesity-related comorbidities (diabetes: ICD-9-CM 250, 357.2, 362.0, 366.41; hypertension (401-405); 8 additional obesity-related comorbidities summarized in **Table 1**), and (c) sleep apnea (see **Table 1** for details). All variables, with the exception of BMI, were binary (0 = absence, 1 = presence).

Data Analytic Plan

To describe and explore variability in facility-level rates of psychological diagnoses and sleep apnea diagnosis, we calculated the rate of each respective diagnosis (number of patients

with the diagnosis divided by the total number of patients in the facility) in each of the 140 VHA facilities. Next, in order to evaluate the relation between sleep apnea, obesity, and psychological diagnoses (anxiety disorder, mood disorder, substance abuse disorder) we conducted three primary analyses using generalized linear mixed effects models. Independent models were generated for each binary dependent variable (i.e., anxiety disorder, mood disorder, substance use disorder). In the event of a clinically significant finding, subsidiary analyses were conducted for each specific disorder comprising the significant category of psychopathology. Within all models, a random effect for facility was included to account for grouping of patients within VHA facilities. PROC GLIMMIX procedures available within SAS V 9.2 were used to perform estimation and statistical inference for generalized linear mixed effects models.

RESULTS

Rates of Diagnosis

In FY2010, PTSD (12.30%) was the most common psychological diagnosis among obese veterans, followed by: MDD (6.40%), SUD (4.19%), bipolar disorder (I and II; 2.63%), generalized anxiety disorder (1.75%), panic disorder (.91%), agoraphobia (.35%), and social anxiety disorder (0.11%). Additionally, 6.68% of obese veterans received a diagnosis of sleep apnea.

Facility-Level Correlates of Psychological Disorder Diagnosis

In relation to facility-level correlates of psychological diagnosis, the intraclass correlation (ICC) of the intercept-only model indicated that 9.4% of the total variance in mood disorder diagnosis was between facilities rather than explainable by patient factors. Similarly, 10.3% of the total variance in anxiety disorder diagnosis and 20.3% of variance in SUD diagnosis were attributable to differences between facilities.

Final Model

Results from the final multi-predictor analyses are provided below. Results are discussed in relation to each diagnostic classification (i.e., mood disorders, anxiety disorders, SUDs). Next, in the case of a clinically significant finding, results are presented for each specific disorder comprising the respective classification of psychopathology.

Mood Disorders

After accounting for the correlated nature of patients within facility, individuals with a diagnosis of sleep apnea were at increased odds of receiving a mood disorder diagnosis (OR = 1.85; CI = 1.80-1.88; $p < 0.001$). Results remained after accounting for BMI, such that after holding BMI constant, a diagnosis of sleep apnea was associated with increased odds of a mood disorder diagnosis (OR = 1.75; CI = 1.62-1.89; $p < 0.001$). In comparison, when holding sleep apnea diagnosis constant, BMI was not associated with the odds of having a mood disorder diagnosis (OR = 1.04; CI = 1.03-1.04). Subsidiary analyses indicated that individuals with a sleep apnea diagnosis had a 1.4 times ($p < 0.001$) greater likelihood of having a diagnosis of MDD, and a 1.01 times ($p < 0.001$) greater likelihood in having a bipolar disorder diagnosis. Results remained after accounting for BMI such that when holding BMI constant, individuals with sleep apnea had greater odds of having a diagnosis of MDD (OR = 0.59; CI = 0.58-0.60; $p < 0.001$) and to a lesser extent, bipolar disorder (OR = 0.48; CI = 0.46-0.49; $p < 0.001$). Consistent with the primary analysis, results were nonsignificant when holding sleep apnea constant.

Anxiety Disorders

After accounting for the correlated nature of patients within facility, individuals with a diagnosis of sleep apnea were at greater odds of receiving an anxiety disorder diagnosis (OR = 1.82; CI = 1.77-1.84; $p < 0.001$). Results remained after accounting for BMI, such that after holding BMI constant, a diagnosis of sleep apnea was associated with increased odds of an anxiety disorder diagnosis (OR = 1.71; CI = 1.61-1.82). In comparison, when holding sleep apnea diagnosis constant, BMI was not clinically significantly associated with the odds of having an anxiety disorder diagnosis (OR = 1.02; CI = 1.02-1.02). Subsidiary analyses indicated that individuals with a sleep apnea diagnosis had 1.5-fold greater odds of having a PTSD diagnosis, a 1.3-fold increase in odds of a panic disorder diagnosis, and a 1.2-fold increase in having a diagnosis of both generalized anxiety disorder and agoraphobia (all *p's* < 0.001). Results remained after accounting for BMI. Here, when holding BMI constant, individuals with sleep apnea had the greatest odds of having a diagnosis of PTSD (OR = 0.58; CI = 0.58-0.59; $p < 0.001$), followed by panic disorder (OR = 0.55; CI = 0.53-0.56; $p < 0.001$), generalized anxiety disorder (OR = 0.54; CI = 0.53-0.56; $p < 0.001$), and agoraphobia (OR = 0.54; CI = 0.51-0.57; $p < 0.001$). Again, consistent with the primary analysis, results were nonsignificant when holding sleep apnea constant.

Substance Use Disorders

After accounting for the correlated nature of patients within facility, individuals with a diagnosis of sleep apnea were not at clinically greater odds of receiving a substance use disorder diagnosis (OR = 0.94; CI = 0.92-0.97). Due to the nonsignificant findings, further analyses were not conducted.

DISCUSSION

Results from this study demonstrate that, among obese veterans in the VA Health Care System, a diagnosis of sleep apnea is associated with increased risk for having a mood or anxiety disorder, but not a substance use disorder. The strongest associations were observed for MDD and PTSD. In addition, results remained after accounting for BMI, such that when holding BMI constant, individuals with sleep apnea had increased odds of both mood and anxiety disorders, specifically MDD, bipolar disorder, PTSD, panic disorder, generalized anxiety disorder, and agoraphobia.

Obese veterans with sleep apnea had clinically significant greater odds of having a mood disorder. This finding is consistent with previous research.[20] In addition, when holding BMI constant, a significant relation emerged for mood disorders. This

indicates that the association between sleep apnea and mood disorders is attributable, at least in part, to factors other than BMI. While mixed results exist for the relation between sleep apnea and MDD, results from specificity analyses supported previous research,[20] indicating an association between sleep apnea and MDD (and to a lesser extent bipolar disorders) as the strongest association within the mood disorders. As results demonstrated that the association was above and beyond BMI, it is unlikely that among this sample BMI was affecting the nature of the relation between sleep apnea and MDD. Two primary theoretical models have been posited to explain this relation. First, some have suggested that the relation between sleep apnea and MDD is explained by depression secondary to a general medication condition.[38] Additional work has suggested that hypoxemia, fragmented sleep, and the daytime consequences of poor sleep (fatigue, excessive daytime sleepiness) have been shown to increase depressed mood.[39] Unfortunately, the cross-sectional nature of the present investigation does not allow for an understanding of the temporal relations of the observed associations.

Obese veterans with sleep apnea also had clinically significant greater odds of having an anxiety disorder. This finding adds to the literature base supporting an association between sleep apnea and anxiety.[20] Further, results remained after accounting for BMI, such that when holding BMI constant, sleep apnea was still associated with anxiety disorders. Consistent with the findings regarding mood disorders, this suggests that the relation between sleep apnea and anxiety is above and beyond the impact of BMI. In terms of specific anxiety disorders, results indicated that sleep apnea had the strongest association with PTSD (followed by panic disorder and generalized anxiety disorder), a consistent finding in the recent literature.[20]

As expected, we did not observe an association between sleep apnea and substance use disorders. This is consistent with previous research conducted among veterans,[20] however, is in contrast to a host of additional work suggesting an association between substance use disorders and sleep apnea.[40,41] This finding may be influenced by data collection methods. This is to say, all data were collected from outpatient VA records. It is possible that individuals with severe substance abuse disorders (a) do not seek treatment within the VA, or (b) are more likely to use inpatient and residential services, which were not included here.

While this study has a number of strengths, including the use of a large sample across the VA health care system, and accounting for differential rates of diagnosis across facilities, there are some limitations which should be considered when interpreting these results. First, the data presented here are cross-sectional in nature and therefore causal or temporal conclusions cannot be made, nor can we identify mechanisms that may be involved in the observed associations. However, as findings have replicated those of Sharafkhaneh and colleagues,[20] future research would now benefit from determining mechanisms that may further explain the differential relations between sleep apnea and mood/anxiety versus substance use disorders. Second, a number of individuals were excluded due to missing height and/or weight assessments. Future research would benefit from more consistent inclusion of these assessments. Third, all data were obtained from a retrospective database review of ICD-9-CM diagnostic codes. While the reliance on ICD-9-CM diagnostic codes within DSS data introduces the potential for miscoding or misclassification, ICD-9-CM codes have generally been found to be a valid proxy for estimating disorder[42] and have been consistently used within VA research.[20,43] Future research would benefit from the inclusion of longitudinal work using standardized assessments. For example, inclusion of multi-modal assessment would strengthen confidence in diagnoses, especially in relation to sleep apnea. Here, inclusion of a sleep laboratory assessment to confirm sleep apnea status would be beneficial. This form of assessment would also allow for the determination of history and type of sleep apnea, as well as the patients' involvement in treatment for sleep apnea, which our current data cannot provide. Fourth, as our sample was comprised entirely of obese veterans, we may have a restricted range of BMI, which may have affected the observed findings. Finally, the use of an entirely veteran sample may limit the generalizability of the findings. While our prevalence rates of PTSD are consistent with past VA research[20] and VA diagnostic trends,[44] observed rates of MDD were significantly lower than among other VA samples.[20] These findings should be replicated among other VA, as well as non-veteran and female samples.

Despite these limitations, results provide preliminary clinical implications. Namely, findings indicate a strong association between mood and anxiety disorders and sleep apnea among obese veterans. This highlights the importance of conducting sleep apnea assessments among obese veterans with mood and anxiety disorders (especially MDD and PTSD), as well as conducting anxiety and mood assessments among obese veterans with sleep apnea. Such information could aid in the allocation of resources in order to optimize treatments for psychopathology and sleep apnea.

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VANCOUVER -- Combat veterans with post-traumatic stress disorder (PTSD) almost universally suffer sleep problems -- with more cases of sleep apnea than might otherwise be expected -- U.S. Army researchers found.

In a group of 135 young, otherwise healthy combat veterans with PTSD, 98.5% reported sleep complaints, Nick Orr, MD, and colleagues at the Walter Reed Army Medical Center in Washington, D.C., reported here at the annual international scientific meeting of the American College of Chest Physicians (CHEST).

Despite their relatively young age (around 35) and slightly overweight physique, 54% of the PTSD patients who underwent polysomnography at Walter Reed were diagnosed with obstructive sleep apnea (OSA) -- whereas, in the general population, the rate of OSA is only 20%.

It can be all too easy to dismiss daytime sleepiness and other symptoms as part of depression and PTSD, Orr explained. But these results argue for screening all military PTSD patients for sleep apnea, Orr said in an interview.

"You'll be darned if you just keep treating it with medications, cognitive behavioral therapy, and all the other modalities you use for PTSD, when you haven't addressed possible sleep apnea, which could get restorative sleep and kind of break the cycle for the PTSD symptoms," he told *MedPage Today*.

Session co-moderator Andreea L. Antonescu-Turcu, MD, of the Medical College of Wisconsin and chief of pulmonology at the Zablocki VA Medical Center, both located in Milwaukee, agreed that the study results should justify the importance of screening for sleep problems in military patients with PTSD -- even when they don't fit the classical profile for OSA.

"As the data are coming out it probably should be part of their routine evaluations to screen for sleep disordered breathing," she told *MedPage Today*. "Maybe this is part of their disorder that we have to address early on in patients with PTSD."

The reason for the well-recognized sleep problems in PTSD isn't clear, but recent reports have argued that these symptoms should be considered a central feature of the disorder and not just a consequence of it, Orr noted.

His group retrospectively analyzed electronic medical records for all 135 service members (91.9% men, average age 35.3) with combat-related PTSD seen at the Walter Reed sleep clinic from March 2006 through April 2010.

Orr noted that these returning soldiers were assigned to the Warrior Transition Brigades, which were asked to refer PTSD cases with with traumatic brain injury to the sleep clinic.

Not surprisingly, the majority of veterans in the current study had been injured (80 of the 135) and about 70% were traumatic brain injuries, primarily mild concussions from blast incidents.

The average body mass index (BMI) was 28.91 -- putting most of the patients in the overweight but not obese category.

Comorbid psychiatric illness was nearly universal with PTSD in the study patients; 88.9% suffered from depression and 44.4% were diagnosed with anxiety.

Sleep complaints among the study patients included excessive daytime somnolence in 88.2% -- confirmed by an average Epworth Sleepiness Scale score in the "sleepy" range (10.7) -- as well as sleep fragmentation in 67.4% and difficulty falling asleep in 55.6%.

Polysomnography done in 80.7% of the study patients diagnosed insomnia in 55% and OSA in 54%.

Those patients with OSA were generally older, had a higher BMI, and were less likely to have suffered trauma or a traumatic brain injury compared with those who did not have sleep apnea (all $P \leq 0.001$).

Orr's group cautioned that they were unable to determine how many of the service members in the study had OSA before being deployed -- but the researchers assumed that it was largely preexistent.

High medication use, including painkillers and sedatives, might have contributed to the sleep characteristics of these populations, the investigators noted.

But Orr pointed out that comorbid depression and use of medication were similar in PTSD patients with and without OSA. Also, "the injured population had less obstructive sleep apnea, so if the narcotics were causing central apneas then why was it the opposite?" he asked.

The study was limited to service members returning from combat situations. But in terms of generalizability, Orr noted that sleep disordered breathing was almost universal in a prior study of female sexual assault victims and in another study conducted among crime victims with sleep problems -- most of whom also had PTSD.

One problem with finding sleep apnea in this fairly young PTSD population was that compliance with treatment -- continuous positive airway pressure (CPAP) -- is a problem, cautioned co-author Jacob Collen, MD, also of Walter Reed.

Whether CPAP -- if adhered to -- can actually reverse some of the symptoms of PTSD still remains to be seen, he said in an interview with *MedPage Today.*

Orr reported having no conflicts of interest to disclose.

Antonescu-Turcu reported having no conflicts of interest to disclose.

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Recognizing Obstructive Sleep Apnea in Patients With Traumatic Brain Injury

Christopher J. Lettieri, MD | November 11, 2013

Editor's Note:

Obstructive sleep apnea (OSA) is associated with numerous comorbid conditions. In many, a causative relationship has either been well established or is strongly associated. As the knowledge of sleep-disordered breathing and its consequences continues to grow, so does the list of associated or consequential conditions. The following is part 5 of a 5-part series exploring more recently identified consequences of OSA.

Introduction

Approximately 1.7 million people sustain a traumatic brain injury (TBI) every year in the United States, with 1.4 million seeking treatment, 250,000 hospitalizations, and 50,000 deaths.[1-3] Mild TBI comprises the majority of cases (70%-90%).[4]

Sleep disturbances occur with increased frequency in patients with TBI compared with the general population. Subjective complaints of sleep/wake disturbances are exceedingly common, with sleep fragmentation, insomnia, impaired daytime functioning, or hypersomnolence reported in 46%-98% of patients.[3,5-13] Objective sleep/wake disturbances have been observed in up to 72.5% of these patients.[3,5,8,10] When present, sleep disturbances can adversely affect outcomes.

Baumann and colleagues[9] evaluated 96 patients 4 days after injury, and 65 individuals were reevaluated 6 months later. All individuals underwent comprehensive evaluations, including subjective questionnaires, neuroimaging, laboratory studies, and objective measures of sleep, including overnight polysomnography, multiple sleep latency testing, maintenance of wakefulness testing, and actigraphy. Daytime somnolence was reported in 28% of the cohort. The majority of patients (72%) developed new sleep disorders after their injury. Objective criteria for posttraumatic hypersomnia were met in 22% of participants.

Development of OSA After TBI

Sleep-disordered breathing is common after TBI and develops in 12%-36% of patients.[3,5,7,10,11] In a retrospective study of 60 adults with TBI (40% mild severity, 20% moderate, and 40% severe), Verma and colleagues[7] found that 50% reported daytime hypersomnia and 30% were diagnosed with OSA. Similarly, Castriotta and colleagues[12] evaluated 10 randomly selected patients with TBI. Of these, 7 were found to have sleep-disordered breathing and 3 met criteria for posttraumatic narcolepsy or posttraumatic hypersomnia.

In a separate study, Castriotta and colleagues[10] prospectively evaluated 87 patients at least 3 months after a TBI. Polysomnography was abnormal in 46% of patients; 23% of patients were diagnosed with OSA, 11% with posttraumatic hypersomnia, 6% with posttraumatic narcolepsy, and 7% with periodic limb movement disorder. The study found no correlation between subjective and objective measures of sleepiness. No significant differences in age, race, sex, level of education, injury severity, or time after injury were found between those with and without concomitant sleep disorders.

Collen and colleagues[5] assessed 116 consecutive soldiers who sustained mild to moderate TBI while serving in Iraq and Afghanistan. Among the cohort, 96.6% were men, with a mean age of 31.1 ± 9.8 years and a mean body mass index of 27.8 ± 4.1 kg/m^2. All participants underwent comprehensive sleep evaluations, including polysomnography and multiple sleep latency testing. Nearly all patients (97.4%) reported subjective sleep complaints, with hypersomnia and sleep fragmentation reported in 85.2% and 54.3%, respectively.

Obstructive sleep apnea syndrome (OSAS) was found in 34.5%, whereas 55.2% had insomnia. Of note, the authors observed that the mechanism of injury affected both subjective sleep complaints and objective findings. Patients with blast injuries developed more anxiety (50.6% vs 20.0%; P = .002) and insomnia (63% vs 40%; P = .02), whereas patients with blunt trauma had significantly more OSAS (54.3% vs 25.9%; P = .003). In multivariate analysis, blunt trauma was a significant predictor of OSAS (odds ratio, 3.09; 95% confidence interval, 1.02-9.38; P = .047).

Impact of OSA on Outcomes

Impaired sleep can have an adverse impact on cognition, attention, and judgment. Among patients with TBI, the presence of sleep complaints portents worse outcomes, is associated with diminished quality-of-life measures, and has been shown to impair rehabilitation efforts and progression.

Failure to recognize sleep disorders in TBI may adversely affect recovery. Wilde and colleagues[13] assessed the impact of sleep disturbances on cognition in a clinical trial comparing 19 patients who had TBI and OSA with 16 patients who had only TBI. The 2 groups were similar in age, education, presenting Glasgow Coma Scale score, and time since injury. Patients with TBI and OSA performed worse on measures of verbal and visual delayed recall, and comparably on motor, visual construction, and attention tasks. Researchers also found more lapses in attention in those with both conditions. The authors concluded that TBI coupled with OSA is associated with significant impairments of sustained attention and memory compared with patients who have TBI alone.

Castriotta and colleagues[11] evaluated the impact of therapy for sleep disorders in 57 patients at least 3 months after a TBI. Of the cohort, 23% had OSA. The authors found that although continuous positive airway pressure effectively ablated obstructive events, it did not lead to improvement in objective measures of sleepiness. Similar to other reports, TBI patients may have additional causes of persistent sleepiness, in particular a centrally mediated posttraumatic hypersomnia syndrome.

Conclusions

TBI is a growing societal concern that is increasingly recognized among athletes, elderly persons, and military personnel. These injuries encompass multifaceted disease processes and are commonly associated with psychiatric conditions (depression, PTSD, and anxiety), neuromuscular and neurocognitive impairments (chronic pain, physical rehabilitation, and impaired cognition), and sleep-related disorders (sleep apnea, posttraumatic hypersomnia, periodic limb movement disorder, insomnia, and circadian rhythm sleep disturbances). Sleep disorders in patients with TBI are often underdiagnosed and undertreated.

There is increasing recognition that sleep disruption can complicate TBI, and unrecognized or untreated sleep disorders can worsen outcomes, increase disability, or impair rehabilitation. Although sleep complaints are nearly universal among persons who have had a TBI, it appears that the mechanism of injury may play a role in the development of specific sleep disorders. Given the extremely high prevalence of sleep complaints, patients with TBI should be evaluated for sleep disorders or referred for formal sleep evaluations, because recognizing and treating these conditions may improve outcomes.

Because of the inherent cognitive limitations in TBI patients as reporters of their symptoms, all TBI patients with suspected sleep disturbances should undergo a comprehensive, objective evaluation, especially given the established adverse impact of sleep disruption on cognition in this already impaired population.

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Role of Low-Level Laser Therapy in Neurorehabilitation

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Abstract

This year marks the 50th anniversary of the discovery of the laser. The development of lasers for medical use, which became known as low-level laser therapy (LLLT) or photobiomodulation, followed in 1967. In recent years, LLLT has become an increasingly mainstream modality, especially in the areas of physical medicine and rehabilitation. At first used mainly for wound healing and pain relief, the medical applications of LLLT have broadened to include diseases such as stroke, myocardial infarction, and degenerative or traumatic brain disorders. This review will cover the mechanisms of LLLT that operate both on a cellular and a tissue level. Mitochondria are thought to be the principal photoreceptors, and increased adenosine triphosphate, reactive oxygen species, intracellular calcium, and release of nitric oxide are the initial events. Activation of transcription factors then leads to expression of many protective, anti-apoptotic, anti-oxidant, and pro-proliferation gene products. Animal studies and human clinical trials of LLLT for indications with relevance to neurology, such as stroke, traumatic brain injury, degenerative brain disease, spinal cord injury, and peripheral nerve regeneration, will be covered.

Disclosure key can be found on the Table of contents and at www.pmrjournal.org

INTRODUCTION

It was not long after the discovery of the first lasers (the ruby laser in 1960 and the helium-neon [HeNe] laser in 1961) that they began to be used in medical applications. In 1967, Endre Mester in Hungary noticed the ability of the HeNe laser to increase hair growth [1] and stimulate wound healing in mice [2], and, shortly afterward, he began to use lasers to treat patients with nonhealing skin ulcers [3]. Since those early days, the use of low-power lasers (as opposed to high-power lasers that can destroy tissue by a photothermal effect) has steadily increased in diverse areas of medical practice that require healing, prevention of tissue death, pain relief, reduction of inflammation, and regenerative medicine. Some of the different organ systems, diseases, and injuries that have been effectively treated with low-level laser therapy (LLLT) are schematically shown in Figure 1.

Nevertheless, this modality, which is variously known as LLLT or photobiomodulation, remains controversial. The reasons for this lack of general acceptance among both the medical community and the general public at large are 2-fold. First, widespread uncertainty and confusion exists about the mechanisms of action of LLLT at the molecular, cellular, and tissue levels. Second, a large number of parameters (eg, wavelength, fluence, irradiance, treatment timing and repetition, pulsing, and polarization) can be chosen in designing LLLT protocols. Furthermore, a biphasic dose response exists in laser therapy [4], which describes the observation that increasing the overall “dose” of the laser either by increasing the power density or by increasing the illumination time may have a counter-productive effect compared with the benefit obtained with lower doses. Taken together, these considerations may explain why a number of negative studies have been published; however, this should not be taken to imply that LLLT in general does not work but rather that the laser parameters used in those particular studies were ineffective.

In recent years, the development of light-emitting diodes (LEDs) as alternative light sources for LLLT has added to the confusion. These devices produce light with wavelengths similar to those of lasers, but they have broader output peaks (ie, they are less monochromatic) and lack the coherence that is a particular feature of laser light. LEDs have the advantage of being significantly less expensive than laser diodes (by a factor of approximately 100 on a milliwatt basis), and the LLLT community is engaged in a vigorous ongoing debate about their respective benefits.

This review covers the mechanisms that are thought to operate at molecular and cellular levels in LLLT. Many of the most compelling applications of LLLT are in the field of neurology (both central and peripheral). Many serious brain diseases and injuries can be successfully treated with noninvasive transcranial laser therapy. Furthermore, in the peripheral nervous system, LLLT can be used effectively for nerve regeneration and pain relief.

CELLULAR AND MOLECULAR MECHANISMS OF LLLT

LLLT uses low-powered laser light in the range of 1-1000 mW, at wavelengths from 632-1064 nm, to stimulate a biological response. These lasers emit no heat, sound, or vibration. Instead of generating a thermal effect, LLLT acts by inducing a photochemical reaction in the cell, a process referred to as biostimulation or photobiomodulation. Photo-biology works on the principle that, when light hits certain molecules called chromophores, the photon energy causes electrons to be excited and jump from low-energy orbits to higher-energy orbits. In nature, this stored energy can be used by the system to perform various cellular tasks, such as photosynthesis and photomorphogenesis. Numerous examples of chromophores exist in nature, such as chlorophyll in plants, bacteriochlorophyll in blue-green algae, flavoproteins, and hemoglobin found in red blood cells. The respective colors

of chromophores are determined by the part of the spectrum of light they absorb: chlorophyll is green, flavoprotein is yellow, and hemoglobin is red [5].

Mitochondria are considered the power generators of the eukaryotic cell, converting oxygen and nutrients through the oxidative phosphorylation process and electron transport chain into adenosine triphosphate (ATP), as shown in Figure 2. The basic idea behind cellular respiration is that high-energy electrons are passed from electron carriers, such as reduced nicotinamide adenine dinucleotide (NADH) and the reduced form of flavin adenine dinucleotide ($FADH_2$), through a series of transmembrane complexes (including cytochrome c oxidase [CCO]) to the final electron acceptor, generating a proton gradient. The gradient is used by F_OF_1 ATP synthase to produce ATP. Various in vitro experiments, such as those that use rat liver isolates, found that cellular respiration was upregulated when mitochondria were exposed to an HeNe laser or other forms of illumination. Laser irradiation caused an increase in mitochondrial products (such as ATP [6], NADH, protein, ribonucleic acid [RNA] [7]) and a reciprocal augmentation in oxygen consumption. A similar effect is produced when tissue that contains mitochondria is exposed to low-level radiation. Visible and near-infrared (NIR) light is absorbed by the organelle, and an upregulation of cellular respiration is observed [8].

Once it was observed that LLLT's mechanism of action is at the level of the mitochondria, it remained to be determined what specific structure within the mitochondria acted as the chromophore. Four membrane-bound complexes have been identified in mitochondria, each constituting an extremely complex transmembrane structure embedded in the inner membrane. Complex IV, also known as CCO, is a large transmembrane protein complex found in mitochondria, which is a component of the respiratory electron transport chain (Figure 3). CCO appears to absorb the same spectrum of light as that observed for the action spectra for the biological response to light in the NIR range. Thus it is reasonable to assume that CCO acts as an important chromophore in LLLT [9]. CCO consists of 2 copper centers and 2 heme-iron centers that are capable of absorbing light over a wide range, including NIR.

The next reasonable question to consider is: What action does CCO modulate once it absorbs the energy from light? On the cellular level, LLLT may cause photodissociation of nitric oxide (NO) from CCO. In a stressed cell, NO produced by mitochondrial NO synthase displaces oxygen from CCO, which results in a downregulation of cellular respiration and a subsequent decrease in the production of energy-storing compounds, such as ATP. By dissociating NO from CCO, LLLT prevents the displacement of oxygen from CCO and thereby promotes unhindered cellular respiration [10] (see Figure 4). Increased CCO enzyme activity can be measured [11]; increased ATP production [12] and increased electron transport [13] also have been reported. The basic idea behind cellular respiration is that high-energy electrons are passed from electron carriers, such as NADH and $FADH_2$, through a series of transmembrane complexes (including CCO) to the final electron acceptor. Increased cellular ATP produced by LLLT may contribute to the positive effects, both by raising cellular energy levels and by upregulating the cyclic AMP molecule (biochemically formed from ATP) that is involved in many signaling pathways.

Oxygen acts as the final electron acceptor and is, in the process, converted to water. Part of the oxygen that is metabolized produces reactive oxygen species (ROS) as a natural by-product. ROS (eg, superoxide and hydrogen peroxide) are chemically active molecules that play an important role in cell signaling, regulation of cell cycle progression, enzyme activation, and nucleic acid and protein synthesis [14]. Because LLLT promotes the metabolism of oxygen, it also acts to increase ROS production. In turn, ROS activates certain redox-sensitive transcription factors such as nuclear factor-κB [NF-κB] and activator

protein 1, which leads to the upregulation of various stimulatory and protective genes. The ultimate effect of LLLT is likely to be produced by transcription factor activation, which modulates the host's downstream cellular and tissue responses (see Figure 5).

Almost certainly, other mechanisms through which LLLT produces its effects are at play in addition to the one just described. For example, NO is a potent vasodilator via its effect on cyclic guanine monophosphate production. Cyclic guanine monophosphate is also involved in many other signaling pathways. LLLT may cause the photodissociation of NO from intracellular stores (ie, nitrosylated forms of both hemoglobin and myoglobin, in addition to CCO) [15]. LLLT promotes the synthesis of deoxyribonucleic acid (DNA) and RNA [16] and increases the production of proteins [17]. It also modulates enzymatic activity [18], affects intracellular and extracellular pH [17,18], and accelerates cell metabolism [18,19]. The expression of multiple genes related to cellular proliferation, migration, and the production of cytokines and growth factors also have been shown to be stimulated by low-level light [20].

Light is a powerful force and has a myriad of effects. The specific mechanisms of action may vary among various clinical applications of LLL and will be discussed in the respective sections below. Furthermore, in spite of a great number of studies that explored how LLLT works, the exact mechanism of action remains to be fully elucidated.

STROKE

Transcranial LLLT (808 nm) has significantly improved recovery after ischemic stroke in rats when they received one treatment 24 hours after sustaining a stroke [21,22]. Stroke was induced in rats by 2 different methods: (1) permanent occlusion of the middle cerebral artery through a craniotomy or (2) insertion of a filament. The laser was used transcranially on the exposed (shaved skin) skull by placing the tip of the 4-mm diameter fiber optic onto the skin at 2 locations on the head (3 mm dorsal to the eye and 2 mm anterior to the ear) on the contralateral hemisphere to the stroke. These locations had been determined from prior measurements to be sufficient to illuminate 1 brain hemisphere as a result of dispersion of the laser beam by the skin and the skull. Results of previous studies had shown that LLLT of the contralateral, or both hemispheres, demonstrated no difference in functional outcome [23]. An NIR gallium arsenic diode laser was used transcranially to illuminate the hemisphere contralateral to the stroke at a power density of 7.5 mW/cm^2 to the brain tissue [22]. In both models of stroke, the neurologic deficits at 3 weeks after stroke were significantly reduced (by 32%) ($P < .01$) in the laser-treated rats compared with control subjects.

In this study, the number of newly formed neuronal cells, assessed by double immunoreactivity to bromodeoxyuridine and tubulin isotype III, as well as migrating cells (double Cortin immunoreactivity), was significantly elevated in the subventricular zone of the hemisphere ipsilateral to the induction of stroke when treated by LLLT [21,22]. No significant difference in the stroke lesion area was found between control and laser-irradiated rats. The researchers suggested that an underlying mechanism for the functional benefit after LLLT in this study was possible induction of neurogenesis. Results of other studies also suggested that, because improvement in neurologic outcome may not be evident for 2-4 weeks in the poststroke rat model, delayed benefits may in part be due to induction of neurogenesis and migration of neurons [24,25]. In addition, transcranial LLLT may prevent apoptosis and improve outcomes by exerting a neuroprotective effect, although these exact mechanisms are poorly understood [26].

Other studies in rat and rabbit models also have observed that transcranial LLLT improves functional outcome after stroke [25,27,28]. A recent rabbit study combined transcranial

LLLT with thrombolytic therapy by using tissue plasminogen activator, with no increase in bleeding and good safety [29].

In the aforementioned studies, it has long been hypothesized that increased mitochondrial function (ie, increased ATP production) in brain cells irradiated with NIR LLLT was one of the major mechanisms involved with the beneficial behavioral effects observed after LLLT treatment. A recent animal study with rabbits has shown a direct relationship between the level of cortical fluence (energy density) delivered (in J/cm^2) and cortical ATP content in embolized rabbits [30]. Five minutes after embolization (right carotid), the rabbits were exposed to 2 minutes of NIR transcranial LLLT with use of an 808-nm laser source (continuous wave [CW] or pulsed wave [PW] at 100 Hz or at 1000 Hz on the skin surface, posterior to bregma at midline). Three hours after embolization, the cerebral cortex was excised and processed for measurement of ATP content. Embolization decreased cortical ATP content in ischemic cortex by 45% compared with naive rabbits.A linear relationship up to 4.5 J/cm^2 in fluence delivered, was observed for the relationship between cortical fluence (in J/cm^2) verus percent increase in cortical ATP content (over sham-treated embolized rabbits). This linear relationship was observed with a power density of 7.5 mW/cm^2 CW (0.9 J/cm^2), where an increase of 41% in cortical ATP was observed; and with a power density of 37.5 mW/cm^2 PW (100 Hz, 4.5 J/cm^2), where an increase of 157% in cortical ATP was observed. An increase in cortical ATP of 221% was observed with fluence of 31.5 J/cm^2, delivered with a power density of 262.5 mW/cm^2 PW, 1000 Hz. This suggests that a near-plateau effect was present regarding the fluence level delivered above 4.5 J/cm^2. It was surprising, however, that the increased cortical ATP levels of 157% and 221%, were higher than those measured in naive rabbits that had never suffered stroke. Because the authors observed that the PW modes (100 Hz and 1000 Hz) were more effective than the CW mode to increase cortical ATP, they hypothesized that in future stroke studies in animals and in humans, even greater improvement in clinical rating scores might be achieved by optimizing the method of NIR transcranial LLLT delivery, including the length of treatment and the mode of treatment (PW).

Transcranial LLLT has been shown to significantly improve outcome in acute human stroke patients when applied approximately 18 hours after the stroke occurs over the entire surface of the head (20 points in the 10/20 electroencephalographic system), regardless of the stroke location [31]. Only one LLLT treatment was administered, and, 5 days later, significantly greater improvement was found in the real-treated group but not in the sham-treated group ($P < .05$, National Institutes of Health Stroke Severity Scale). This significantly greater improvement was still present 90 days after –the stroke occurred, at which time 70% of the patients treated with real LLLT had a successful outcome compared with only 51% of control subjects. An NIR (808 nm) laser was used, which delivered a fluence of 0.9 J/cm^2 over the entire surface (2 minutes per each of the 20 points; power density of 7.5 mW/cm^2).

In a second, similar study with the same transcranial LLLT protocol, an additional 658 acute stroke patients were randomly assigned to receive real or sham treatments of transcranial LLLT. Similar significant beneficial results ($P < .04$) were observed for the patients who had a moderate or moderate to severe stroke (n = 434) and received the real laser protocol but not for the patients who had a severe stroke [32]. When all 656 cases were included in the data analysis (including the severe stroke cases), no significant real versus sham LLLT effect was seen. When data for both stroke studies were pooled (n = 778 [120 plus 658]) [31,32], a highly significant beneficial effect was seen for the real transcranial LLLT group ($P = .003$) compared with those who received the sham laser treatment [33].

Lampl et al [31] wrote that “Although the mechanism of action of infrared laser therapy for stroke is not completely understood . . . infrared laser therapy is a physical process that can

produce biochemical changes at the tissue level. The putative mechanism . . . involves stimulation of ATP formation by mitochondria and may also involve prevention of apoptosis in the ischemic penumbra and enhancement of neurorecovery mechanisms."

To date, no studies have been conducted to examine transcranial LLLT treatment of chronic stroke patients. Naeser et al [34] studied the application of LLLT-laser acupuncture (instead of needles) to stimulate acupuncture points on the body in chronic stroke patients with paralysis. Seven stroke patients (range, 48-71 years; 5 men) were treated, 5 of whom had single left hemisphere stroke, and 2 of whom had single right hemisphere stroke. Five patients were treated for hemiplegia, including severely reduced or no voluntary isolated finger movement, and 2 patients had hand paresis only. Six of the 7 patients received laser acupuncture during the chronic phase after the stroke had occurred (10 months to 6.5 years after stroke onset), clearly beyond the spontaneous recovery phase, which is considered to be up to 6 months after the stroke occurs [35,36]. The patients served as their own controls; no sham LLLT was administered. One patient (who had hand paresis) received LLLT during the acute phase after the stroke occurred (1 month after the stroke occurred). The patients did not receive any physical therapy or occupational therapy treatments while participating in this study.

A 20-mW gallium aluminum arsenide (780 nm) NIR CW laser with a 1-mm-diameter aperture was used (Unilaser, Copenhagen, Denmark). (At the time of this study, more powerful red or NIR lasers were not yet available.) Treatment consisted of stimulation of shallow acupuncture points (located on the hands and face) for 20 seconds per point (51 J/cm^2). Deeper acupuncture points (located on the arms and legs) were treated for 40 seconds per point (103 J/cm^2). Acupuncture points were treated on both the paralyzed side (arm, leg, and/or face) and on the nonparalyzed side by using primarily acupuncture meridians of the large intestine, triple warmer, gall bladder, liver, small intestine, and stomach [34]. The patients were treated 2-3 times per week for 3-4 months. They received a total of 20, 40, or 60 treatments (based on patient availability and transportation). Within a few days before the first treatment and a few days after the last treatment, physical therapy and/or occupational therapy testing was performed by therapists blinded to the acupuncture treatment program to which the patient had been assigned: LLLT, real or sham needle, or no acupuncture. Overall, 5 of 7 of the patients (71.4%) showed improvement.

The 2 patients who showed no improvement had severe paralysis. We have observed that severity of paralysis and potential for improvement after LLLT-laser acupuncture (or needle acupuncture) is related to lesion location on chronic computed tomography (CT) scan acquired at least 3 months poststroke onset. Patients with lesion in more than half of the "periventricular white matter area" (PVWM) (adjacent to the body of the lateral ventricle, superior to the posterior limb, internal capsule), an area containing multiple efferent and afferent pathways (eg, thalamocortical, occipitofrontal, pathways from SMA/cingulate gyrus to the body of caudate, medial subcallosal fasciculus, and others), had severe paralysis which did not improve following LLLT-laser acupuncture (or needle) acupuncture treatments [34,37,38]. This area is diagrammed in Figure 6. The CT scan for a chronic stroke patient who had good response after LLLT-laser acupuncture treatments [34,37,38]. This area is diagrammed in Figure 7.

The 3 chronic stroke patients with hemiplegia who showed improvement after LLLT had an increase of 11%-28% in isolated, active range of motion for shoulder abduction, knee flexion, and/or knee extension (mean, 15.8%; SD, 7.1). This percentage increase after LLLT-laser acupuncture was similar to that observed after a series of 20 or 40 needle acupuncture treatments [37,38]. The person with hand paresis who was treated with LLLT at 33 months after stroke onset showed an increase of 2-6 lb in grip strength, 3-jaw chuck, tip

pinch, and lateral pinch in the affected hand. These results are similar to those obtained with needle acupuncture [39]. These findings are intriguing and suggest that some recovery of motor function can occur with needle acupuncture or LLLT acupuncture applied to body acupuncture points in chronic stroke patients.

A reduction in hand spasticity also has been observed when chronic stroke patients are treated with a combination of red-beam laser applied to hand acupuncture points plus microamps transcutaneous electrical nerve stimulation (TENS). Figure 8 shows an immediate reduction in hand spasticity after the first hand treatment when LLLT-laser acupuncture and microamps TENS were used with 2 chronic stroke patients. This LLLT and microamps TENS hand treatment program also may be used with patients who have hand spasticity related to other etiologies, including, for example, traumatic brain injury (TBI), "stiff man syndrome," and spinal cord injury (SCI) (personal observation, M.A.N., 2001). Similar to red and NIR LLLT, microamps TENS increases ATP levels when applied to the skin [40]. However, Cheng et al [40] observed that when stronger milliamps TENS was used (eg, similar to conventional TENS), the ATP levels were decreased. Hence when microamps TENS is used (as shown in Figure 8) [41], it is advisable to keep the sensation below threshold for the patient to increase ATP (not decrease ATP).

TRAUMATIC BRAIN INJURY

Each year in the United States, more than 1.4 million new cases of TBI occur, and more than 80,000 persons are left with permanent disability [42]. Mild TBI (mTBI) from single and multiple events is the most frequent type of head injury experienced by military personnel deployed to Iraq and Afghanistan [43]. TBI is known to cause damage that ranges from observable to microscopic throughout the gray and white matter of the brain. Diffuse axonal injury [44] is often observed in the anterior corona radiata and frontotemporal regions [45]. Two regions highly susceptible to damage within the frontal lobes are the prefrontal cortex and the anterior cingulate gyrus. Cognitive processing problems result from tissue damage and inefficient cellular function in these brain regions. The prefrontal cortex is involved with maintaining, monitoring, and manipulating information in working memory [46] and particularly in sustained attention [47,48].

In the first reported study of the use of transcranial LLLT to treat traumatic brain injury, an animal model was used [49]. Mice were subjected to closed-head injury (CHI) by using a weight-drop procedure, and 4 hours after CHI, either sham or real NIR LLLT (808 nm) was administered transcranially. The control group received no laser therapy (n = 8); the laser-treated group (n = 16) received 1 transcranial LLLT treatment by using a 200-mW, 808-nm NIR laser with a 3-mm-diameter probe tip (Photothera Inc, Carlsbad, CA). Either 10 or 20 mW/cm^2 was administered. A single point was treated on the skull (a skin incision was made) that was located 4 mm caudal to the coronal suture line on the midline. The point was treated for 2 minutes (1.2-2.4 J/cm^2). At 24 and 48 hours after CHI, no significant difference in motor behavior was seen between mice in the laser-treated and control groups. After 5 days, the motor behavior was significantly better ($P < .05$) in the laser-treated group; in addition, the neurobehavioral scores were 26%-27% better (lower scores indicated better motor behavior). At 28 days after CHI, the brain-tissue volume was examined for mice in each group. The mean lesion size of 1.4% in the laser-treated group (SD 0.1) was significantly smaller ($P < .001$) than in the control group (12.1%, SD 1.3). No difference in lesion size or behavior was observed in the mice treated with 10 mW/cm^2 and those treated with 20 mW/cm^2. The researchers suggested various possible mechanisms, including an increase in ATP, total antioxidants, angiogenesis, neurogenesis, heat shock proteins content, and an antiapoptotic effect, similar to observations reported after LLLT treatment of ischemic heart skeletal muscles [50-54].

Moreira et al [55] conducted a study in 2009 using phototherapy with low-intensity lasers and observed the effect on local and systemic immunomodulation after cryogenic brain injury in rats. Brain and blood samples were analyzed by enzyme-linked immunosorbent assay for the production of cytokines interleukin (IL)-6 , IL-10, IL-1b, and tumor necrosis factor (TNF)-α. The study concluded that laser phototherapy could positively affect the balance of IL-1b, TNF-α, and IL-6 in rats and thereby prevent cell death after TBI.

Wu et al [56] reported another mouse study of LLLT mediated by transcranial laser therapy. A nonfocal (diffuse) TBI was produced by a CHI caused by a calibrated weight-drop device. A neurologic severity score for each mouse was determined based on 10 standardized performance tests (involving beam balancing and maze exiting) administered at specified times. Mice with a neurologic severity score of 7-8 (moderately severe brain injury) were used in the study. Mice were given a single treatment to the top of the head with 36 J/cm^2 of a 665-nm, 810-nm, or 980-nm laser 4 hours after the closed head TBI. Both 665-nm and 810-nm lasers were highly effective in improving the neurologic performance of the mice during the succeeding 4 weeks. The 980-nm wavelength was ineffective (negative control). We believe that this difference in results can be explained by the absorption spectrum of the different chromophores; CCO has peaks at 660 nm and 810 nm, whereas water has a peak at 980 nm.

In humans, 2 persons with chronic mTBI recently have been reported to have improved cognition after a series of treatments with transcranial, red, and NIR LEDs [57,58]. The LED cluster heads were applied to the forehead and scalp areas (the hair was not shaved off but was parted underneath each 2-inch-diameter LED cluster head). Each cluster head had 61 diodes (9 red 633-nm diodes and 52 NIR 870-nm diodes). Each diode was 12-15 mW, and the total power output was 500 mW. The LED cluster heads were applied to bilateral frontal, parietal, and temporal areas and to the mid-sagittal suture line.

Each LED cluster head was applied for 10 minutes per placement. With the device used here (parameters described above), 1 joule per cm^2 (J/cm^2) energy density was produced during every 45 seconds of exposure time. The energy density dose at the forehead-scalp was 13.3 J/ cm^2; the power density was 22.2 mW/cm^2 (±20%). The power density refers to the mW of power applied per cm^2. The ± refers to the range of fluctuation (plus or minus 20%) on the power density per cm^2. This power density is well below that used in other transcranial laser or LED studies to treat acute stroke cases or severe depression cases (225 mW/cm^2) [59]. It is estimated that only approximately 3% of the photons delivered to the forehead-scalp surface will reach 1 cm, to the cortex [60]. The dose of 13.3 J/cm^2 per placement area was estimated to deliver only 0.4 J/cm^2 to the brain cortex. No sensation of heat or pain was reported during the LED application to the skin or scalp. These LED cluster heads (MedX Health Corp, Mississauga, Ontario, Canada) are approved by the U.S. Food and Drug Administration for treatment of musculoskeletal pain; they were used off-label for treatment of cognition in the mTBI cases. No potential existed for ocular damage because the LEDs produce noncoherent light. These LED cluster heads also have been approved by the Food and Drug Administration for home treatment.

A 66-year-old woman (case 1) began transcranial LED treatments 7 years after a motor vehicle–related TBI. Before LED treatment, she could focus on her computer for only 20 minutes. After 8 weekly LED treatments, her focused computer time increased to 3 hours. She has treated herself nightly at home for 5.5 years, with transcranial LED. She maintains her improved cognition at age 72 years.

Case 2 involved a 52-year-old retired, high-ranking female military officer who had a history of multiple TBIs. Her brain MRI showed frontoparietal atrophy. She was medically

disabled for 5 months before beginning nightly transcranial LED treatments at home (see Figure 9, A and B). After 4 months of nightly LED treatments, she returned to work full time as an executive consultant for an international technology consulting firm and discontinued medical disability. Neuropsychological tests performed after 9 months of transcranial LED showed significant improvement in cognition (see Figure 9, C). After LED treatments, she improved on tests of executive function (inhibition and inhibition accuracy, +2 SD) and on memory (immediate and delayed recall +1, +2 SD). The improvement of +1 or +2 standard deviations on her scores refers to the degree of improvement on her scores after 9 months of LED treatments (versus before LED treatments). The SDs are provided with the test materials, and they are based on the published norms for each test.

Both patients with TBI reported that they needed to continue with home treatments. If they stop treatment for 1 or 2 weeks, then their cognitive problems started to return. Both patients with TBI reported improved sleep. The second patient with TBI reported a decrease in her posttraumatic stress disorder symptoms after a few months of using the transcranial LEDs, and Schiffer et al [59] also reported a reduction in posttraumatic stress disorder symptoms in 3 of 10 patients with major depression who were treated with transcranial LED.

Several possible mechanisms may be associated with the improved cognition in the mTBI cases treated with transcranial LEDs [58]. Mitochondria display a significant amount of dysfunction after TBI [61-63]. The primary mechanism for improvement posited in one study with human acute stroke patients was an increase in ATP, with photons being used by CCO in the mitochondria to increase ATP, especially in the cortex [64].

An increase in ATP after red and/or NIR LED treatments in patients with chronic TBI would have beneficial effects, including an increase in cellular respiration and oxygenation. Oxidative stress plays a role in the damage present after TBI [65]. One hypothesis is that LLLT produces low levels of ROS in mitochondria of illuminated cells and that these ROS cause NF-κB activation via the redox sensitive sensor enzyme protein kinase D1, which results in upregulation of the mitochondrial superoxide dismutase [66]. A single exposure of LLLT-LED in vitro with fibroblasts has been observed to increase NF-κB in the short term [67]. In stimulated dendritic cells in the longer term, however, NF-κB and pro-inflammatory cytokines were reduced [68]. Thus, in the long term, repeated LED treatments are hypothesized to decrease inflammation (less NF-κB) and upregulate gene products that are cytoprotective, such as superoxide dismutase, glutathione peroxidase, and heat shock protein 70 [54,69]. It is hypothesized that an overall protective response occurs with repeated LED treatments and that major ROS-mediated damage and chronic inflammation that occur in the brain after TBI may actually be reduced.

Acupuncture points located on the scalp were treated with the red-NIR LEDs [57]. This includes points along the Governing Vessel (GV) acupuncture meridian, located on the midline of the skull (including, in part, the mid-sagittal suture line). Some acupuncture points located on the GV meridian have been used historically to help treat patients in coma [70] and stroke [71], for example, GV 16 (inferior to occipital protuberance), GV 20 (vertex), and GV 24 (near center-front hairline); these points were treated in both patients with TBI reported in this study.

Transcranial red-NIR LED may have irradiated the blood via the valveless, emissary veins located on the scalp surface but interconnecting with veins in the superior sagittal sinus (M. Dyson, oral personal communication, June 2009). If red-NIR photons penetrate deeply enough to reach the cortex, then it also is possible they are entering small vessels located between the arachnoid and the pia mater, including those that supply arterial blood to superficial areas of the cortex. Direct in vitro blood irradiation with a red-beam laser has

been observed to improve erythrocyte deformability (flexibility) and rheology [72,73]. A beneficial effect from direct-laser blood irradiation in vivo has been observed during stenting procedures where a low-level, red-beam laser (10 mW, 650 nm) was used, with the beam placed directly into a coronary artery [74]. The restenosis rate was reduced and no adverse effects or complications were noted. Thus blood irradiation at the scalp may have affected local intracerebral blood and circulation; however; whether this effect occurred is unknown and would require further study.

An increase in regional cerebral blood flow may have occurred, specifically to the frontal lobes. The second TBI case showed significant improvement on objective, neuro-psychological testing for executive function (inhibition) after administration of LED. These results suggest improved function in the prefrontal cortex and anterior cingulate gyrus regions. Significant improvement on “inhibition” on the Stroop test particularly suggests improved function of the medial prefrontal cortex, anterior cingulate gyrus area [75]. It is possible that this medial prefrontal cortex area could have been treated with NIR photons, especially when the LED cluster head was placed over the midline, front hairline area. The dorsolateral prefrontal cortex also was likely irradiated when the LEDs were placed on the left and right high-frontal areas of the scalp. Increased regional cerebral blood flow also could have occurred in frontal pole areas with the TBI cases, as was observed in the recent transcranial LED study to treat major depression [59]. Additional controlled studies with real and sham transcranial LLLT and LED are recommended to investigate whether these methods can be applied to improve cognition and reduce symptom severity in persons with acute and chronic TBI. The LED technology is not expensive ($1400 for a single LED cluster head and approximately $4000 to $5000 for a unit with 3 LED cluster heads). The transcranial LED treatment protocol can be used in the home.

DEGENERATIVE CENTRAL NERVOUS SYSTEM DISEASE

The positive effects of transcranial laser therapy on stroke and TBI have led to early investigations into whether LLLT may have benefits for persons with degenerative brain disorders, which are a rapidly growing affliction of the world's aging population. Moges et al [76] tested whether LLLT had a role to play in treating familial amyotrophic lateral sclerosis (FALS), which is a neurodegenerative disease characterized by progressive loss of motor neurons and death. Mitochondrial dysfunction and oxidative stress play an important role in motor neuron loss in ALS. The study combined LLLT (with use of an 810-nm diode laser with 140-mW output power targeting a 1.4-cm2 spot area for 120 seconds using 12 J/cm^2 energy density) and riboflavin to test the survival of motor neurons in a mouse model of FALS. Motor function (determined with use of the Rota rod test) was significantly improved in the LLLT group in the early stage of the disease. Immunohistochemical expression of the astrocyte marker glial fibrillary acidic protein was significantly reduced in the cervical and lumbar enlargements of the spinal cord as a result of LLLT.

Trimmer et al [77] carried out preliminary studies that may have relevance to Parkinson disease (PD). Mitochondria supply the ATP needed to support axonal transport, which contributes to many other cellular functions essential for the survival of neuronal cells. Furthermore, mitochondria in PD tissues are metabolically and functionally compromised. The researchers measured the velocity of mitochondrial movement in human transmitochondrial cybrid “cytoplasmic hybrid” neuronal cells with mitochondrial DNA from patients with sporadic PD and disease-free age-matched volunteer control subjects (CNT). PD and CNT cybrid neuronal cells were exposed to NIR laser light (an 810-nm diode laser using 50 mW/cm^2 for 40 seconds), and axonal transport of labeled mitochondria was measured. The velocity of mitochondrial movement in PD cybrid neuronal cells was significantly reduced compared with mitochondrial movement in disease-free CNT cybrid

neuronal cells, and 2 hours after LLLT, the average velocity of mitochondrial movement in PD cybrid neurites was significantly increased and restored to levels comparable with those of CNT. Mitochondrial movement in CNT hybrids was unaltered by LLLT. PD cybrid neuronal cell lines with the most dysfunctional mtETC assembly and oxygen utilization profiles were least responsive to LLLT.

Zhang et al [78] likewise did preliminary experiments with relevance to Alzheimer disease. They showed that LLLT (0.156 -0.624 J/cm^2 from a 5-mW HeNe laser) could protect rat pheochromocytoma PC12 cells (a model of cortical neurons) from apoptosis caused by amyloid β peptide (Aβ25-35). This protection was mediated by protein kinase C activation caused by an increase in the cell survival protein bcl-xl and a decrease in cell death protein bax. Although no peer-reviewed publications have been published to date, it is known that transcranial LLLT has been applied to patients with moderate Alzheimer disease.

Michalikova et al [79] treated middle-aged (12–month-old) female CD-1 mice with a daily 6-minute exposure to 1072-nm LED light for 10 days and found that LLLT yielded a number of significant behavioral effects upon testing in a 3-dimensional maze. Middle-aged mice showed significant deficits in a working memory test, and LLLT reversed this deficit. LLLT-treated middle-aged mice were more considerate in their decision making, which resulted in an overall improved cognitive performance comparable with that of young (3-month-old) CD-1 mice. These results suggest that LLLT could be applied in cases of general cognitive impairment in elderly persons.

SPINAL CORD INJURY

SCI is a severe central nervous system trauma with no effective restorative therapies. Light therapy has biomodulatory effects on central and peripheral nervous tissue. Several groups investigated the effectiveness of LLLT on SCI. Roch-kind et al [80] demonstrated that LLLT applied simultaneously to the injured sciatic nerve and the corresponding segment of the spinal cord accelerates the process of regeneration of the injured peripheral nerve.

Light therapy (810 nm, 150 mW) significantly increased the axonal number and distance of regrowth in 2 SCI models: a contusion model and a dorsal hemisection model [81,82]. In addition, LLLT returned aspects of function to baseline levels and significantly suppressed immune cell activation and cytokine-chemokine expression [81].

Moreover, light therapy significantly improved the average length of axonal regrowth and increased the total axon number for both injury models. A statistically significant lower angle of rotation of the feet was observed during a walking test in the hemisection model and a statistically significant overall functional recovery in contusion model was seen in the LLLT groups. These results suggest that light may be a promising therapy for human SCI [82].

PERIPHERAL NERVE

The use of new therapeutic instruments such as electric stimulation, ultrasound, and LLLT for peripheral nervous system regeneration is currently being investigated in an attempt to achieve early functional recovery. LLLT has been used in several clinical and experimental research studies on peripheral nerves injuries.

In a pilot double-blind randomized study, Rochkind et al showed that postoperative 780-nm laser phototherapy enhances the regenerative process of the peripheral nerve after reconnection of the nerve defect by using a PGA neurotube. Morphologically, the laser-treated group showed an increased total number of myelinated axons [83]. These researchers

also reported that, in patients with long-term peripheral nerve injury, 780-nm laser therapy (250 mW) can progressively improve nerve motor function, which leads to significant functional recovery [84].

Barbosa et al [85] observed that, compared with the 830-nm laser group and the sham group, rats in the 660-nm laser group had the best sciatic functional index scores on average, which indicates that the use of these parameters was more efficient. Differences in sciatic functional index were found among the 660-nm laser group and the other ones at the 14th day [85]. However, Gigo-Benato et al [86] found that pulsed (905 nm) continuous (808 nm) combined laser biostimulation showed the best effectiveness in promoting peripheral nerve regeneration.

CONCLUSION

LLLT is steadily moving into mainstream medical practice. As the Western populations continue to age, the incidence of the degenerative diseases of old age will only continue to increase and produce an evermore severe financial and societal burden. Moreover, despite the best efforts of “big pharma,” distrust of pharmaceuticals is growing in general because of uncertain efficacy and troublesome adverse effects. LLLT has no reported adverse effects, and no reports of adverse events can be directly attributed to laser or light therapy. We believe that the high benefit:risk ratio of LLLT should be better appreciated by medical professionals in the rehabilitation and physical medicine specialties. The introduction of affordable LED devices powered by rechargeable batteries will lead to many home-use applications of LLLT. The concept of “wearable” light sources is not far off. Moreover, the particular benefits of LLLT to both the central and peripheral nervous systems suggest that much wider use of LLLT could or should be made in cases of both brain diseases and injuries.

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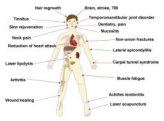

Figure 1.
Diagram of the various medical applications of low-level light therapy.

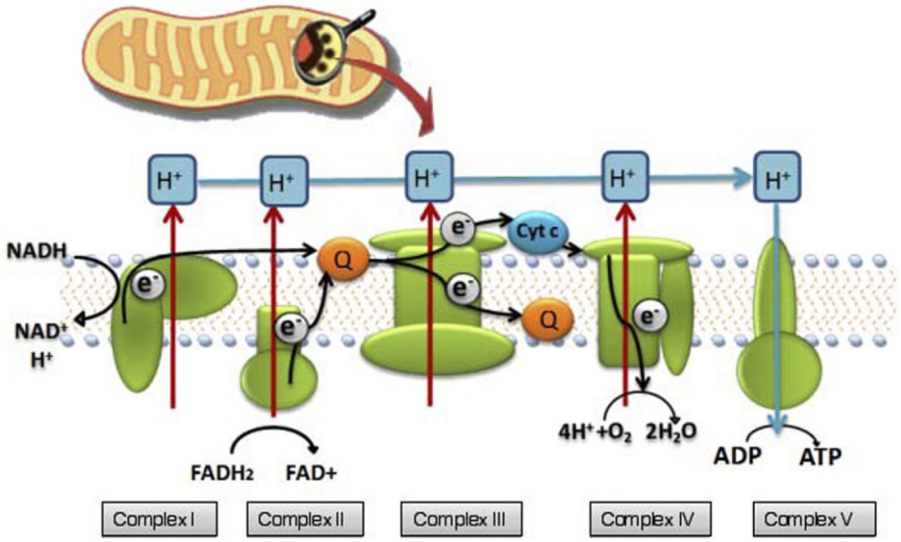

Figure 2.
Illustration of mitochondrion, as well as of the electron transport chain and oxidative metabolism.

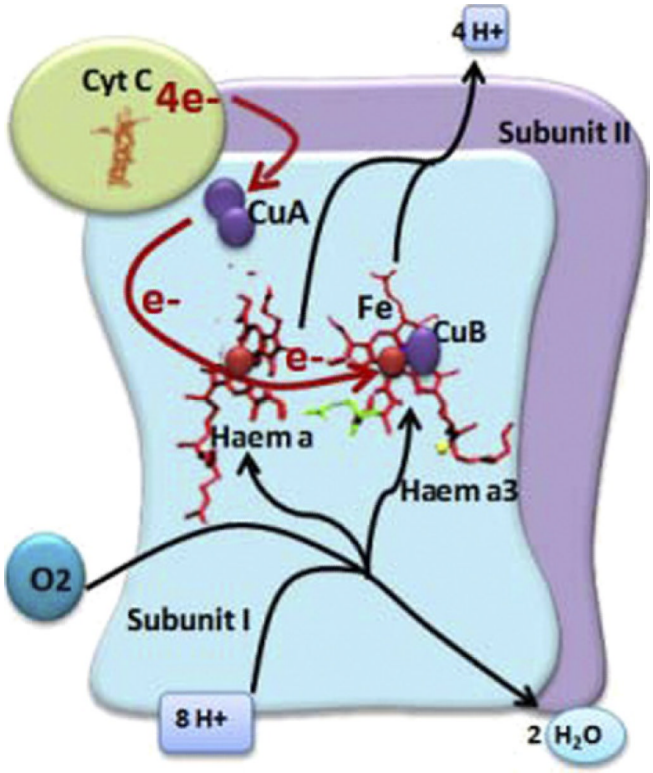

Figure 3.
Complex IV (cytochrome c oxidase) is the principal chromophore involved in low-level light therapy. It has 2 copper centers and 2 heme prosthetic groups. Cytochrome c is oxidized and oxygen is reduced to water during respiration.

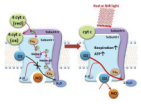

Figure 4.
Nitric oxide can bind to copper (or heme) centers in cytochrome c oxidase and inhibit respiration. The nitric oxide may be photodissociated by absorption of red or near infrared light, allowing oxygen to return and sharply increasing respiration and adenosine triphosphate formation.

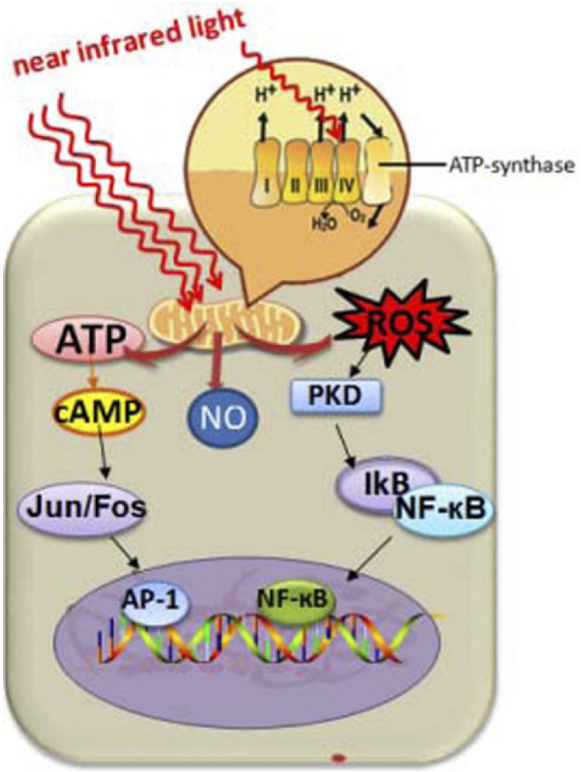

Figure 5.
Diagram that illustrates the mechanism of low-level light therapy (LLLT) on the cellular and molecular level. Near infrared light, absorbed by the mitochondria, causes upregulation of the cellular respiratory chain. A host of downstream cellular responses involving nitric oxide, reactive oxygen species, and cyclic adenosine monophosphate ensues, which ultimately dictates LLLT effects.

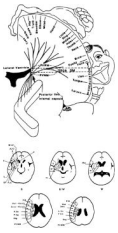

Figure 6.
Location of periventricular white matter (PVWM) area (*black arrow*), adjacent to the body of the lateral ventricle, located immediately superior to the posterior limb, internal capsule (computed tomography slice angulation, coronal and axial views). An extensive lesion in the PVWM was associated with severe paralysis and poor response following low-level light therapy (LLLT) or needle acupuncture treatments in chronic stroke patients with upper extremity, lower extremity, and hand paralysis. Patients with a lesion that was present in less than half of the PVWM area and who had a lesion that was not adjacent to the body of the lateral ventricle had less severe paralysis and good response after a series of LLLT or needle acupuncture treatments (34,37-39). Chronic stroke patients who had some preserved isolated finger flexion and extension before LLLT had the best potential for improvement after LLLT or needle acupuncture treatment. Other cases often had reduced spasticity after LLLT or needle acupuncture treatments.

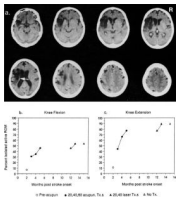

Figure 7.

(a.) Computed tomography (CT) scan of a 65-year-old woman obtained 5 months after stroke onset shows sparing of the most posterior portion of the periventricular white matter (PVWM) (*white arrow*), that is, likely sparing of some of the leg fibers. This patient showed improvement in knee flexion (b.) and knee extension (c.) after low-level light therapy (LLLT)-laser acupuncture treatments, which were initiated at 12 months after stroke onset. Knee extension increased from 77%-89% after 40 LLLT treatments, and her ability to climb up and down stairs improved. (She had shown some improvement on lower extremity tests after needle acupuncture treatments applied earlier after her stroke.) No improvement was seen in the upper extremity after LLLT or needle acupuncture, likely because of an extensive lesion in the more anterior portions of the PVWM. The arm paralysis was severe, scoring 0% isolated active range of motion for all arm tests at all times. The improvement in knee flexion and knee extension remained stable at 2 months after the last LLLT-laser acupuncture treatment (15 months after the stroke occurred). (Reprinted with author's permission, [34])

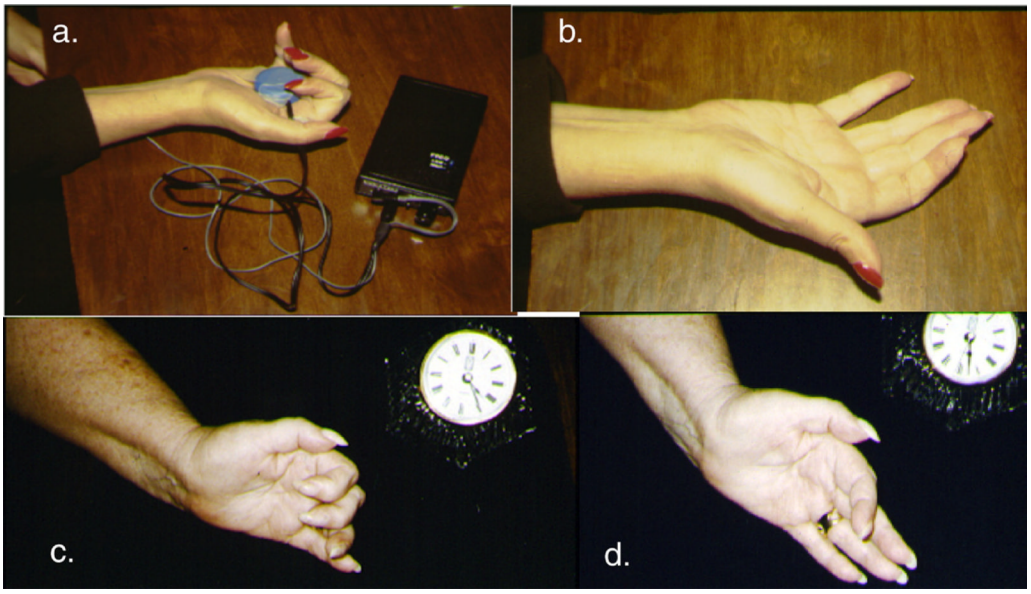

Figure 8.

(a.) Before the first low-level laser therapy (LLLT) and microamps transcutaneous electrical nerve stimulation (TENS) acupuncture treatment. It was 1.5 years after stroke onset and the patient still had right hand spasticity and was unable to extend her fingers into full extension. Microamps TENS was applied for 20 minutes to acupuncture point Heart 8 (in the palm of the hand) and Triple Warmer 5 (proximal to the dorsum of the wrist). Red-beam laser (670 nm, 5 mW, 4 J/cm2) was applied to the 6 Jing-Well points, located at base of fingernail beds on the hand, plus a few additional hand points. (b.) Immediately after the first 20-minute LLLT and microamps TENS acupuncture treatment, the patient had less hand spasticity and better control to open the fingers into full extension. More treatments are required for a longer-lasting effect. The patient can treat herself at home by using this LLLT and microamps TENS protocol, which is painless and noninvasive [41]. (c.) and (d.) A similar stroke case is shown.

Figure 9.

(a.) Red and near-infrared (NIR) light-emitting diode (LED) cluster head (2-inch diameter) for transcranial LED treatments. (b.) Sample placement location on right forehead for one of the LED cluster heads during transcranial LED treatment. (c.) Graph that shows significant improvement in cognition on tests of Executive Function (inhibition, and inhibition accuracy, +2 SD) after LED treatments in the second patient with chronic, mild traumatic brain injury. The patient returned to full-time employment after 4 months of nightly transcranial LED treatments. (c reprinted with permission, (58).)

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Concussions Cause Long-Term Effects Lasting Decades

Written by Joseph Nordqvist
Last reviewed: Tue 9 June 2015
email
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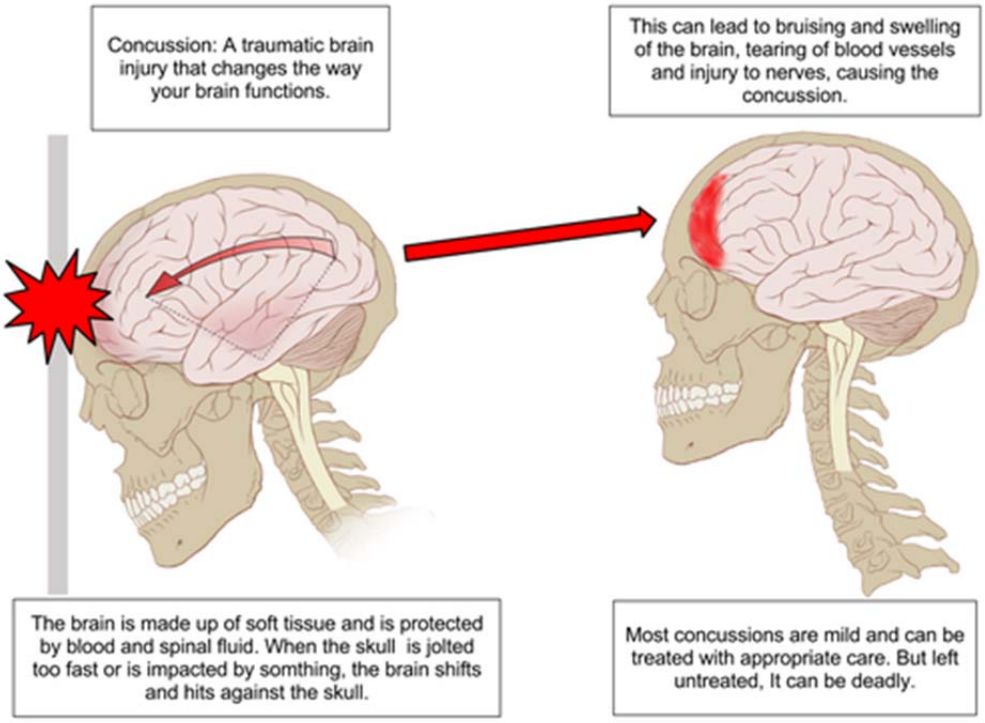

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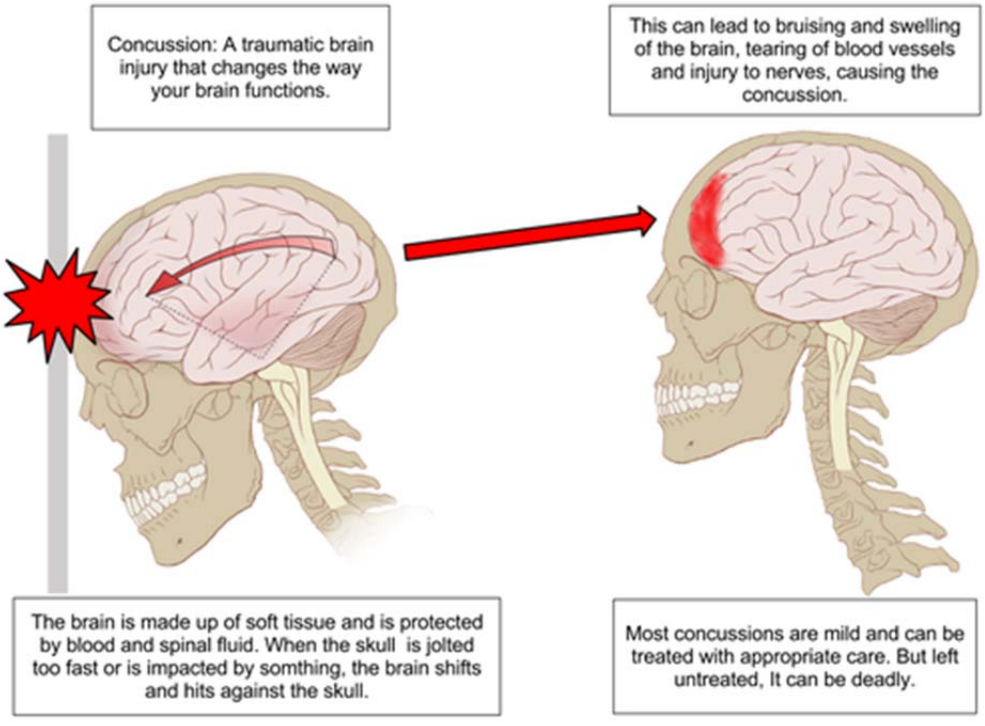

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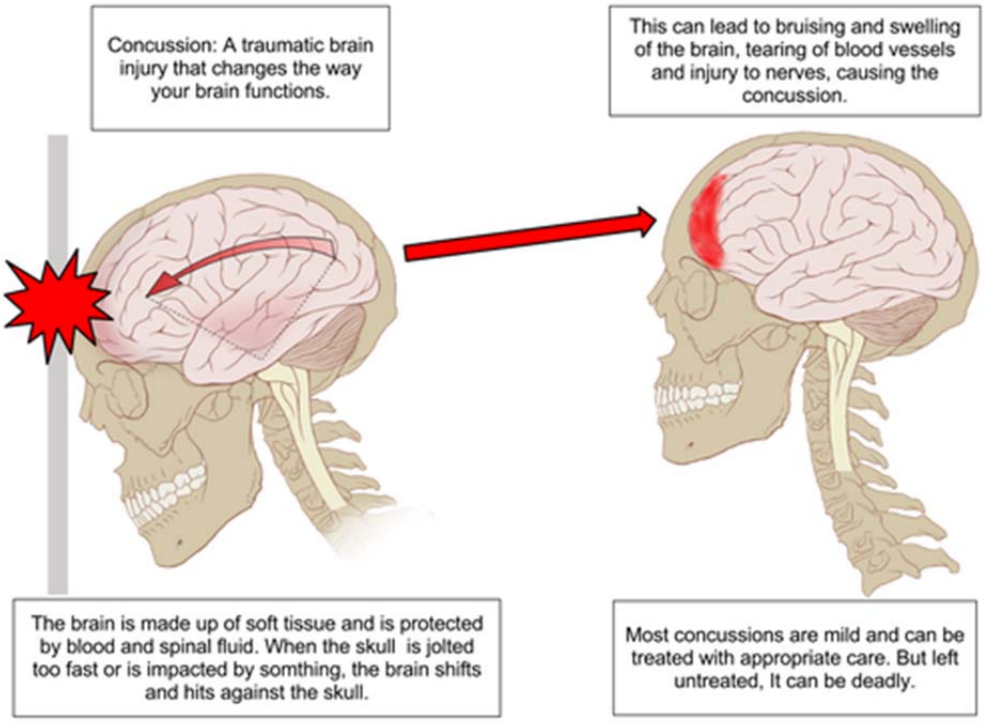

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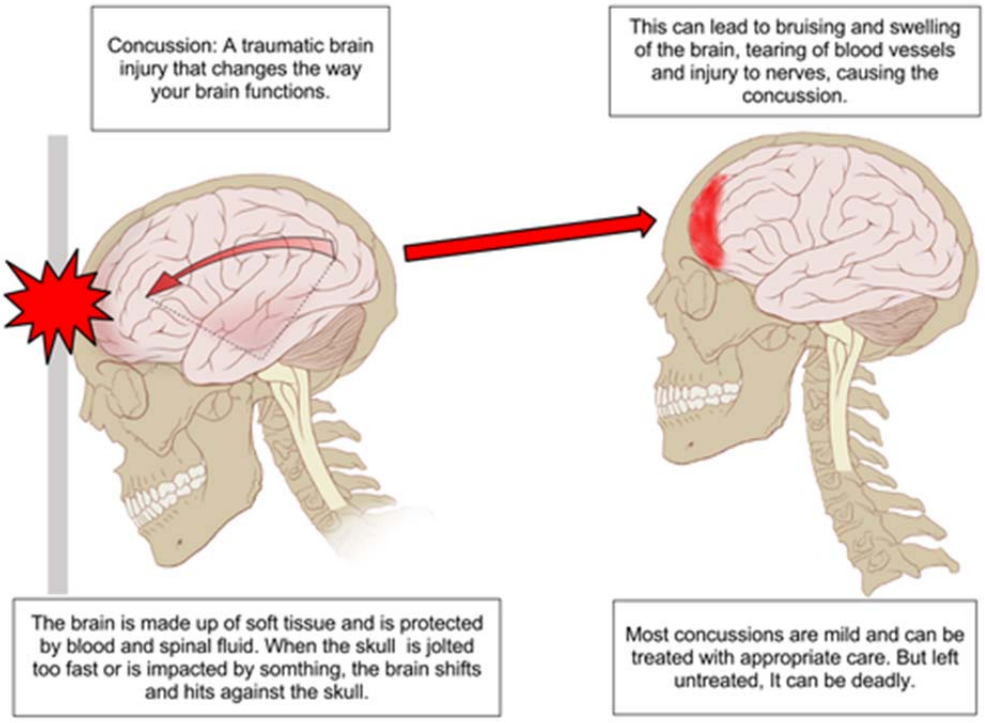

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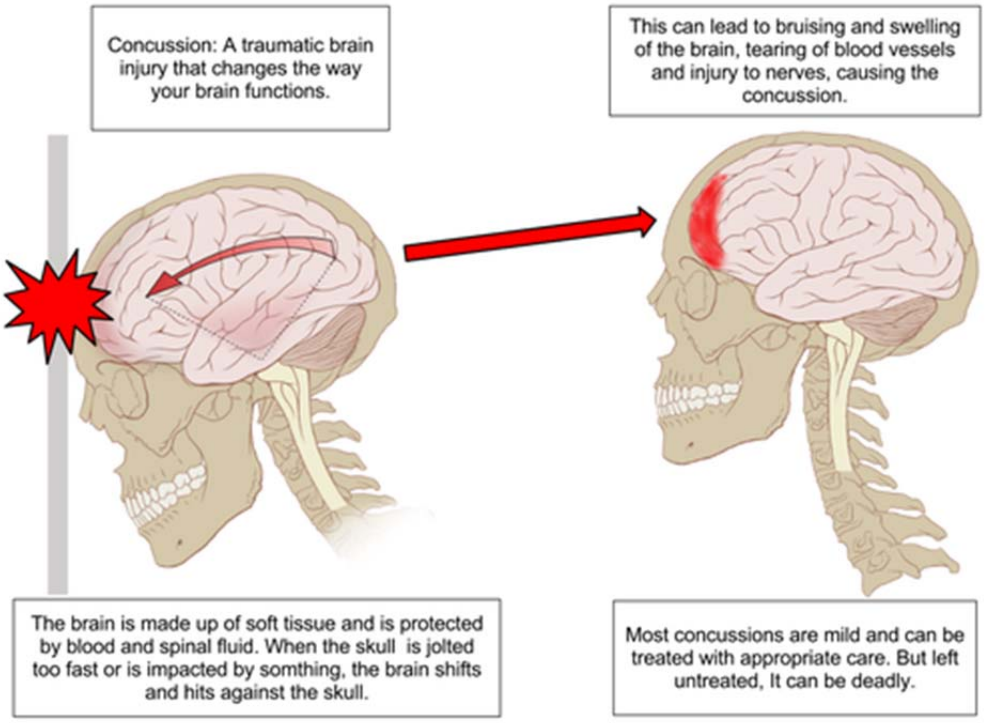

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Arch Gen Psychiatry. 2004 Jan;61(1):53-61.

Psychiatric illness following traumatic brain injury in an adult health maintenance organization population.

Fann JR, Burington B, Leonetti A, Jaffe K, Katon WJ, Thompson RS.

Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98105-6560, USA. fann@u.washington.edu

BACKGROUND: Psychiatric illness after traumatic brain injury (TBI) has been shown to be prevalent in hospitalized and tertiary care patient populations. OBJECTIVE: To determine the risk of psychiatric illness after TBI in an adult health maintenance organization population. DESIGN: Prospective cohort study. SETTING: Large staff-model health maintenance organization. PARTICIPANTS: Nine hundred thirty-nine health plan members diagnosed as having TBI in 1993 and enrolled in the prior year, during which no TBI was ascertained. Three health plan members per TBI-exposed subject were randomly selected as unexposed comparisons, matched for age, sex, and reference date. MAIN OUTCOME MEASURE: Psychiatric illness in the 3 years after the TBI reference date, determined using computerized records of psychiatric diagnoses according to the International Classification of Diseases, Ninth Revision, Clinical Modification, prescriptions, and service utilization. RESULTS: Prevalence of any psychiatric illness in the first year was 49% following moderate to severe TBI, 34% following mild TBI, and 18% in the comparison group. Among subjects without psychiatric illness in the prior year, the adjusted relative risk for any psychiatric illness in the 6 months following moderate to severe TBI was 4.0 (95% confidence interval [CI], 2.4-6.8) and following mild TBI was 2.8 (95% CI, 2.1-3.7; P<.001) compared with those without TBI. Among subjects with prior psychiatric illness, the adjusted relative risk for any psychiatric illness in the 6 months following moderate to severe TBI was 2.1 (95% CI, 1.3-3.3) and following mild TBI was 1.6 (95% CI, 1.2-2.0; P =.005). Prior psychiatric illness significantly modified the relationship between TBI and subsequent psychiatric illness (P =.04) and was a significant predictor (P<.001). Persons with mild TBI and prior psychiatric illness had evidence of persisting psychiatric illness. CONCLUSIONS: **Both moderate to severe and mild TBI are associated with an increased risk of subsequent psychiatric illness. Whereas moderate to severe TBI is associated with a higher initial risk, mild TBI may be associated with persistent psychiatric illness.**

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Major depression following traumatic brain injury.

Jorge RE, Robinson RG, Moser D, Tateno A, Crespo-Facorro B, Arndt S.

Department of Psychiatry, University of Iowa, 500 Newton Road, Iowa City, IA 52242, USA. ricardo-jorge@uiowa.edu

BACKGROUND: Major depression is a frequent psychiatric complication among patients with traumatic brain injury (TBI). To our knowledge, however, the clinical correlates of major depression have not been extensively studied. OBJECTIVE: To determine the clinical, neuropsychological, and structural neuroimaging correlates of major depression occurring after TBI. DESIGN: Prospective, case-controlled, surveillance study conducted during the first year after the traumatic episode occurred.Settings University hospital level I trauma center and a specialized rehabilitation unit. METHODS: The study group consisted of 91 patients with TBI. In addition, 27 patients with multiple traumas but without evidence of central nervous system injury constituted the control group. The patients' conditions were evaluated at baseline and at 3, 6, and 12 months after the traumatic episode. Psychiatric diagnosis was made using a structured clinical interview and DSM-IV criteria. Neuropsychological testing and quantitative magnetic resonance imaging were performed at the 3-month follow-up visit. RESULTS: Major depressive disorder was observed in 30 (33%) of 91 patients during the first year after sustaining a TBI. Major depressive disorder was significantly more frequent among patients with TBI than among the controls. Patients with TBI who had major depression were more likely to have a personal history of mood and anxiety disorders than patients who did not have major depression. Patients with major depression exhibited comorbid anxiety (76.7%) and aggressive behavior (56.7%). Patients with major depression had significantly greater impairment in executive functions than their nondepressed counterparts. Major depression was also associated with poorer social functioning at the 6-and 12-month follow-up, as well as significantly reduced left prefrontal gray matter volumes, particularly in the ventrolateral and dorsolateral regions. CONCLUSIONS: **Major depression is a frequent complication of TBI that hinders a patient's recovery. It is associated with executive dysfunction, negative affect, and prominent anxiety symptoms. The neuropathological changes produced by TBI may lead to deactivation of lateral and dorsal prefrontal cortices and increased activation of ventral limbic and paralimbic structures including the amygdala.**

J Neuropsychiatry Clin Neurosci 16:306-314, August 2004

A Neuropsychological Comparison of Psychotic Disorder Following Traumatic Brain Injury, Traumatic Brain Injury Without Psychotic Disorder, and Schizophrenia

Daryl Fujii, Ph.D., Iqbal Ahmed, M.D. and Earl Hishinuma, Ph.D.;
defujii@hsh.health.state.hi.us

Neuropsychological functioning in individuals with psychotic disorder following traumatic brain injury (PDFTBI), traumatic brain injury without psychosis (TBIWP), and schizophrenia were compared against each other and to the means of normal subjects. It was predicted that the PDFTBI group would be similar to the schizophrenic group in patterns of deficits, but milder in severity. Compared to scores from a normal sample, the PDFTBI group scored significantly lower in intelligence, vocabulary, verbal memory, and executive functioning, while the schizophrenic group scored significantly lower in intelligence, working memory, verbal memory, visual spatial abilities, and executive functioning. No differences were found between normal subjects and the TBIWP group. Implications of our findings for the conceptualization of psychotic disorders are discussed.

Archives of Clinical Neuropsychology

The construct of problem solving in higher level neuropsychological assessment and rehabilitation

Joseph F. Rath, Donna M. Langenbahn, Dvorah Simon, Rose Lynn Sherr, Jason Fletcher and Leonard Diller

Three inter-related studies examine the construct of problem solving as it relates to the assessment of deficits in higher level outpatients with traumatic brain injury (TBI). Sixty-one persons with TBI and 58 uninjured participants completed measures of problem solving and conceptually related constructs, which included neuropsychological tests, self-report inventories, and roleplayed scenarios. In Study I, TBI and control groups performed with no significant differences on measures of memory, reasoning, and executive function, but medium to large between-group differences were found on timed attention tasks. The largest between-group differences were found on psychosocial and problem-solving self-report inventories. In Study II, significant-other (SO) ratings of patient functioning were consistent with patient self-report, and for both self-report and SO ratings of patient problem solving, there was a theoretically meaningful pattern of correlations with timed attention tasks. In Study III, a combination of self-report inventories that accurately distinguished between participants with and without TBI, even when cognitive tests scores were in the normal range, was determined. **The findings reflect intrinsic differences in measurement approaches to the construct of problem solving and suggest the importance of using a multidimensional approach to assessment.**

Ashman, T.A., Spielman, L.A., Hibbard, M.R., Silver, J.M., Chandna, T., & Gordon, W.A. (in press). Psychiatric challenges in the first 6 years after traumatic brain injury: Cross-sequential analyses of axis I disorders. Archives of Physical Medicine and Rehabilitation.

Hibbard, M.R., Ashman, T.A., Spielman, L., Chun, D., Charatz, H., & Melvin, S. (in press). Predictors of depression post-TBI. Archives of Physical Medicine and Rehabilitation.

Curr Psychiatry Rep. 2003 Jul;5(3):197-201.

Psychotic disorder and traumatic brain injury.

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Traumatic brain injury (TBI) can result in serious and disabling neuropsychiatric disorders, such as cognitive deficits and personality change, as well as severe and chronic psychosis. This review focuses on the relationship between TBI and schizophrenia-like psychosis (SLP) including its epidemiology, diagnostic criteria, clinical presentation, psychopathology, risk factors, and pathophysiology. The relationships between post-traumatic epilepsy and SLP, and brain trauma and schizophrenia, are also discussed. The risk of SLP does increase after TBI. The clinical presentation has considerable overlap with primary schizophrenic disorder, with a prominence of persecutory and other delusions and auditory hallucinations, as well as a lack of negative symptoms. The onset is often gradual, with a subacute or chronic course. More severe and diffuse brain injury, especially of the temporal and frontal lobes, is the most prominent risk factor. Genetic load may also play a role, but presence of epilepsy could be a protective factor. Further large and systematic longitudinal studies are needed.

Int Rev Psychiatry. 2003 Nov;15(4):328-40.

Psychosis following traumatic brain injury.

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Psychosis is a relatively infrequent but potentially serious and debilitating consequence of traumatic brain injury (TBI), and one about which there is considerable scientific uncertainty and disagreement. There are several substantial clinical, epidemiological, and neurobiological differences between the post-traumatic psychoses and the primary psychotic disorders. The recognition of these differences may facilitate identification and treatment of patients whose psychosis is most appropriately regarded as post-traumatic. In the service of assisting psychiatrists and other mental health clinicians in the diagnosis and treatment of persons with post-traumatic psychoses, this article will review post-traumatic psychosis, including definitions relevant to describing the clinical syndrome, as well as epidemiologic, neurobiological, and neurogenetic factors attendant to it**. An approach to evaluation and treatment will then be offered, emphasizing identification of the syndrome of post-traumatic psychosis, consideration of the differential diagnosis of this condition, and careful selection and administration of treatment interventions.**

Actas Esp Psiquiatr. 2003 Nov-Dec;31(6):353-60. Related Articles, Links

[Psychiatric and neuropsychological legal assessment of traumatic brain damage and Law]

[Article in Spanish]

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Medico-legal assessment of people who have suffered injuries in road traffic accidents must use Law 30/95 as a reference frame. Psychiatric and neuropsychological syndromes secondary to traumatic brain injury (TBI) are no exception and pose demanding challenges to physicians and psychologists. This paper analyzes descriptive and nosological difficulties face by psychiatrists and psychologists; their expert contribution includes translation of official diagnostic entities into categories published in the annex of Law 30/95. Our psychopathological repertoire was created in the 19th century and has hardly been revised since. The wide and varied types of neuropsychological impairments encountered in TBI have to be diagnosed within a very narrow range of DSM-IV and ICD-10 categories. The most common conflicts encountered in the medicolegal arena are revised: the differential diagnosis between dementia and combinations of organic personality disorder with cognitive impairment; differential diagnosis between spontaneous psychiatric illness (bipolar disorder, schizophrenia) and psychiatric syndromes secondary to brain injury (posttraumatic psychosis, organic bipolar disorder); differential diagnosis between concussional syndrome and organic personality disorder, cognitive impairment or organic affective disorder. Specific diagnostic guidelines are suggested for each of these clinical situations. Actas Esp Psiquiatr 2003;31(6):353-360

Arch Phys Med Rehabil. 2003 Nov;84(11):1621-8. Related Articles, Links

Depression assessment after traumatic brain injury: an empirically based classification method.

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OBJECTIVES: To describe the patterns of depression in patients with traumatic brain injury (TBI), to evaluate the psychometric properties of the Neurobehavioral Functioning Inventory (NFI) Depression Scale, and to classify empirically NFI Depression Scale scores. DESIGN: Depressive symptoms were characterized by using the NFI Depression Scale, the Beck Depression Inventory (BDI), and the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) Depression Scale. SETTING: An outpatient clinic within a Traumatic Brain Injury Model Systems center. PARTICIPANTS: A demographically diverse sample of 172 outpatients with TBI, evaluated between 1996 and 2000. INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: The NFI, BDI, and MMPI-2 Depression Scale. The Cronbach alpha, analysis of variance, Pearson correlations, and canonical discriminant function analysis were used to examine the psychometric properties of the NFI Depression Scale. RESULTS: Patients with TBI most frequently reported problems with frustration (81%), restlessness (73%), rumination (69%), boredom (66%), and sadness (66%) with the NFI Depression Scale. The percentages of patients classified as depressed with the BDI and the NFI Depression Scale were 37% and 30%, respectively. The Cronbach alpha for the NFI Depression Scale was.93, indicating a high degree of internal consistency. As hypothesized, NFI Depression Scale scores correlated highly with BDI (r=.765) and MMPI-2 Depression Scale T scores (r=.752). The NFI Depression Scale did not correlate significantly with the MMPI-2 Hypomania Scale, thus showing discriminant validity. Normal and clinically depressed BDI scores were most likely to be accurately predicted by the NFI Depression Scale, with 81% and 87% of grouped cases, respectively, correctly classified. Normal and depressed MMPI-2 Depression Scale scores were accurately predicted by the NFI Depression Scale, with 75% and 83% of grouped cases correctly classified, respectively. Patients' NFI Depression Scale scores were mapped to the corresponding BDI categories, and 3 NFI score classifications emerged: minimally depressed (13-28), borderline depressed (29-42), and clinically depressed (43-65). CONCLUSIONS: Our study provided further evidence that screening for depression should be a standard component of TBI assessment protocols. Between 30% and 38% of patients with TBI were classified as depressed with the NFI Depression Scale and the BDI, respectively. Our findings also provided empirical evidence that the NFI Depression Scale is a useful tool for classifying postinjury depression. (*Note: depression screening measures all have very low ppp versus the traditional criterion variable of depression)*

Am J Psychiatry 2002 Aug;159(8):1315-21

Comment in:

Am J Psychiatry. 2002 Aug;159(8):1261-4.

Axis I and II psychiatric disorders after traumatic brain injury: a 30- year follow-up study.

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OBJECTIVE: Patients who had suffered traumatic brain injury were evaluated to determine the occurrence of psychiatric disorders during a 30-year follow-up. METHOD: Sixty patients were assessed on average 30 years after traumatic brain injury. DSM-IV axis I disorders were diagnosed on a clinical basis with the aid of the Schedules for Clinical Assessment in Neuropsychiatry (version 2.1), and axis II disorders were diagnosed with the Structured Clinical Interview for DSM-III-R Personality Disorders. Cognitive impairment was measured with a neuropsychological test battery and the Mini- Mental State Examination. RESULTS: Of the 60 patients, 29 (48.3%) had had an axis I disorder that began after traumatic brain injury, and 37 (61.7%) had had an axis I disorder during their lifetimes. The most common novel disorders after traumatic brain injury were major depression (26.7%), alcohol abuse or dependence (11.7%), panic disorder (8.3%), specific phobia (8.3%), and psychotic disorders (6.7%). Fourteen patients (23.3%) had at least one personality disorder. The most prevalent individual disorders were avoidant (15.0%), paranoid (8.3%), and schizoid (6.7%) personality disorders. Nine patients (15.0%) had DSM-III-R organic personality syndrome. **CONCLUSIONS: The results suggest that traumatic brain injury may cause decades- lasting vulnerability to psychiatric illness in some individuals. Traumatic brain injury seems to make patients particularly susceptible to depressive episodes, delusional disorder, and personality disturbances. The high rate of psychiatric disorders found in this study emphasizes the importance of psychiatric follow-up after traumatic brain injury.**

J Neurol Neurosurg Psychiatry. 2002 May;72(5):615-20.

Psychiatric illness and subsequent traumatic brain injury: a case control study.

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OBJECTIVE: To determine whether psychiatric illness is a risk factor for subsequent traumatic brain injury (TBI). METHODS: Case control study in a large staff model health maintenance organisation in western Washington State. Patients with TBI, determined by International classification of diseases, 9th revision, clinical modification (ICD-9-CM) diagnoses, were 1440 health plan members who had TBI diagnosed in 1993 and who had been enrolled in the previous year, during which no TBI was ascertained. Three health plan members were randomly selected as control subjects, matched by age, sex, and reference date. Psychiatric illness in the year before the TBI reference date was determined by using computerised records of ICD-9-CM diagnoses, psychiatric medication prescriptions, and utilisation of a psychiatric service. RESULTS: For those with a psychiatric diagnosis in the year before the reference date, the adjusted relative risk for TBI was 1.7 (95% confidence interval (CI) 1.4 to 2.0) compared with those without a psychiatric diagnosis. Patients who had filled a psychiatric medication prescription had an adjusted relative risk for TBI of 1.6 (95% CI 1.2 to 2.1) compared with those who had not filled a psychiatric medication prescription. Patients who had utilised psychiatric services had an adjusted relative risk for TBI of 1.3 (95% CI 1.0 to 1.6) compared with those who had not utilised psychiatric services. The adjusted relative risk for TBI for patients with psychiatric illness determined by any of the three psychiatric indicators was 1.6 (95% CI 1.4 to 1.9) compared with those without any psych iatric indicator. CONCLUSION: Psychiatric illness appears to be associated with an increased risk for TBI.

NeuroRehabilitation. 2002;17(4):357-68.
Evaluation and treatment of psychosis after traumatic brain injury.
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A review of research studies to date suggests that psychosis is a relatively rare, but serious, complication of traumatic brain injury (TBI). Psychotic syndromes occur more frequently in individuals who have had a TBI than in the general population. Onset of symptoms can be early or late. Psychosis can occur during the period of post-traumatic amnesia, in association with post-traumatic epilepsy, in association with TBI-related mood disorders, and as a chronic, schizophrenia-like syndrome. TBI can interact with genetic vulnerability to increase the risk of developing illnesses such as schizophrenia. Thorough diagnostic assessment is the foundation of rational and effective pharmacotherapy for psychosis after TBI. Atypical antipsychotic drugs have emerged as first line drugs for treatment of psychotic disorders from all causes, including TBI. Anticonvulsant, antidepressant or other drugs may also be needed in some cases. Medication approaches must be adjusted for the particular characteristics and vulnerabilities of the patient with a TBI.

Curr Psychiatry Rep. 2002 Oct;4(5):354-62.
Traumatic brain injury in older adults.
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Traumatic brain injury (TBI) is a serious health risk for older adults, and the consequences of TBI range from full recovery to death. For many who survive, there is a legacy of cognitive, physical, and emotional disability. Falls are the major cause of head injury in older adults. There are many risk factors including pre-existing brain disease, other diseases, and, sometimes, iatrogenic factors. Efforts directed at prevention are of great importance. Outcome studies indicate that outcome is generally worse for older people than for younger people with similar injuries, but older individuals also deserve aggressive rehabilitation directed at the best possible recovery. This review will discuss the symptoms and syndromes that commonly result from TBI with comments about treatment.

NeuroRehabilitation 2002;17(2):105-13

The phenomenology of depression after brain injury.

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One important challenge in neuropsychiatry is how to diagnose depression in patients with acute brain lesions, since there may be an overlap between symptoms of depression and signs associated with the neurologic disease. The best approach is to assess the presence of depressive symptoms using semi-structured or structured psychiatric interviews such as the Present State Exam, the Structured Clinical Interview for DSM- IV, or the Schedules for Clinical Assessment in Neuropsychiatry. The diagnosis of a depressive syndrome should be made using standardized diagnostic criteria for mood disorders due to neurological disease such as in the DSM-IV or the ICD-10. Depression rating scales, such as the Hamilton Depression Scale and the Center for Epidemiologic Scales for Depression may be used to rate the severity of depression and monitor the progression of antidepressant treatment. Most studies in acute and chronic neurologic disorders demonstrated the specificity of both autonomic and psychological symptoms for the syndrome of depression. The present review article examines important considerations before a diagnosis of depression in neurologic disease, discusses a variety of psychiatric instruments that are used to examine the presence and severity of depression in neurologic disease, examines relevant phenomenological issues, and proposes different diagnostic strategies.

Curr Treat Options Neurol. 2002 Jan;4(1):59-75.

Emotional Disturbances Following Traumatic Brain Injury.

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Mood disturbances are common sequelae of traumatic brain injury (TBI), but the scientific database for such disorders is very limited in descriptive, prognostic, and treatment data. Post-TBI symptoms often cross diagnostic boundaries and include cognitive loss, amotivation, psychosis, mood, changes, or other domains. The treating physician must be mindful that clear diagnostic boundaries may not exist. Premorbid level of functioning commonly affects post-TBI level of functioning. When setting treatment goals, this must be considered. Patients who had lower levels of psychosocial functioning before the injury may not fare as well afterwards. Treatment of post-TBI mood symptoms should proceed after a full diagnostic work-up including imaging and electroencephalographic (EEG) studies, neuropsychologic testing, and physical and laboratory examinations. Once the diagnostic picture is established, treatment should then proceed with a multidisciplinary team (physician, social worker, neuropsychologist, and others). For the medications, consider both target symptoms and side effects; start medications with low doses and raise slowly, give full therapeutic trials before switching or adding second agents, avoid benzodiazepines if possible, limit anticholinergic or antidopaminergic agents, and avoid providing large quantities of lethal medications. When starting medications for the treatment of mood disorders following TBI, several general principles of treatment in this population should be considered, including: balancing treatment of target symptoms with the potential for adverse effects; making use of side effects to treat comorbid problems when present (ie, relatively antidepressant for depression and marked insomnia); using a "start low, go slow" approach; continuing dose escalation to full therapeutic levels (ie, completing therapeutic trials) before switching or adding augmenting agents; avoiding agents with predictable and functionally important adverse effects (ie, benzodiazepines, strongly anticholinergic or antidopaminergic agents); and avoiding prescription of large and potentially lethal quantities of medications.

J Cogn Neurosci 2002 Jul 1;14(5):709-20

Is the human amygdala critical for the subjective experience of emotion? Evidence of intact dispositional affect in patients with amygdala lesions.

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It is thought that the human amygdala is a critical component of the neural substrates of emotional experience, involved particularly in the generation of fear, anxiety, and general negative affectivity. Although many neuroimaging studies demonstrate findings consistent this notion, little evidence of altered emotional experience following amygdala damage has been gathered in humans. In a preliminary test of the amygdala's role in phenomenal affective states, we assessed the extent of experienced positive and negative affective states in patients with amygdala damage and age-, sex-, and education-matched controls. To assess chronic changes in experienced affect, all groups were administered the Positive and Negative Affect Schedules (PANAS, Watson, Clark, & Tellegen, 1988). In the first study, we examined the effects of amygdala lesions on affective traits in 10 left and 10 right amygdala-damaged patients, 1 patient with bilateral amygdala damage (SP), and 20 control subjects. Subjects were asked to indicate the typicality of different experiential states of positive (e.g., inspired, excited) and negative (e.g., afraid, nervous) valence. In a second study, we examined more closely the effects of bilateral amygdala damage on the day-to-day generation of affective states by administering the PANAS daily for a 30-day period to patient SP and age-, sex-, and education-matched controls. In both experiments, no differences in the magnitude and frequency of self-reported positive or negative affect were found between control subjects and patients with amygdala damage. Moreover, principal components analyses of the covariation among different affects (across individuals in Study 1 and within individuals across days in Study 2) confirmed a two-factor (positive vs. negative) description of experienced affect in controls. A highly similar two-factor description of experienced affect was found in patients with amygdala lesions. This suggests that the underlying structure of affective states was intact following amygdala damage. It is concluded that the human amygdala may be recruited during phenomenal affective states in the intact brain, but is not necessary for the production of these states.

Brain Inj. 2001 Mar;15(3):189-209.

Traumatic brain injury (TBI) 10-20 years later: a comprehensive outcome study of psychiatric symptomatology, cognitive abilities and psychosocial functioning.

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The goal of this study was to measure the very long-term mental and psychosocial outcomes of severe traumatic brain injury (TBI). Seventy-six persons with severe TBI were evaluated extensively by means of standardized scales, neuropsychological tests and evaluations by family members, at an average of 14.1 (SD = 5.5) years post-injury. Six mental and functional domains were examined: psychiatric symptomatology, cognitive abilities, vocational status, family integration, social functioning, and independence in daily routines. The findings indicate a long-term differential effect of severe TBI, with seriously affected psychiatric symptomatology, family and social domains, as compared to moderately influenced cognitive, vocational and independent functioning. Relatively high rates of depression, psychomotor slowness, loneliness and family members' sense of burden were found. In addition to their epidemiological importance, the results indicate that persons with TBI and their families may need professional assistance to maintain a reasonable psychosocial quality of life, even more than a decade post-injury.

J Neuropsychiatry Clin Neurosci. 2001 Winter;13(1):61-9.

Comment in:
* J Neuropsychiatry Clin Neurosci. 2001 Fall;13(4):533-4.

Risk factors in psychosis secondary to traumatic brain injury.

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Psychosis is a rare but devastating sequela of traumatic brain injury (TBI). This study examined risk factors for developing a psychosis secondary to TBI (PSTBI). Demographics of 25 inpatients with PSTBI were statistically analyzed for risk factors. Data from the PSTBI group were also compared with data from a control group of TBI patients without psychosis. Results indicate the PSTBI group was more likely to have had a previous congenital neurological disorder or to have sustained a head injury prior to adolescence. The PSTBI also had a higher proportion of males. Discussion focuses on potential models for developing PSTBI.

J Am Acad Child Adolesc Psychiatry. 2001 May;40(5):572-9.

Lifetime and novel psychiatric disorders after pediatric traumatic brain injury.

Bloom DR, Levin HS, Ewing-Cobbs L, Saunders AE, Song J, Fletcher JM, Kowatch RA.

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OBJECTIVE: To assess lifetime and current psychiatric disorders at least 1 year after traumatic brain injury (TBI) in children and adolescents. METHOD: Forty-six youths who sustained a TBI between the ages of 6 through 15 years were evaluated at least 1 year post-TBI to identify the presence of lifetime and/or novel psychiatric disorders. Semistructured interviews of the parent and child and standardized parent self-report rating instruments were used. RESULTS: Attention-deficit/hyperactivity disorder and depressive disorders were the most common lifetime and novel diagnoses. A wide variety and high rate of novel psychiatric disorders were identified; 74% of these disorders persisted in 48% of the injured children. Internalizing disorders were more likely to resolve than externalizing disorders. Both interviews and parent ratings were sensitive to current externalizing behaviors; interviews more often detected internalizing disorders, whereas parent ratings also identified cognitive difficulties. CONCLUSIONS: **Findings were generally consistent with previous research demonstrating the high rate of novel psychiatric disorders following pediatric TBI. Psychiatric interviews were sensitive in identifying both lifetime and novel disorders.**

Brain Inj. 2000 Jan;14(1):45-61.

Axis II psychopathology in individuals with traumatic brain injury.

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PRIMARY OBJECTIVES: To determine the frequency and nature of post-TBI personality disorders (PDs) in a community-based sample of individuals with TBI. RESEARCH DESIGN: One hundred individuals with TBI were administered a structural clinical interview to determine Axis II psychopathology. METHODS OF PROCEDURES: The Structured Clinical Interview for DSM-IV Personality Disorders, Clinician Version (SCID II) was used to determine 12 Axis II personality disorders. SCID II questions were modified so that symptom onset could be rated as occurring pre-injury vs. post-TBI. Data were analysed using student T-tests, chi-square analysis and one way analyses of variance. OUTCOMES AND RESULTS: Pre-TBI PDs were diagnosed in 24% of the sample; antisocial PD and obsessive-compulsive PD were the most common diagnoses. Post-TBI, 66% of the sample met criteria for at least one PD, with PDs independent of TBI severity, age at injury, and time since injury. The most common post-TBI PDs were: borderline, avoidant, paranoid, obsessive-compulsive and narcissistic. Men were more likely to be diagnosed with antisocial PD and narcissistic PD. Individuals with pre-TBI PDs were at greater risk of acquiring additional psychopathology post-TBI. Personality traits endorsed by more than 30% of the sample post-TBI reflected loss of self-confidence, attempts to cope with cognitive and interpersonal failures and negative affect. CONCLUSION: These findings argue against a specific TBI personality syndrome, but rather a diversity of personality disorders reflective of the persistent challenges and compensatory coping strategies developed by individuals post-TBI. Prospective need for clinical assessment, pro-active education and focused treatment approaches are discussed.

Curr Treat Options Neurol. 2000 Mar;2(2):169-186. Related Articles, Links

Neuropsychiatric Aspects of Traumatic Brain Injury.

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Traumatic brain injury (TBI) may produce a variety of neuropsychiatric problems, including impaired cognition, depression, mania, affective lability, irritability, anxiety, and psychosis. Despite the common occurrence of these symptoms following TBI, there are relatively few studies that provide clear guidance regarding management. Many symptoms (eg, irritability, affective lability, fatigue, sleep disturbance, and impaired cognition) are primarily consequences of brain injury rather than symptoms of a comorbid psychiatric disorder such as major depression. Although it is difficult to study the complicated treatments needed for such symptom complexes, we are able to recommend an approach to the evaluation and treatment of neuropsychiatric problems following traumatic brain injury. A thorough assessment of the patient is a prerequisite to the prescription of any treatment. This assessment should include a thorough developmental, psychiatric, and medication history; a detailed mental status examination; a complete neurologic examination; and quantification of neuropsychiatric symptoms using standardized and accepted inventories (eg, Neurobehavioral Rating Scale, Neuropsychiatric Inventory). All symptoms must be evaluated in the context of the patient's premorbid history and current treatment because neuropsychiatric symptoms may be influenced by either factor or by both factors. Psychotherapy is an important component of the treatment of neuropsychiatric problems following TBI. Additionally, patients should be encouraged to become involved with local TBI support groups. When medications are prescribed, it is essential to use cautious dosing (low and slow) and empiric trials with continuous reassessment of symptoms using standardized scales and monitoring for drug-drug interactions. In general, medications with significant sedative, antidopaminergic, and anticholinergic properties should be avoided, and benzodiazepines should be used sparingly, if at all. Although patients with TBI may be particularly susceptible to adverse effects of psychopharmacologic medications, at times dosages similar to those used for the non-brain-injured psychiatric patient may be needed. When a single medication does not provide adequate relief of symptoms or cannot be tolerated at therapeutic doses, an alternative strategy is to augment the effect of one medication by using a second low-dose agent with a different mechanism of action.

Brain Inj 2000 Jun;14(6):513-33

Psychiatric treatment outcome following traumatic brain injury.

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The relationship between self-reported history of traumatic brain injury (TBI) and psychiatric treatment outcome was investigated. TBI was hypothesized to be frequent, associated with cognitive deficits on neuropsychological testing, and less amenable to standard psychiatric treatment. Subjects were 42 psychiatric patients with a self-reported history of TBI and 25 psychiatric patients with no TBI history. Subjects received approximately 2 weeks of inpatient psychiatric treatment. Subjects received neuropsychological testing and completed the Brief Symptom Inventory weekly. TBI was frequent (66% of subjects); multiple injuries were common. Neuropsychological performance was generally average in both groups with few group differences. Subjects, on average, reported significantly decreased psychiatric symptoms on discharge. However, the TBI group appeared to improve less than the control group; group status was a significant predictor of treatment outcome. Implications of results for assessment and treatment of psychiatric disorders in patients with a history of TBI are discussed.

J Neuropsychiatry Clin Neurosci 2000 Summer;12(3):316-27

Can traumatic brain injury cause psychiatric disorders?

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Traumatic brain injury (TBI) may cause psychiatric illness. This article reviews the evidence on the basis of an established set of causation criteria. The evidence is convincing for a strong association between TBI and mood and anxiety disorders. Substance abuse and schizophrenia are not strongly associated with TBI, and there is little research into the rates of personality disorders after TBI. Evidence for a biologic gradient is lacking, but such a gradient may not be relevant to TBI. Evidence for the correct temporal sequence is present. Preliminary evidence suggests a biologic rationale for TBI causing psychiatric illness. Further and methodologically improved research is supported and required.

Am J Psychiatry 1999 Mar;156(3):374-8

Rate of psychiatric illness 1 year after traumatic brain injury.

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OBJECTIVE: Neuro/behavioral symptoms are not uncommon after a traumatic brain injury. However, psychiatric syndromes per se have rarely been studied in patients with such an injury. The purpose of this study was to evaluate the type and extent of psychiatric syndromes in patients with traumatic brain injury. METHOD: One hundred ninety-six hospitalized adults were studied 1 year after a traumatic brain injury with the use of a two-stage psychiatric diagnostic procedure. Psychiatric diagnoses were made according to ICD-10 criteria on the basis of data from the Schedules for Clinical Assessment in Neuropsychiatry interview. RESULTS: Of 164 patients interviewed, 30 (18.3%) had an ICD-10 diagnosis of a psychiatric illness. Among the 120 patients who were 18-64 years old, 21.7% had a psychiatric illness, compared with 16.4% in a study of the general population. A depressive illness was present in 13.9% of the traumatic brain injury patients, compared with 2.1% of the general population, and panic disorder was present in 9.0%, compared with 0.8% of the general population. CONCLUSIONS: In comparison with the general population, a higher proportion of adult patients had developed psychiatric illnesses 1 year after a traumatic brain injury; the rates of depressive episode and panic disorder were significantly higher in the study group. A history of psychiatric illness, an unfavorable global outcome according to the Glasgow Outcome Scale, a lower score on the Mini-Mental State examination, and fewer years of formal education seemed to be important risk factors in the development of a psychiatric illness. Compensation claims, however, were not associated with the rate of psychiatric illness.

Arch Phys Med Rehabil. 1998 Jan;79(1):90-103.

Depression following traumatic brain injury. Rosenthal M, Christensen BK, Ross TP.

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OBJECTIVE: Review the existing literature on the incidence, neurobiological and psychosocial correlates, and methods of assessment and treatment of depression following traumatic brain injury (TBI). DATA SOURCES: Computerized database searches of the English-language literature from Index Medicus, Psychological Abstracts, Excerpta Medica, and Cumulative Index of Nursing and Allied Health Literature. STUDY SELECTION: Given the relatively small number of publications specifically related to TBI and depression, all studies appearing in the peer-reviewed literature were included in the review. In addition, studies examining depression and other neurologic diseases (eg, stroke) were also reviewed as to the potential applicability of the theoretical model or methodology used. CONCLUSIONS: Depression occurs with sufficient frequency to be considered a significant consequence after TBI. Depression can impede the achievement of optimal functional outcome, whether in the acute or chronic stages of recovery. It appears that a combination of neuroanatomic, neurochemical, and psychosocial factors is responsible for the onset and maintenance of depression. Its treatment is typically psychopharmacologic, with best results obtained from nontricyclic antidepressants. These results have not been confirmed in double-blind clinical trials, however. Future research should use comprehensive, integrative models of depression that include demographic, biologic, and psychosocial factors; enhanced functional neuroimaging techniques; controlled studies of psychopharmacologic and other interventions; and prospective designs with long-term follow-up.

Semin Clin Neuropsychiatry. 1998 Jul;3(3):211-223. Related Articles, Links

Traumatic Brain Injury and Psychosis: What Is the Connection?

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Psychotic syndromes occur more frequently in individuals who have had a traumatic brain injury (TBI) than in the general population. Psychotic syndromes following a TBI can present in the period of post-traumatic anmesia, in association with post-traumatic epilepsy, in association with TBI-related mood disorders, and as a chronic, schizophrenia-like syndrome. Individuals with schizophrenia (a chronic psychotic disorder) have a higher frequency of prior TBI than individuals with other psychiatric disorders. These observations suggest an intriguing link between psychosis and TBI. The study of the neuroanatomical and neuropathological substrate of schizophrenia, and of the core symptoms of the disorder ("negative" symptoms, hallucinations, delusions), suggests that abnormalities in the structure and function of certain brain regions play a role in the genesis and maintenance of these core symptoms. The key brain regions include the dorsolateral prefrontal cortex, temporal lobe structures, basal ganglia, thalamus, and cingulate gyrus. These brain regions are commonly injured in many patients with TBI, suggesting a possible mechanism underlying the observed link between TBI and psychosis. This article reviews the literature on TBI and psychosis, and suggests an approach to the evaluation and treatment of individuals with TBI and psychosis.

Axis I psychopathology in individuals with TBI.

Hibbard MR, Uysal S, Kepler K, Bogdany J, Silver J.

Journal of Head Trauma Rehabilitation, 1998, 13(4), 24-39.
Department of Rehabilitation Medicine, The Mount Sinai Medical Center, New York, New York 10029, USA.

OBJECTIVES: To assess the incidence, comorbidity, and patterns of resolution of DSM-IV mood, anxiety, and substance use disorders in individuals with traumatic brain injury (TBI). DESIGN: The Structured Clinical Interview for DSM-IV Diagnoses (SCID) was utilized. Diagnoses were determined for three onset points relative to TBI onset: pre-TBI, post-TBI, and current diagnosis. Contrasts of prevalence rates with community-based samples, as well as chi-square analysis and analysis of variance were used. Demographics considered in analyses included gender, marital status, severity of injury, and years since TBI onset. SETTING: Urban, suburban, and rural New York state. PARTICIPANTS: 100 adults with TBI who were between the ages of 18 and 65 years and who were, on average, 8 years post onset at time of interview. MAIN OUTCOME MEASURES: SCID Axis I mood diagnoses of major depression, dysthymia, and bipolar disorder; anxiety diagnoses of panic disorder, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and phobia; and substance use disorders. RESULTS: Prior to TBI, a significant percentage of individuals presented with substance use disorders. After TBI, the most frequent Axis I diagnoses were major depression and select anxiety disorders (ie, PTSD, OCD, and panic disorder). Comorbidity was high, with 44% of individuals presenting with two or more Axis I diagnoses post TBI. Individuals without a pre-TBI Axis I disorder were more likely to develop post-TBI major depression and substance use disorders. Rates of resolution were similar for individuals regardless of previous psychiatric histories. Major depression and substance use disorders were more likely than were anxiety disorders to remit. CONCLUSION: TBI is a risk factor for subsequent psychiatric disabilities. The need for proactive psychiatric assessment and timely interventions in individuals post TBI is indicated.

J Am Acad Child Adolesc Psychiatry. 1997 Sep;36(9):1278-85.
Traumatic brain injury in children and adolescents: psychiatric disorders at two years.
Max JE, Robin DA, Lindgren SD, Smith WL Jr, Sato Y, Mattheis PJ, Stierwalt JA, Castillo CS.
Department of Psychiatry, University of Iowa, Iowa City 52242, USA.
OBJECTIVE: To extend findings regarding predictive factors of psychiatric outcome from the first to the second year after traumatic brain injury (TBI) in children and adolescents. METHOD: Subjects were children aged 6 to 14 years at the time they were hospitalized after TBI. The study used a prospective follow-up design. Assessments of preinjury psychiatric, behavioral, adaptive functioning, family functioning and family psychiatric history status were conducted. Severity of injury was assessed by standard clinical scales and neuroimaging was analyzed. The outcome measure was the presence of a psychiatric disorder, not present before the injury ("novel"), during the second year after TBI. RESULTS: Fifty subjects enrolled, and the analyses focused on 42 subjects followed at 24 months. Severity of injury, preinjury family function, and preinjury lifetime psychiatric history predicted the development of a "novel" psychiatric disorder present in the second year. CONCLUSION: These data suggest that there are children, identifiable through clinical assessment, at increased risk for "novel" psychiatric disorders in the second year after TBI.

Brain Inj 1996 May;10(5):319-27

Psychiatric disorders after traumatic brain injury.

van Reekum R, Bolago I, Finlayson MA, Garner S, Links PS.

Department of Psychiatry, University of Toronto, Canada

Substantial psychological and neurobehavioural evidence is available to support the hypothesis that traumatic brain injury (TBI) is a risk factor for subsequent psychiatric disorders. However, studies utilizing established psychiatric diagnostic schemes to study these outcomes after TBI are scarce, and no studies have included an assessment of personality disorders in addition to the major psychiatric disorders. This study utilizes structured psychiatric interviews to measure the prevalence of DSM-III(R) disorders in a sample of 18 subjects derived from a TBI rehabilitation programme. Results revealed high rates for major depression, bipolar affective disorder, generalized anxiety disorder, borderline and avoidant personality disorders. Co-morbidity was also high. A preliminary study of postulated predictive factors revealed possible roles for sex and for initial severity of injury. The study supports the association between TBI and psychiatric disorder, and suggests the need for monitoring, for prevention, and for treatment of psychiatric disorders after TBI.

Am J Psychiatry 1995 Oct;152(10):1493-9

Psychiatric disorders and functional disability in outpatients with traumatic brain injuries.

Fann JR, Katon WJ, Uomoto JM, Esselman PC.

Department of Psychiatry and Behavioral Sciences, University of Washington Medical Center, Seattle, USA.

OBJECTIVE: This study examined psychiatric sequelae of traumatic brain injuries in outpatients and their relation to functional disability. METHOD: Fifty consecutive outpatients with traumatic brain injuries who came to a brain injury rehabilitation clinic for initial evaluation were examined for DSM-III-R diagnoses with the use of the National Institute of Mental Health Diagnostic Interview Schedule. The patients completed the Medical Outcomes Study Health Survey to assess functional disability and a questionnaire to assess postconcussion symptoms and self-perceptions of the severity of their brain injuries and cognitive functioning. RESULTS: Thirteen (26%) of the patients had current major depression, and an additional 14 (28%) reported a first-onset major depressive episode after the injury that had resolved. Twelve (24%) had current generalized anxiety disorder, and four (8%) reported current substance abuse. The group with depression and/or anxiety was significantly more impaired than the nondepressed/ nonanxious patients according to the Medical Outcomes Study Health Survey measures of emotional role functioning, mental health, and general health perceptions. The depressed/anxious group also rated their injuries as significantly more severe and their cognitive functioning as significantly worse, despite the lack of significant differences in objective measures of severity of injury and Mini-Mental State examination scores. The depressed patients reported significantly more postconcussion symptoms that were increasing in severity over time. CONCLUSIONS: Depression and anxiety are common in outpatients with traumatic brain injuries. Patients with depression or anxiety are more functionally disabled and perceive their injury and cognitive impairment as more severe. Depressed patients report more increasingly severe postconcussion symptoms.

Am J Psychiatry 1993 Jun;150(6):916-21

Secondary mania following traumatic brain injury.

Jorge RE, Robinson RG, Starkstein SE, Arndt SV, Forrester AW, Geisler FH.

Department of Psychiatry, College of Medicine, University of Iowa.

OBJECTIVE: In this study patients were examined during the first year after traumatic brain injury to determine the presence of secondary mania. METHOD: A consecutive series of 66 patients with closed-head injury were evaluated in the hospital and at 3-, 6-, and 12-month follow-ups. The patients were examined with a semistructured psychiatric interview and scales for measurement of impairment in activities of daily living, intellectual function, and social functioning. Patients fulfilling the DSM-III-R criteria for mania were compared to patients with major depression and to patients without affective disturbances in regard to their background characteristics, impairment variables, and lesion locations. RESULTS: Six patients (9%) met the criteria for mania at some point during follow-up. The presence of temporal basal polar lesions was significantly associated with secondary mania even when the effect of other lesion locations was taken into account. Secondary mania was not found to be associated with the severity of brain injury, degree of physical or cognitive impairment, level of social functioning, or previous family or personal history of psychiatric disorder. The duration of mania, however, appeared to be brief, lasting approximately 2 months. CONCLUSIONS: The 9% frequency of secondary mania in these patients with traumatic brain injury is significantly greater than that seen in other brain-injured populations (e.g., patients with stroke). The major correlate was the presence of a temporal basal polar lesion.

Re: preinjury variables, see the review paper, Preinjury Factors Affecting Disability Following TBI, on the villa, under the Masquerades of Brain Injury Series

direct link: http://villamartelli.com/#MBI

…and also see the Recent TBI Abstracts, under the Neuroscience Abstracts section on villamartelli.com for
recent papers relating to preinjury and post-injury factors...

ScienceDaily
Your source for the latest research news

Web address:
http://www.sciencedaily.com/releases/2013/03/130307110547.htm?goback=%2Egde_1061567_member_222587584

Even Mild Traumatic Brain Injuries Can Kill Brain Tissue

Mar. 7, 2013 — Scientists have watched a mild traumatic brain injury play out in the living brain, prompting swelling that reduces blood flow and connections between neurons to die.

Dr. Sergei Kirov is a neuroscientist and Director of the Human Brain Lab at the Medical College of Georgia at Georgia Regents University. (Credit: Phil Jones)

"Even with a mild trauma, we found we still have these ischemic blood vessels and, if blood flow is not returned to normal, synapses start to die," said Dr. Sergei Kirov, neuroscientist and Director of the Human Brain Lab at the Medical College of Georgia at Georgia Regents University.

They also found that subsequent waves of depolarization -- when brain cells lose their normal positive and negative charge -- quickly and dramatically increase the losses.

Researchers hope the increased understanding of this secondary damage in the hours following an injury will point toward better therapy for the 1.7 million Americans annually experiencing traumatic brain injuries from falls, automobile accidents, sports, combat and the like. While strategies can minimize impact, no true neuroprotective drugs exist, likely because of inadequate understanding about how damage unfolds after the immediate impact.

Kirov is corresponding author of a study in the journal *Brain* describing the use of two-photon laser scanning microscopy to provide real-time viewing of submicroscopic neurons, their branches and more at the time of impact and in the following hours.

Scientists watched as astrocytes -- smaller cells that supply neurons with nutrients and help maintain normal electrical activity and blood flow -- in the vicinity of the injury swelled quickly and significantly. Each neuron is surrounded by several astrocytes that ballooned up about 25 percent, smothering the neurons and connective branches they once supported.

"We saw every branch, every small wire and how it gets cut," Kirov said. "We saw how it destroys networks. It really goes downhill. It's the first time we know of that someone has watched this type of minor injury play out over the course of 24 hours."

Stressed neurons ran out of energy and became silent but could still survive for hours, potentially giving physicians time to intervene, unless depolarization follows. Without sufficient oxygen and energy, internal pumps that ensure proper polarity by removing sodium and pulling potassium into neurons, can stop working and dramatically accelerate brain-cell death.

"Like the plus and minus ends of a battery, neurons must have a negative charge inside and a positive charge outside to fire," Kirov said. Firing enables communication, including the release of chemical messengers called neurotransmitters.

"If you have six hours to save tissue when you have just lost part of your blood flow, with this spreading depolarization, you lose tissue within minutes," he said.

While common in head trauma, spreading depolarization would not typically occur in less-traumatic injuries, like his model. His model was chemically induced to reveal more about how this collateral damage occurs and whether neurons could still be saved. Interestingly, researchers found that without the initial injury, brain cells completely recovered after re-polarization but only partially recovered in the injury model.

While very brief episodes of depolarization occur as part of the healthy firing of neurons, spreading depolarization exacerbates the initial traumatic brain injury in more than half of patients and results in poor prognosis, previous research has shown. However, a 2011 review in the journal *Nature Medicine* indicated that short-lived waves can actually protect surrounding brain tissue. Kirov and his colleagues wrote that more study is needed to determine when to intervene.

One of Kirov's many next steps is exploring the controversy about whether astrocytes' swelling in response to physical trauma is a protective response or puts the cells in destruct mode. He also wants to explore better ways to protect the brain from the growing damage that can follow even a slight head injury.

Currently, drugs such as diuretics and anti-seizure medication may be used to help reduce secondary damage of traumatic brain injury. Astrocytes can survive without neurons but the opposite is not true, Kirov said. The ratio of astrocytes to neurons is higher in humans and human astrocytes are more complex, Kirov said.

The research was supported by the National Institutes of Health.

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Journal Reference:

1. J. Sword, T. Masuda, D. Croom, S. A. Kirov. **Evolution of neuronal and astroglial disruption in the peri-contusional cortex of mice revealed by in vivo two-photon imaging**. *Brain*, 2013; DOI: 10.1093/brain/awt026

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Note: If no author is given, the source is cited instead.

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Combination of Light and Melatonin Time Cues for Phase Advancing the Human Circadian Clock

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Study Objectives: Photic and non-photic stimuli have been shown to shift the phase of the human circadian clock. We examined how photic and non-photic time cues may be combined by the human circadian system by assessing the phase advancing effects of one evening dose of exogenous melatonin, alone and in combination with one session of morning bright light exposure.

Design: Randomized placebo-controlled double-blind circadian protocol. The effects of four conditions, dim light (~1.9 lux, ~0.6 Watts/m^2)-placebo, dim light-melatonin (5 mg), bright light (~3000 lux, ~7 Watts/m^2)-placebo, and bright light-melatonin on circadian phase was assessed by the change in the salivary dim light melatonin onset (DLMO) prior to and following treatment under constant routine conditions. Melatonin or placebo was administered 5.75 h prior to habitual bedtime and 3 h of bright light exposure started 1 h prior to habitual wake time.

Setting: Sleep and chronobiology laboratory environment free of time cues.

Participants: Thirty-six healthy participants (18 females) aged 22 ± 4 y (mean ± SD).

Results: Morning bright light combined with early evening exogenous melatonin induced a greater phase advance of the DLMO than either treatment alone. Bright light alone and melatonin alone induced similar phase advances.

Conclusion: Information from light and melatonin appear to be combined by the human circadian clock. The ability to combine circadian time cues has important implications for understanding fundamental physiological principles of the human circadian timing system. Knowledge of such principles is important for designing effective countermeasures for phase-shifting the human circadian clock to adapt to jet lag, shift work, and for designing effective treatments for circadian sleep-wakefulness disorders.

Keywords: Light response, zeitgeber, phase shift

Citation: Burke TM; Markwald RR; Chinoy ED; Snider JA; Bessman SC; Jung CM; Wright Jr KP. Combination of light and melatonin time cues for phase advancing the human circadian clock. *SLEEP* 2013;36(11):1617-1624.

INTRODUCTION

The mammalian master circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus.[1,2] The SCN provides environmental and biological timing information to the rest of the body so that physiology and behavior are coordinated for optimal functioning relative to the time of day.[3,4] The SCN receives input about environmental time through photic pathways via rod, cone, and melanopsin photoreceptors in the retina.[5,6] The SCN also receives input about behavioral and physiological states through non-photic pathways (e.g., serotonergic input from the raphe nucleus).[7-10] Misalignment between environmental time and internal biological timing (e.g., shift work, jet lag, circadian sleep-wakefulness disorders) can result in adverse psychological, neurobehavioral, and physiological consequences.[11-16] Photic and non-photic stimuli have both been used to phase shift the human circadian clock; however, there is limited information about how combinations of phase-shifting stimuli influence the timing of the circadian clock in humans. Findings from research in non-humans suggest the combination of photic and non-photic stimuli interact to increase or attenuate the magnitude of circadian phase shifts[17-21] and contribute to circadian entrainment.[22] In humans, Wirz-Justice et al.[23] examined the combination of exogenous melatonin, timed to advance the circadian clock, and bright light exposure, timed to delay the circadian clock, and found an additive interaction such that the combination resulted in no phase shift relative to the control condition. These findings suggest that information from photic and non-photic stimuli may be combined by the human circadian system. We hypothesized that combinations of properly timed photic and non-photic stimuli will induce a greater phase shift response than individual stimuli. Such potential combined effects of photic and non-photic stimuli by the human circadian clock has important implications for entrainment of the human circadian clock to 24-hour and near-24-hour day lengths such as required by some orbital space flight missions or by a mission to the planet Mars,[24-27] for the treatment of circadian sleep-wakefulness disorders,[28] and for circadian adaptation to jet lag and shift work schedules.[16,29]

Although light is a strong synchronizer of the SCN to the external environment,[30,31] non-photic stimuli, such as activity, exercise, restricted food availability, and exogenous melatonin have also been shown to shift the timing of the mammalian circadian system.[32-37] Both light and melatonin have been found to phase shift the circadian system of humans; in the majority of studies conducted to date, subjects were exposed to multiple days of light exposure or melatonin administration.[38-48] Fewer investigations have examined the influence of one session of light exposure or one dose of melatonin.[23,49-55] Nonetheless, findings in general are consistent in showing that bright light exposure in the evening produces the largest phase delays and bright light exposure in the early morning

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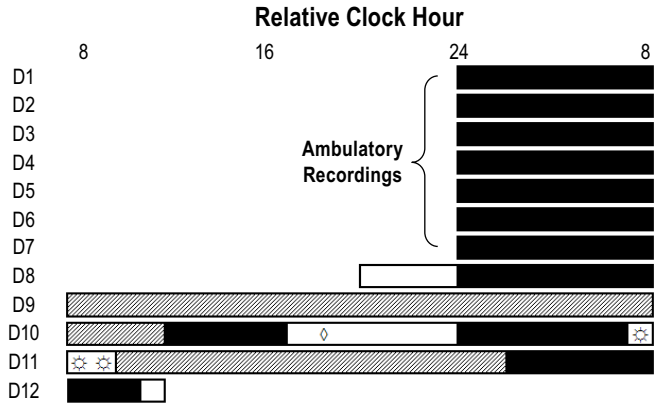

Figure 1—12 daylong phase-shifting protocol. The first 7 days (D1-7) of study were ambulatory recording of subjects maintaining consistent sleep-wakefulness schedules. This was followed by 5 days living in the laboratory (D8-12). Example times for a subject with a habitual bedtime at midnight. Black bars represent scheduled sleep opportunities, open bars represent scheduled wakefulness not part of constant routines, and the hatched bars represent constant routines. The protocol consisted of 2 constant routines which were used to estimate circadian phase. Subjects received melatonin or rice powder-filled placebo (◊) 5.75 h prior to habitual bedtime. Subjects were awakened from sleep early so that exposure to bright or dim light (☼) could begin 1 h prior to habitual wake time.

produces the largest phase advances. Melatonin administration on the other hand produces the largest phase advances in the late afternoon/early evening, and melatonin administration in the early morning following habitual wake time produces the largest phase delays.[38,44,47] Few studies have directly compared the phase resetting response to one day of light exposure and one day of melatonin administration.

Using a circadian protocol to evaluate the phase resetting response of the human circadian clock to photic and non-photic stimuli, we sought to examine the influence of one session of bright light exposure and one dose of exogenous melatonin, alone and in combination. This experiment was based upon previous research in humans showing that light and melatonin alone can phase shift circadian rhythms[23,34,49,56-63] and findings from animal and human studies showing that melatonin can attenuate light induced phase shifts.[23,33,50,64] This study tested the hypothesis that the circadian phase advance induced by the combination of morning bright light exposure and late afternoon exogenous melatonin administration would induce a greater phase shift than either stimulus alone. Four experimental conditions were compared: dim light-placebo (DLP), dim light-melatonin (DLM), bright light-placebo (BLP), and bright light-melatonin (BLM). Timing of photic and non-photic stimuli was based on existing light and melatonin phase response curves (PRCs) and was selected to induce large phase shifts. Specifically, to achieve a large phase advance, a single 3-h light exposure with an intensity of ~3000 lux was applied in the early morning when longer light exposures show the largest phase advances,[51,53] and a single 5 mg dose of melatonin was administered in the late afternoon/early evening when multiple consecutive days of exogenous melatonin administration shows the largest phase advances.[38,44,47]

METHODS

Participants

Thirty-six young healthy subjects (18 females, 18 males) aged 22.0 ± 3.8 y, body mass index (BMI) 22.3 ± 2.1 (mean ± SD) participated. Prior to the study, subjects underwent detailed health screening. Health of subjects was determined by medical evaluation at the Clinical and Translational Research Center (CTRC) and Sleep and Chronobiology Laboratory at the University of Colorado Boulder based on physical exam, blood chemistries, clinical electrocardiography, and medical, psychiatric, and sleep histories. Exclusion criteria included: known medical, psychiatric or sleep disorders, abnormal blood chemistries, illicit drug or nicotine use, habitual sleep duration < 7 h or > 9 h, medication use (exception for oral contraceptives), BMI outside the range of 18.5 to 27, shift work within one year prior, or travel across more than one time zone in the three weeks prior to in-laboratory procedures. Study procedures were approved by the Institutional Review Board at the University of Colorado Boulder and the Scientific Advisory and Review Committee of the Colorado Clinical and Translational Sciences Institute. Subjects gave written informed consent and were compensated for their participation.

Experimental Design

Pre-Study Control: Ambulatory Wakefulness-Sleep-Activity Recordings

Subjects maintained a regular ~8-h sleep-wakefulness schedule based on their habitual sleep and wake times for one week prior to the in-laboratory study. Regular sleep-wakefulness schedules were verified via sleep logs, time-stamped voice-recorder of bed and wake times, and wrist actigraphy recordings (Actiwatch-L, Philips Mini Mitter, Bend, OR). Subjects were instructed to refrain from over-the-counter medications, supplements, and caffeine for two weeks prior, naps one week prior, exercise three days prior, and alcohol two days prior to the in-laboratory protocol. Subjects self-reported compliance with the above requests. Additionally, upon admission to the in-laboratory protocol, urine toxicology and an alcohol breath test (Lifeloc Technologies Model FC10, Wheat Ridge, CO) were performed and female subjects were given a pregnancy test to verify absence of pregnancy. Five of the female subjects were taking oral contraceptives; two were randomized to the DLM, and one each to each of the other conditions.

In-Laboratory Protocol

Subjects were studied individually in specially designed sleep and circadian research suites that provided an environment free of external time cues for five calendar days. Following pre-study assessments (Days 1-7), subjects were scheduled to arrive at the Sleep and Chronobiology Laboratory ~4 h prior to habitual sleep time (Figure 1). All protocol events such as meal times, pill administration, light exposure, and sleep opportunities were scheduled relative to the subject's habitual wake time. Ambient temperature was maintained in thermoneutral range (~22.2°C). Except for the bright light exposure conditions, lighting in the angle of gaze was maintained at dim levels equivalent to candle light (~1.9 lux; ~0.6 Watts/m^2) during scheduled wakefulness

and darkness during scheduled sleep opportunities. The first day of the in-laboratory protocol, Day 8, consisted of a habituation episode followed by an 8-h nighttime sleep opportunity. Days 9-10 consisted of a 28-h modified constant routine (CR1).[31] The constant routine protocol is used to estimate circadian phase while controlling for the effects of environmental and behavioral influences. Subjects maintained wakefulness while being exposed to dim light under bedrest conditions with the head of the bed raised to ~35°. Brief bathroom breaks, using a commode ~1 m from the bed, were scheduled so that they did not occur within the 15 min before a saliva sample; bedpans and urinals were provided at unscheduled times, otherwise constant posture was maintained. Isocaloric, hourly snacks prepared by the CTRC nutritionist, were used to equally distribute food and fluid intake over the constant routine. Melatonin or placebo was administered on Day 10. Exposure to bright light occurred on Days 10-11. This was followed by a second 19-h constant routine (CR2) on Day 11 to reassess circadian melatonin phase.

Experimental Conditions

Subjects were randomly assigned to experimental condition: DLP, DLM, BLP, BLM. Pill administration of either placebo or 5 mg melatonin was double-blind and scheduled in the late afternoon 5.75 h prior to habitual bedtime. Implementation of pill allocation was performed by the CTRC pharmacist who provided pills identical in appearance. Pills consisted of 5 opaque capsules of either 1 mg immediate release melatonin (5 mg total dose; Life Extension Foundation, Inc.), or identical looking capsules of rice flour placebo. The Clinical Trials.gov ID of this study was NCT00387179 and we administered melatonin under FDA IND 76168. The allocation sequence was concealed until interventions were assigned and data were prepared for statistical analysis.

Subjects were awakened 1 h earlier than habitual wake time on Day 10-11 and exposed to either 3 h of continuous bright light or dim light. Commercially available ceiling mounted fluorescent lamps (Sylvania Octron 32W T8 bulb; Danvers, MA, USA) provided broad spectrum white light exposure, similar to natural, midday, daylight (6500-K color temperature). During the light exposure, subjects were under the direct supervision of research assistants who remained in the suite to ensure the intended intensity of illumination was achieved. Subjects wore clear Uvex glasses (Uvex Winter Optical, Smithfield, RI, USA) to further block any UV light and maintained constant posture while alternating between fixing their gaze on a target for 6 min or free gaze for 6 min.[51,53] Average light intensities during the fixed gaze were 2984 ± 367 lux (~7 Watts/m^2) for the bright light conditions and 1.9 ± 0.4 lux (~0.6 Watts/m^2) for the dim light conditions. Illuminance in the angle of gaze at eye level was measured with a research photometer (International Light, Newburyport, MA, USA) and irradiance was measured with a HOBO Micro Station Data Logger with HOBO Silicon Pyranometer Smart Sensor (Onset, Pocasset, MA, USA).

Circadian Phase Assessment and Analysis

Salivary melatonin was collected every 30 min at night and every 60 min during the day (hours 3-10 of habitual wakefulness) of each CR. Collected saliva was centrifuged and then frozen at -80°C until assayed. Salivary melatonin concentration was determined by ELISA assay according to manufacturer instructions (IBL International, Hamburg, Germany).

We first tested whether the phase angle of entrainment and thus the timing of the photic and non-photic stimuli was similar among conditions. We calculated the salivary dim-light melatonin onset (DLMO) to bedtime phase angle of entrainment as the timing of the DLMO minus bedtime, and thus negative numbers indicate a DLMO prior to bedtime.[25,27,65] Circadian phase shifts were determined by the change in the timing of the salivary DLMO between CR1 and CR2. The salivary DLMO was defined as the linearly interpolated time point when melatonin levels exceeded and remained 2 standard deviations above the stable baseline mean.[66-69] Circadian phase shifts were analyzed with a mixed model ANOVA assigning drug and light conditions as fixed factors. Planned one-tailed independent t-tests were used to determine significance for our directional hypotheses. Specifically we hypothesized: (1) that melatonin and bright light experimental conditions would induce significant phase advance shifts compared to the dim light-placebo control condition, which was expected to show a delay drift due to the on average longer than 24-h circadian period;[25,70-72] (2) that bright light-placebo would induce a significant phase advance shift compared to dim-light melatonin; and (3) that bright light-melatonin would induce a significant phase advance shift compared to dim light-melatonin and bright light-placebo. In addition to the above statistical tests, effect sizes (Cohen *d*) were calculated to determine the size of phase resetting effects. Standard interpretations of effect size were used:[73] small, $d = 0.2$; moderate, $d = 0.5$; large, $d = 0.8$.

RESULTS

Average DLMO Threshold and Phase Angle of Entrainment

Using the current DLMO definition, an average DLMO threshold level of 10.4 pg/mL was observed. This level is consistent with prior findings of an average 10.2 pg/mL salivary melatonin threshold using the same DLMO definition.[66]

The phase angle of entrainment between DLMO and bedtime was not statistically different among conditions prior to treatment (P = 0.19): DLP -2.36 ± 0.75 h (mean ± SD; 95%CI: -2.94 to -1.79 h); DLM -2.68 ± 0.41 h (95%CI: -3.00 to -2.37 h); BLP -2.79 ± 1.04 h (95%CI: -3.59 to -1.99 h); BLM -2.02 ± 0.89 h (95%CI: -2.70 to -1.34 h). The average phase angle was -2.46 h (± 0.83 h SD) with a maximum phase angle of -4.96 h and a minimum phase angle of -0.65 h. Post hoc analyses did not find association between initial phase angle and the resulting phase shift reported below when testing all three treatments combined in one analysis or when testing each treatment individually (all P > 0.25).

Phase Resetting Response

Figure 2 shows circadian phase shifts for individual subjects and the condition means for the melatonin and light conditions. Significant main effects for bright light ($F_{1,32} = 14.04$, $P < 0.001$) and for melatonin ($F_{1,32} = 10.58$, $P < 0.01$) were observed for circadian phase shifts. The interaction effect between light exposure and pill condition was not significant ($F_{1,32} = 0.29$, $P = 0.60$). We found a mean phase delay in the DLP condition of ~26 min. Significant circadian phase advances were found for

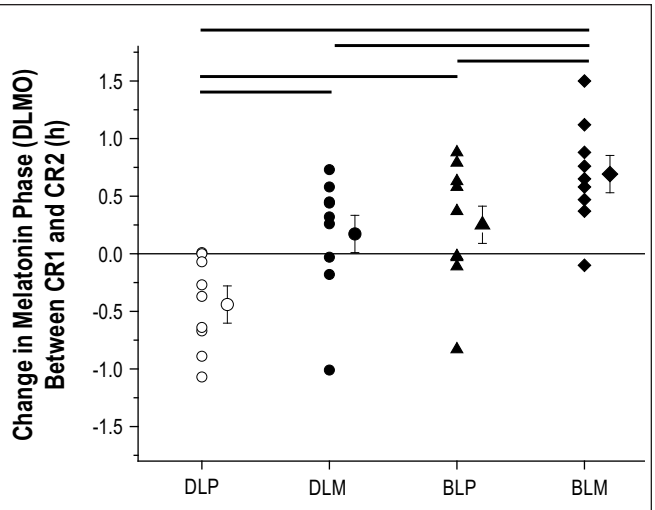

Figure 2—Phase resetting response to bright light and melatonin. On the y-axis, phase advances are plotted as positive values and phase delays are plotted as negative values with a value of zero representing no phase shift. Plotted are phase shifts for individual subjects within each condition as well as the condition mean ± SEM. DLP, dim light-placebo; DLM, dim light-melatonin; BLP, bright light-placebo; BLM, bright light-melatonin. Thicker lines above plot represent significant effects between conditions at either end of the line (P < 0.05). On average, DLM, BLP, and BLM induced ~37 min, ~42 min, and ~68 min phase advances relative to DLP, respectively.

DLM, BLP, and BLM conditions compared to DLP ($P < 0.05$) with large effect sizes, $d = 1.40$, 1.53, and 2.81, respectively. There were no statistical differences found between DLM and BLP ($P = 0.37$) conditions with a less than small effect size, $d = 0.16$. The largest phase advance shift was found for the BLM condition, which induced a phase shift significantly larger than DLM and BLP ($P < 0.05$) with large effect sizes, $d = 1.12$ and 0.93, respectively.

DISCUSSION

We found that photic and non-photic time cues are combined by the internal circadian clock in humans, furthering our knowledge about basic circadian principles as applied to humans and providing evidence for the effectiveness of combined treatments to induce desired phase shifts of circadian timing. Uniquely, and consistent with our hypotheses, the current findings indicate that a single exposure to 3 h of ~3000 lux bright light in the morning combined with a single 5 mg dose of exogenous melatonin in the late afternoon/early evening can be combined to induce a greater circadian phase advance of the human circadian clock than either treatment alone. Our findings also reveal that under controlled dim light conditions, a single administration of 5 mg melatonin in the early evening is able to induce a comparable phase advance to that induced by a single 3-h exposure to ~3000 lux bright light in the morning, inconsistent with our hypothesis that light exposure would induce a greater shift than melatonin. These findings have important implications for understanding fundamental physiological principles of the human circadian timing system, for adapting the human circadian clock to 24-hour and near-24-hour day lengths,[24-27] and for the treatment of circadian sleep-wakefulness disorders (e.g., adapting to eastward travel and treatment of delayed sleep phase disorder).[28,43] The combination of properly timed light exposure and melatonin administration may provide an effective means of advancing the human circadian clock such that the combination can produce a phase shift that is greater than that of either given alone.

Large effect sizes of all conditions relative to dim light-placebo suggest the strong ability of light and melatonin stimuli for shifting the human circadian clock. Relative to dim light-placebo, the magnitude of the response for exogenous melatonin (5 mg) and bright light exposure (~3000 lux) were similar. This result suggests that under controlled environmental conditions at the specific times of the circadian and sleep-wakefulness cycle, and at the dose of melatonin and intensity and duration of light studied, melatonin may be as effective as bright light exposure to shift the human circadian clock. The finding that photic and non-photic stimuli are combined by the human circadian time keeping system also highlights the need to consider light exposure when using melatonin to shift the circadian clock. For example, uncontrolled evening light exposure in the work/home environment would likely reduce the effectiveness of evening melatonin administration when using melatonin to phase advance the clock.[23] Knowledge of light and melatonin PRCs and the respective crossover times for phase advances and delays is important for optimal timing of treatments, since at most circadian phases light and melatonin induce phase shifts in the opposite direction; although there are narrow circadian phase windows where both appear to induce phase shifts in the same direction.[29,38]

Circadian phase angles of entrainment were on average more than two hours prior to habitual bedtime. The average and range of phase angles observed in the current study are generally consistent with prior findings when circadian phase is assessed using other DLMO thresholds and tested upon entry into the laboratory following at least one week of maintaining habitual ~8-h sleep schedules.[65] The finding that the dim light-placebo condition showed an average phase delay is consistent with previous findings of an average delay drift in phase of the human circadian clock in an environment absent of time cues,[31,52,54] which is likely due to the longer than average circadian period in humans.[25,70-72] Individual differences in the observed circadian phase resetting responses to melatonin and bright light stimuli are also likely driven by individual differences in circadian period.[52] Assessment of circadian period and factoring it out statistically, or exposure of all individuals to each experimental condition would be necessary to control for effects of individual differences in circadian period on the phase resetting response.

Findings from studies of non-humans indicate that non-photic time cues can facilitate entrainment to shifted light-dark cycles[74] such as those induced by jet lag and shift work. Findings from the current study indicate that combined treatments may also facilitate circadian adaptation in humans to such schedules. Findings from two previous studies that examined the combination of photic and non-photic time cues indicate: (1) that during simulated night shift work, five days of exposure to intermittent bright light (5000 lux) in a gradually delaying light-dark cycle induced large and significant phase delay shifts and that the addition of 1.8 mg sustained release melatonin prior to a daytime sleep opportunity did not facilitate the phase

resetting response[40]; and (2) that three days of exposure to intermittent bright light (5000 lux) in a gradually advancing light-dark cycle combined with either 0.5 mg or 3.0 mg melatonin 5 h or 7 h prior to bedtime, respectively, induced relatively large and significant phase advance shifts as compared to a dim light-placebo condition.[75] The latter study by Revell et al., however, did not include dim light-melatonin alone conditions, thus it is unknown whether the combination of the treatments tested would be more effective than either alone. Given the number of treatment days, exposure to light alone may be sufficient to induce large phase shifts reducing the ability to detect differences among conditions due to ceiling effects. In the combined melatonin and light condition of the current study, it is likely that the evening melatonin dose, administered 12.75 hours prior to the beginning of the morning light exposure session, induced a phase advance shift of the circadian clock prior to light exposure and contributes to the current findings. Findings from a study by Paul et al.[76] show that afternoon administration of sustained release 3 mg melatonin and morning exposure to moderate levels of green light (500 nm), combined with an advanced 13.5-h sleep opportunity, induced a significant phase advance shift relative to green light alone and to a dim light-placebo control. Green light alone did not induce a significant phase shift relative to dim light-placebo, whereas melatonin alone induced a significant phase advance relative to dim light-placebo, but not green light alone. Green light exposure was timed 1 h earlier in the combined condition than in the green light alone condition and could have contributed to their findings. Nonetheless, these findings are generally consistent with our findings of the effectiveness of combined treatments of photic and non-photic time cues for phase shifting the human circadian clock. Findings from Crowley et al.[40] also show that multiple days of exposure to bright light are more effective than multiple days of administration of melatonin. Thus, the addition of melatonin when using multiple days of light exposure may not provide additional benefit, assuming that light exposure is properly timed.

Consistent with the present findings of combined light and melatonin stimuli, further evidence for combination of information by the human circadian clock comes from findings that the circadian system is capable of temporal integration of multiple pulses of light in the same session.[54,55]

Phase Resetting with Exogenous Melatonin

In the present study, melatonin administration was timed to induce a maximal phase advance shift based on multiple pulse phase response curves for melatonin.[38,44] More recently, a three-pulse phase response curve has been published comparing a 3 mg dosage of melatonin to 0.5 mg of melatonin,[47] suggesting that a lower dosage of melatonin is as effective at inducing phase shifts of the human circadian clock as the higher dose if timed appropriately. Specifically, Burgess et al. reported 0.5 mg of melatonin had a similar phase shift magnitude as compared to that induced by 3 mg of melatonin; however, the maximal phase shift occurred ~2 h later in the smaller dose relative to DLMO.[47] The latter finding suggests that the 5 mg melatonin dose may have induced a larger phase advance if it were administered earlier relative to DLMO in the current study. Revell et al.[75] found that when the various doses were timed differently relative to DLMO, with the smaller dose closer to DLMO, no dose-relationship was found.

There have been several studies aimed at exploring the ability of a single administration of exogenous melatonin to induce a circadian phase advance. For example, findings from a study by Deacon and Arendt[63] indicate that the phase shift response to a single administration of immediate release melatonin is dose dependent with mean phase advances of plasma melatonin onset of 22, 42, and 86 min, relative to placebo for 0.05, 0.5, and 5 mg doses, respectively. In recent studies by Paul et al.,[69,76] a single administration of either 3 mg immediate release, 3 mg sustained release, or a combined 1 mg immediate release with 2 mg sustained release melatonin preparations induced phase advances between ~29-50 min as compared to placebo. Single administration of 5 mg immediate release melatonin has previously been found to produce an average phase advance of ~44 min relative to a pooled placebo.[34] Our finding of an average ~37 min phase advance relative to placebo following the single administration of 5 mg immediate release melatonin in the later afternoon/early evening is consistent with previous findings.

We did not assess the influence of exogenous melatonin on sleepiness and performance in the current study. Given that properly timed administration of lower doses of melatonin induce phase advances of a similar phase shift magnitude induced by higher doses in sighted[47] and blind humans,[77] and that melatonin may induce dose-dependent impairments in performance and increases in sleepiness,[78] it is important to use the lowest effective dose possible to reduce the risk of accident. If melatonin is taken during the daytime, patients should be warned about potential safety risks (e.g., drowsy driving, occupational accidents).

Phase Resetting with Bright Light Exposure

Light exposure for the current study was timed according to the single pulse 6.7-h light PRC to induce a maximal phase advance shift.[53] Light intensity was selected to be on the asymptotic portion of the luminance intensity curve based on a single 6.5-h light pulse.[51] Thus, had we selected a dimmer light intensity or shorter duration,[79] it is possible that differences in the magnitude of the circadian phase resetting response would have been found when comparing the light and melatonin stimuli. Our light exposure duration was less than half that used in the studies noted, and we did not invert the sleep-wakefulness cycle to have light exposure be in the middle of each day. Instead, subjects maintained their habitual sleep-wakefulness schedule and were awakened 1 h earlier than habitual wake time for light exposure. We avoided starting light exposure earlier so that we reduced the risk of exposing subjects to light on the crossover point between phase delays and advances.[53] Findings from a recent study examining phase delays of the human circadian system varying the intensity (2000, 4000, and 8000 lux) and duration (1, 2, and 3 h) of light exposure showed an effect of duration with larger phase shifts observed with longer exposures, but no significant influence of intensity of light exposure.[80] The latter is consistent with findings that ~1230 lux and ~5700 lux light intensities produced similar phase delays.[81] These studies are consistent with prior findings that light exposures of the

intensities tested, including the light intensity used in the current study, are above the saturating response for inducing phase shifts.[51]

There have also been prior studies in which the ability of a single exposure to light to induce a circadian phase advance has been explored.[49,51,53,61,76] Our finding of an average ~42 min phase advance following a single 3-h morning exposure to ~3000 lux broad spectrum white light relative to placebo is smaller than that reported for 4-6.7-h morning exposures to 3000-12000 lux broad spectrum white light[49,51,53,61,76] and larger than that reported for a 1-h exposure to 350 lux green light.[76] As the circadian phase resetting response to light in humans is also dependent on the spectral characteristics of the light exposure,[82] further research is needed to examine combinations of various lighting regimens and non-photic time cues.

Implications for Use of Photic and Non-Photic Stimuli to Reset Circadian Phase

The phase shifts induced by the photic and non-photic stimuli tested in the current study are physiologically and clinically meaningful. For example, the average sighted human requires a daily phase advance shift of ~9 minutes every day to entrain or synchronize to the 24-h day.[25,31,70-72] Estimates of circadian period that were derived from forced desynchrony protocols[25-27,70-72] and validated by demonstration of the near-24-h entrainment limits of the human circadian clock in dim light,[25] indicate that upper range of circadian periods observed in healthy, sighted humans is near 24.6 h.[72] Thus, the current light and melatonin treatments tested would be sufficient to entrain most sighted, and many blind, humans who show a longer than 24-h circadian period, to the 24-h day.[28,83,84]

As outlined in reviews by the American Academy of Sleep Medicine,[28,43] and in recommended practice parameters,[85] evidence exists showing that light and melatonin treatments are effective and are considered as standard treatment, guideline, or optional treatment for a variety of circadian sleep-wake disorders including jet lag disorder, shift work disorder, delayed and advanced sleep phase disorders, and blind and sighted patients with non-24-hour sleep-wake rhythm disorder. Much of the evidence for light and melatonin treatments are based on basic circadian science, and thus these treatments are also likely to be useful in helping to adapt individuals who do not meet the criteria for a clinical diagnosis to jet lag and shift work. It is important to note, however, that large trials are needed to assess the effectiveness of combined light and melatonin treatments, as much as possible, during real world conditions outside of the controlled laboratory. Such evidence exists for timed daily melatonin administration, which is indicated for the therapy of non-24-hour sleep-wake disorder in blind individuals.[28,85-87] In addition, light and melatonin treatments have been used to treat winter depression, which is thought to have a circadian component to its pathophysiology and treatment.[88] When advancing the human circadian clock is desired, such as when adapting to early morning shift work and eastward jet travel, or when treating delayed sleep phase disorder, our findings indicate that the combination of bright light exposure in the early morning and exogenous melatonin in the evening would provide the greatest phase shift treatment response.

ABBREVIATIONS

CR, constant routine
CTRC, Clinical Translational Research Center
BLM, bright light-melatonin
BLP, bright light-placebo
DLM, dim light-melatonin
DLMO, dim light melatonin onset
DLP, dim light-placebo
PRC, phase response curve
SCN, suprachiasmatic nucleus

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ORIGINAL ARTICLE

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Risk factors for long-term treatment of whiplash injury in Japan: analysis of 400 cases

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Abstract We studied the risk factors for long-term treatment of 400 patients with whiplash injury in Japan. Most of the patients were injured in rear-end car collisions, but none had cervical bone lesions or spinal cord or root lesions. We evaluated the following risk factors: sex, age, degree of vehicle damage, and admission or non-admission to the hospital. The group of patients younger than 20 years old healed more quickly than patients 30 years or older. Damage to more than half of the car was associated with a longer treatment. Patients who were admitted to the hospital need treatment longer than the non-admission group. Thus, age over 30 years, a large amount of damage to the vehicle, and admission to the hospital are predictors of long-term treatment for whiplash injury in Japan.

Keywords Whiplash injury · Motor vehicle accident · Long-term treatment

Introduction

It is difficult to treat patients who have neck pain and other associated symptoms of whiplash injury. Recently, Radanov et al. reported that few patients in Lithuania suffer late whiplash syndrome [11]. However, there are many cases of late whiplash injury in Japan. Some patients are admitted to the hospital, while other patients are treated as outpatients for a long time without effect. The treatment of whiplash injury continues to pose difficulties for many doctors [3, 8]. The Quebec WAD (whiplash associated disorder) cohort study showed that female sex, older age, and lack of seatbelt use are associated with a longer treatment period [9]. The purpose of this study was to investigate the treatment period for Japanese patients with whiplash injury and to clarify the risk factors for long-term treatment.

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Patients and methods

For this study, we selected patients involved in car-to-car motor vehicle accidents who suffered whiplash injury. Patients with cervical nerve root lesions, spinal cord lesions, and bone lesions were excluded from this study. The patients had no other body injuries associated with the car accident. Most of the patients were injured in rear-end collisions. The data about patients were obtained from a Japanese insurance company's database from 1996 to 1998. The total number of patients was 400, 219 men and 181 women, ranging in age from 4 to 87 years. The average age was 38.2 years.

The treatment period was defined from the time at which the patient first came to the hospital to the end of treatment. The duration of treatment ranged from 1 to 477 days, with an average of 83.5 days (Fig. 1). There were four peaks within the treatment period at 10 days, 1 month, 3 months, and 6 months.

The patients were grouped according to age as follows: younger than 20 years old, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, and 70 years or older. The highest incidence of whiplash injury occurred in the 20–29 years age group. The ratio of men to women was similar in all groups (Fig. 2).

The degree of vehicle damage was classified into 6 grades (Table 1). A damaged bumper (grade 2) was most common, followed by a damaged trunk or 1/3 destruction (Fig. 3).

Of the total of 400 patients, 333 (180 men and 153 women) were treated as outpatients, and 67 (39 men and 28 women) were

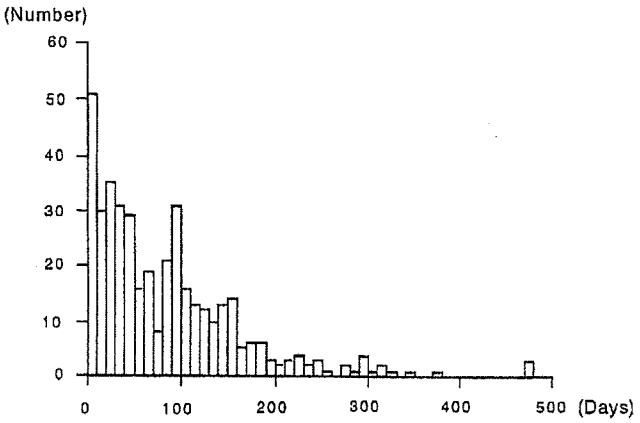

Fig. 1 Duration of treatment ranged from 1 to 477 days. There were four peaks: 10 days, 1 month, 3 months, and 6 months

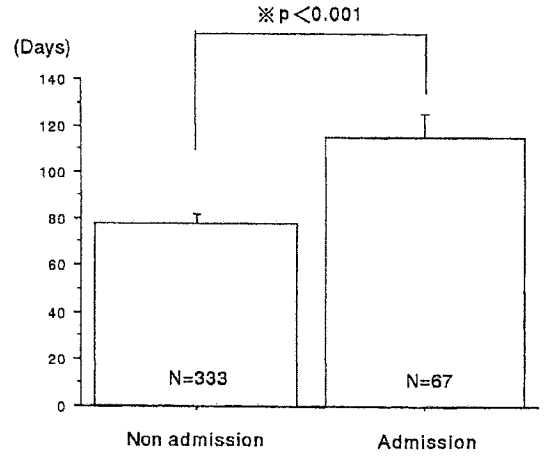

Fig. 6 Comparison of the duration of therapy between the admission and non-admission group. The admission group required treatment longer than non-admission group ($p < 0.001$)

Younger patients, especially those under 20 years old, recovered earlier than older age groups.

We also investigated the relationship between the degree of vehicle damage and the treatment period. Patients in vehicles with grade 0 and grade 4 were under treatment longer than those in the other groups. There was a significant difference between grade 0 and grades 2 and 3 ($p < 0.05$). Grade 4 showed a significant difference ($p < 0.05$) from grades 1, 2, and 3 (Fig. 5).

Between patients treated as outpatients and those admitted to a hospital, there was no difference in sex, age, or degree of damage to the car. In the admission group, the average treatment period was 114.9 days. The outpatient group had 77.7 days of treatment. Thus, there was a significant difference in the duration of treatment between the admission and outpatient groups (Fig. 6).

Discussion

Whiplash injury is a common and troublesome disease, but its definition is not clear. The Quebec WAD classification includes neurological lesions and bone destruction in grades 3 and 4 [9]. This classification makes it difficult to recognize whiplash injury, and many authors have excluded injuries of grades 3 and 4 in their studies [4, 6]. We suggest that grades 3 and 4 of the WAD classification should not be included in whiplash injury. If patients have obvious subjective findings of a root or spinal cord lesion, the injury should be treated as a root injury or spinal cord injury associated with a car accident. In the same way, lesions of the cervical spine should be labeled as fractures or dislocations of the cervical vertebra, because the treatment is fundamentally different from that of a so-called acute neck sprain. Whiplash injury can then be defined as neck injury with no cervical spinal bone lesions or spinal cord or root lesions, in which the cause of the symptoms is not clear. This definition includes symptoms of neck pain, headache, dizziness, disturbance of concentration or memory, and visual disorders.

According to this new definition, an average treatment period for whiplash injury of 83.5 days is too long. Soft-tissue damage usually resolves within 6 weeks. Partheni et al. reported that 91% of patients were healed by 4 weeks [7]. Our data show that only 29% of patients recovered by 4 weeks. Other reports show different recovery rates [5, 8]. Some reports note that the patient's pain still continued 6 months after the injury [10]. These differences may stem from the different systems used by insurance companies and the culture of each country [12]. In Japan, the patients are compensated for their lost incomes and treatment fees by the insurance company. This system promotes the admission and long-term treatment of the patient.

In previous studies, Bjorgen and the Quebec Task Force showed that persistent symptoms were more prevalent among women [1, 9]. Our study showed no significant difference in the duration of treatment between men and women in the treatment period.

Patients younger than 20 years old recover from whiplash earlier than older patients, while patients older than 70 years tend toward long-term treatment. Degenerative changes occur more frequently with increasing age, and these changes disrupt early tissue repair. In addition, elderly people suffer from characteristic diseases, such as osteoarthritis, spondylosis, and other degenerative diseases. Combining whiplash injury with these diseases hinders early recovery from the damage.

To our knowledge, there has been little discussion regarding the degree of vehicle damage and the duration of treatment. Our results suggest that damage to more than half of the car is associated with the duration of treatment. Our study excluded patients with cervical nerve root lesions, spinal cord lesions, bone lesions, and other bodily injuries. Given these facts, great damage to a car has a psychological influence on the patients. Therefore, we should consider psychological therapy in the early treatment period for patients whose cars suffered great damage. Patients associated with grade 5, total destruction of the car, underwent long-term treatment. Because this group did not contain enough patients, we could not establish a significant difference. In contrast, the grade 0 group had longer treatment than the grade 2 and grade 3 groups. This finding suggests that patients in cars that are not damaged might suffer direct force to the cervical spine or malingering. De Mol and Heijer noted that the severity of damage to the car correlated poorly with the personal injury [2]. A more detailed study should be done in the grade 0 group.

A significant difference was found in treatment duration between the admission and non-admission group. The admission group underwent long-term treatment averaging 115 days. In Japan, patients with whiplash injury usually demand admission, because their lost incomes and all treatment fees are compensated by the insurance company, and patients are excessively anxious about late whiplash injury. To decrease the number of admissions, doctors should give correct information to the patients and should not agree to admit those who do not need it.

J Trauma. 2009 Feb;66(2):289-96; discussion 296-7. doi: 10.1097/TA.0b013e3181961da2.

Early predictors of postconcussive syndrome in a population of trauma patients with mild traumatic brain injury.

Dischinger PC[1], Ryb GE, Kufera JA, Auman KM.

Abstract

PURPOSE:

The purpose of this analysis was to determine which of the initial symptoms after mild traumatic brain injury (MTBI) can best predict the development of persistent postconcussive syndrome (PCS).

METHODS:

One hundred eighty MTBI patients admitted to a level I trauma center were enrolled in a prospective study and 110 followed for 3 months. MTBI was defined as a Glasgow Coma Score of 13 to 15 with a transient loss of consciousness or report of being dazed or confused. PCS was defined as the persistence of four or more symptoms long term. Patients were screened at admission and at 3 days to 10 days and 3 months. Symptom checklists were administered to ascertain the presence of symptoms (cognitive, emotional, and physical) after concussion. For a subset of patients that were physically able, balance tests were also conducted. Stepwise logistic regression was used to identify which symptoms best predicted PCS.

RESULTS:

The mean age of the subjects was 35 years, and 65% were men. Physical symptoms were the most prevalent in the 3 days to 10 days postinjury with most declining thereafter to baseline levels. Emotional and cognitive symptoms were less prevalent but more likely to remain elevated at 3 months; 41.8% of subjects reported PCS at 3 months. The strongest individual symptoms that predicted long-term PCS included anxiety, noise sensitivity (NS), and trouble thinking; reported by 49%, 27%, and 31% of the subjects at 3 days to 10 days, respectively. In multivariate regressions including age, gender, and early symptoms, only anxiety, NS and gender remained significant in the prediction of PCS. Interactions revealed that the effect of anxiety was seen primarily among women. NS had an odds ratio of 3.1 for PCS at 3 months.

CONCLUSIONS:

After MTBI, anxiety among women and NS are important predictors of PCS. Other physical symptoms, while more prevalent are poor predictors of PCS.

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19204499 [PubMed - indexed for MEDLINE]

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Circulating Brain-Derived Neurotrophic Factor Has Diagnostic and Prognostic Value in Traumatic Brain Injury.

Korley FK[1], Diaz-Arrastia R[2], Wu AH[3], Yue JK[4], Manley GT[4], Sair HI[5], Van Eyk J[6], Everett AD[7]; TRACK-TBI investigators, Okonkwo DO[8,9], Valadka AB[8,10], Gordon WA[8,11], Maas AI[8,12], Mukherjee P[8,13], Yuh EL[8,13], Lingsma HF[8,14], Puccio AM[8,9], Schnyer DM[8,15].

Author information

Abstract

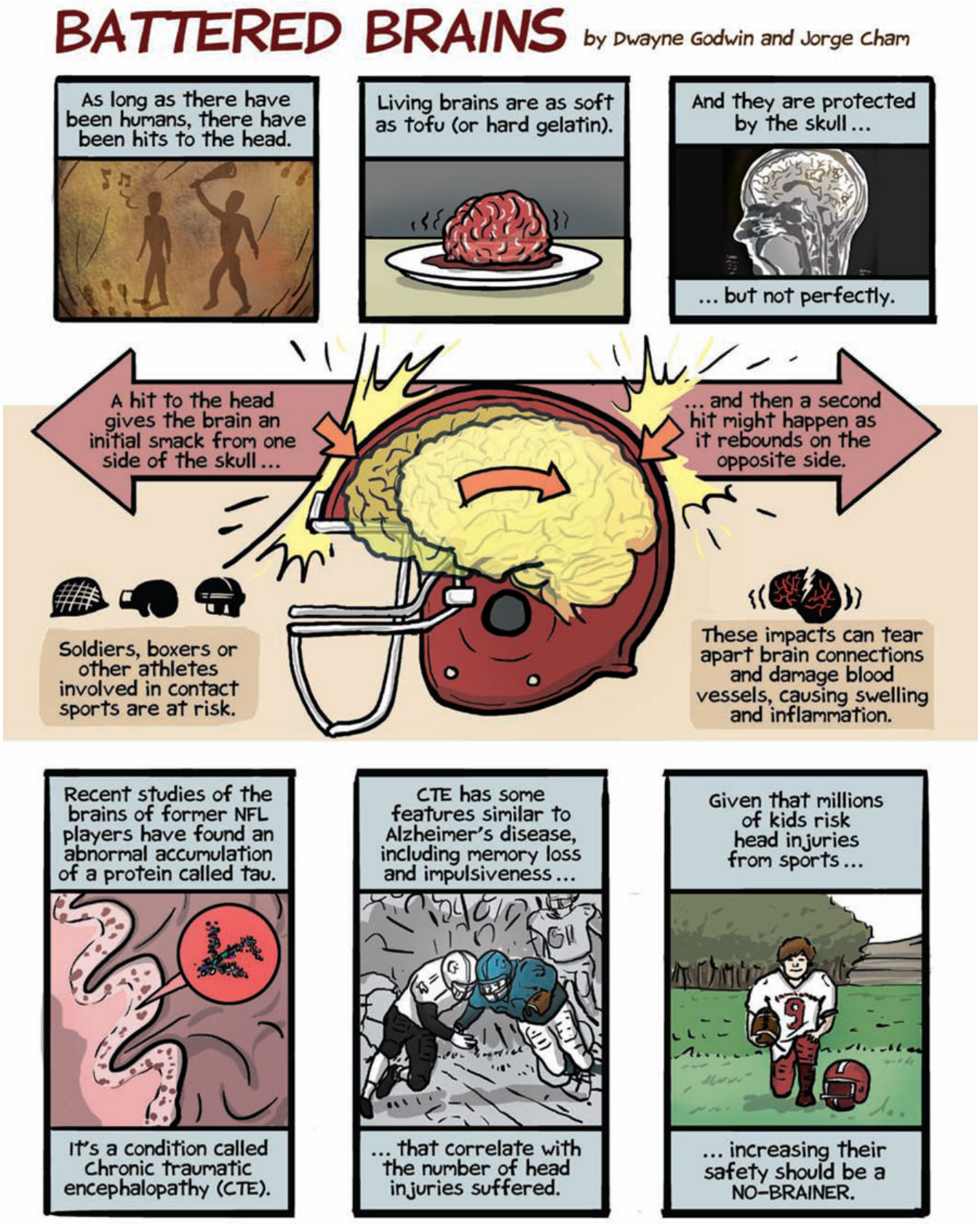
Brain-derived neurotrophic factor (BDNF) is important for neuronal survival and regeneration. We investigated the diagnostic and prognostic values of serum BDNF in traumatic brain injury (TBI). We examined serum BDNF in two independent cohorts of TBI cases presenting to the emergency departments (EDs) of the Johns Hopkins Hospital (JHH; n = 76) and San Francisco General Hospital (SFGH, n = 80), and a control group of JHH ED patients without TBI (n = 150). Findings were subsequently validated in the prospective, multi-center Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) Pilot study (n = 159). We investigated the association between BDNF, glial fibrillary acidic protein (GFAP), and ubiquitin C-terminal hydrolase-L1 (UCH-L1) and recovery from TBI at 6 months in the TRACK-TBI Pilot cohort. Incomplete recovery was defined as having either post-concussive syndrome or a Glasgow Outcome Scale Extended score <8 at 6 months. Median day-of-injury BDNF concentrations (ng/mL) were lower among TBI cases (JHH TBI, 17.5 and SFGH TBI, 13.8) than in JHH controls (60.3; p = 0.0001). Among TRACK-TBI Pilot subjects, median BDNF concentrations (ng/mL) were higher in mild (8.3) than in moderate (4.3) or severe TBI (4.0; p = 0.004. In the TRACK-TBI cohort, the 75 (71.4%) subjects with very low BDNF values (i.e., <the 1st percentile for non-TBI controls, <14.2 ng/mL) had higher odds of incomplete recovery than those who did not have very low values (odds ratio, 4.0; 95% confidence interval [CI]: 1.5-11.0). The area under the receiver operator curve for discriminating complete and incomplete recovery was 0.65 (95% CI: 0.52-0.78) for BDNF, 0.61 (95% CI: 0.49-0.73) for GFAP, and 0.55 (95% CI: 0.43-0.66) for UCH-L1. The addition of GFAP/UCH-L1 to BDNF did not improve outcome prediction significantly. Day-of-injury serum BDNF is associated with TBI diagnosis and also provides 6-month prognostic information regarding recovery from TBI. Thus, day-of-injury BDNF values may aid in TBI risk stratification.

KEYWORDS:

biomarkers; brain-derived neurotrophic factor; glial fibrillary acidic protein; traumatic brain injury; ubiquitin C-terminal hydrolase-L1

How Head Injuries Damage the Brain

Apr 11, 2013 | By Dwayne Godwin and Jorge Cham



Dwayne Godwin is a neuroscientist at the Wake Forest University School of Medicine. Follow him on Twitter @BrainyActs
Jorge Cham draws the comic strip Piled Higher and Deeper *at www.phdcomics.com.*

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This article was originally published with the title "Battered Brains."

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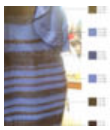
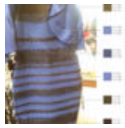

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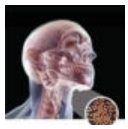

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ironjustice May 29, 2013, 8:22 AM

Why is it that the most common factor in head injury is never mentioned ? Blood spill.

"A likely mechanism of seizure development post-TBI is decompartmentalization of iron from extravasated hemoglobin (Hb)."

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JRCancio May 29, 2013, 4:10 PM

Can anyone suggest a reason; something I have noticed, every once in a while without warning or hint my body will 'jump' i.e., total body and sometimes very violent. I have major pain in every major joint and the pain disipates over a short time. I have told doctors this. It has hit my body with enough force to actually lift me right off my bed when resting; it can happen anywhere and at anytime and though I am aware I am only stunned by the level of body jerking/jumping, shaking and the pain. This I know that when I eat foods loaded with iron - green onions, leeks and other foods/vegetables loaded with iron the incidences of this occur almost never. I will submit on July 5th, 1965 I was involved in a major motor vehicle accident and my head was severely injured and in coma until July 14th., 1965. The best doctors tell me is to take vitamin B-6 which lessens the severity but the frequency has increased.

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wheezercat42@aol.com ↗ **JRCancio** May 29, 2013, 4:42 PM

I have the same thing happen to me (single, strong, full body jumps - usually when I'm dozing off). I've had a number of concussions over the years, although nothing in the last few years. The full body jerks has just started in the last year, and I've had a lot of problems with memory loss and blind spots

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PLOS ONE

Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial

Rahav Boussi-Gross[1☯], Haim Golan[3,4☯], Gregori Fishlev[1], Yair Bechor[1], Olga Volkov[3,4], Jacob Bergan[1], Mony Friedman[1], Dan Hoofien[6,7], Nathan Shlamkovitch[8], Eshel Ben-Jacob[2,5,9,10]*, Shai Efrati[1,2,3,10]*

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Abstract

Background: Traumatic brain injury (TBI) is the leading cause of death and disability in the US. Approximately 70-90% of the TBI cases are classified as mild, and up to 25% of them will not recover and suffer chronic neurocognitive impairments. The main pathology in these cases involves diffuse brain injuries, which are hard to detect by anatomical imaging yet noticeable in metabolic imaging. The current study tested the effectiveness of Hyperbaric Oxygen Therapy (HBOT) in improving brain function and quality of life in mTBI patients suffering chronic neurocognitive impairments.

Methods and Findings: The trial population included 56 mTBI patients 1–5 years after injury with prolonged post-concussion syndrome (PCS). The HBOT effect was evaluated by means of prospective, randomized, crossover controlled trial: the patients were randomly assigned to treated or crossover groups. Patients in the treated group were evaluated at baseline and following 40 HBOT sessions; patients in the crossover group were evaluated three times: at baseline, following a 2-month control period of no treatment, and following subsequent 2-months of 40 HBOT sessions. The HBOT protocol included 40 treatment sessions (5 days/week), 60 minutes each, with 100% oxygen at 1.5 ATA. ''Mindstreams'' was used for cognitive evaluations, quality of life (QOL) was evaluated by the EQ-5D, and changes in brain activity were assessed by SPECT imaging. Significant improvements were demonstrated in cognitive function and QOL in both groups following HBOT but no significant improvement was observed following the control period. SPECT imaging revealed elevated brain activity in good agreement with the cognitive improvements.

Conclusions: HBOT can induce neuroplasticity leading to repair of chronically impaired brain functions and improved quality of life in mTBI patients with prolonged PCS at late chronic stage.

Trial Registration: ClinicalTrials.gov NCT00715052

Citation: Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, et al. (2013) Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial. PLoS ONE 8(11): e79995. doi:10.1371/journal.pone.0079995

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Competing Interests: The authors have declared that no competing interests exist.

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☯ These authors contributed equally to this work.

Introduction

Traumatic brain injury (TBI) and stroke are the major causes of brain damage. Every year, close to two million people in the US suffer TBI, which is the leading cause of death and disability among the general population. Stroke affects almost a million people and is the leading cause of inability to maintain independent life among adults [1,2]. There is no effective treatment/metabolic intervention in the daily clinical practice for post TBI and stroke patients with chronic neurological dysfunction. Intensive therapy and rehabilitation programs are considered essential for maximizing quality of life but are often just partially successful. Clearly, new methods for brain repair should be examined in order to provide sustained relief to brain damage patients. Recent studies reported that hyperbaric oxygen treatment (HBOT) can induce neuroplasticity leading to significant neurological improvement in post-stroke patients at the convalescent stage and at late chronic stages, months to years after the acute event [3,4].

Definitions and classifications

Traumatic brain injury is defined as damage to the brain resulting from external mechanical force, such as rapid acceleration or deceleration, impact, blast waves, or penetration by a projectile. Consequently to the injury, brain function is temporarily or permanently impaired and structural damage may or may not be detectable with current imaging technology. TBI is usually classified based on severity, anatomical features of the injury, and the cause of the injury. The severity is assessed according to the loss of consciousness (LOC) duration, the post-traumatic amnesia (PTA), and the Glasgow coma scale (GCS) grading of the level of consciousness. Approximately (70–90%) of the TBI in the US are classified as mild TBI (mTBI) or concussion – LOC duration of 0–30 minutes, PTA duration of less than a day and GCS grade of 13–15. Post concussion syndrome (PCS) is a set of symptoms succeeding mTBI in most patients. The PCS symptoms include headache, dizziness, neuropsychiatric symptoms, and cognitive impairments [5,6]. In most patients, PCS may continue for weeks or months, and up to 25% of the patients may experience prolonged PCS (PPCS) in which the symptoms last for over six months [7,8,9,10,11,12]. Such individuals are at high risk for emotional and cognitive dysfunction, culminating in inability to carry out ordinary daily activities, work responsibilities and standard social relationships [9,10,11,12].

Associated brain pathology and function impairments

Diffuse axonal injury - diffuse shearing of axonal pathways and small blood vessels - is one of the most common pathological feature associated with mTBI [13]. Another primary pathological feature, usually caused by a direct hit to the skull, is brain contusions, which commonly involve the frontal and anterior temporal lobes [12]. Secondary pathologies of mTBI include ischemia, mild edema, and other bio-chemical and inflammatory processes culminating in impaired regenerative/healing processes resulted from increasing tissue hypoxia [14]. Due to the diffuse nature of injury, cognitive impairments are usually the predominant symptoms, involving deficiencies in several cognitive functions, primarily memory, attention, processing speed, and executive functions, all localized in multiple brain areas. Their potent functions rely on potent network structure and connectivity between different brain areas [12,15,16]. We note that the diffuse nature of the mTBI injury renders the pathological damage hard to be detected by common neuroimaging methods such as CT and MRI so that diagnosis largely relies on subjective reports of the patients, as well as cognitive and quality of life tests. While diffusion tensor imaging (DTI) has the potential to detect diffuse axonal injuries, this method is still not commonly used for diagnosis of mTBI pathology.

Rationale for hyperbaric oxygen treatment (HBOT)

The brain receives 15% of the cardiac output, consumes 20% of the total body oxygen, and utilizes 25% of the total body glucose. Still, this energy supply is only sufficient to keep about five to ten percent of the neurons active at any given time. Thus, at standard healthy condition, at any given time, the brain is utilizing almost all oxygen/energy delivered to it. The regeneration process after brain injury requires much additional energy. This is where hyperbaric oxygen treatment can help – the increased oxygen level in the blood and body tissues during treatment [17,18,19] can supply the energy needed for brain repair. Indeed, several previous studies have demonstrated that elevated levels of dissolved oxygen by HBOT can have several reparative effects on damaged brain tissues [3,19,20,21,22,23,24,25]. Other studies revealed the beneficial effect of HBOT on the injured brain and cognitive function in animal models [26,27,28,29,30]. The elevated oxygen levels can have a significant effect on the brain metabolism, largely regulated by the glial cells (see discussion). Improved energy management leads to multifaceted repair, including activation of angiogenesis and triggering of neuroplasticity (reactivation of quiescent neurons; creation of new synapses and new axonal connections), and might even induce differentiation of neuronal stem cells [22]. The idea that HBOT can promote brain repair is reasonable and has gained experimental support, yet is still largely dismissed by the medical community as is discussed next.

The medical community reservations

A study of the effect of hyperbaric oxygen treatment of severe brain injured patients has been published already two decades ago. Several prospective clinical trials on treatment of mTBI have been published in the last decade [31,32,33], and three studies published in the last two years addressed the effect of HBOT on chronic mild TBI patients [34,35,36]. However, the reported beneficial effects of the hyperbaric treatment were severely questioned by the medical community and triggered high skepticisms to the extent that TBI and stroke patients in the US are rarely treated by hyperbaric oxygen. The HBOT option has been dismissed by the medical community on the grounds of: 1. Lack of knowledge about the connection between metabolism and neuroplasticity. 2. Lack of randomized clinical trial with standard placebo control. 3. Sham control with room air at 1.3Atm yielded significant improvements. These issues are clarified and elaborated on in the discussion section.

The placebo dilemma

People can sense a pressure increase beyond 1.3Atm, hence standard placebo, with normal air pressure, for HBOT could perhaps be attained by exposing the patients to normal pressure combined with falsifying stimulation (e.g., by increasing and decreasing the pressure), which generates a fictitious pressure sensation. Since breathing normal air under hyperbaric conditions leads to elevated tissue oxygen (e.g., about 50% for 1.3Atm), standard placebo could also be attained by giving the patients compressed air with sub-normal oxygen concentration. In the discussion section we explain that the first approach can be effective only for some patients and poses logistic difficulties and the second approach involves ethical issues. In an attempt to evade the placebo dilemma, a recent study of HBOT for mTBI compared the effect of 100% oxygen at 2.4Atm with the effect of room air at 1.3Atm as sham control [36]. The study found significant improvements in both groups and with slightly higher efficacy at 1.3Atm. Based on these results, the authors resented a sweeping conclusion that their study shows that HBOT has no effect on post mTBI brain damage and the observed improvements resulted from placebo associated with spending time in the hyperbaric chamber. As is discussed in great details in the discussion section, we reason that the authors reached wrong conclusions for two main reasons. First, room air at 1.3Atm cannot serve as a proper sham-control since it is not an "ineffectual treatment" (as is required from placebo) since it leads to a significant increase in the level of tissue oxygenation which has been shown to be effective [37,38]. Second, 100% oxygen at 2.4Atm leads to too high oxygen levels which can cause inhibitory effect or even focal toxicity.

The crossover approach

To overcome the placebo issue, a randomized crossover approach was successfully used to test the effect of HBOT in post-stroke patients at late chronic stage [3]. The advantage of the

crossover approach is the triple comparison – between treatments of two groups, between treatment and no treatment of the same group, and between treatment and no treatment in different groups. Up till now, a similar prospective, randomized, crossover trial to evaluate the brain repair effect of HBOT in mTBI patients at late chronic stage has not been done.

The aim of our current study was to provide firm evaluation of the HBOT effects on brain activity and cognitive impairments in mTBI patients with prolonged PCS at late chronic stage.

Methods

The study was performed as a prospective, randomized, controlled, two-group trial. The study was conducted in the hyperbaric institute and the research unit of Assaf-Harofeh Medical Center, Israel. Enrolment of patients started at 2008 and ended at 2012. All patients signed written informed consent. The protocol was approved by Assaf-Harofeh institutional review board.

Participants

Inclusion. The participants were patients of age 18 years or older, who suffered mild TBI (less than 30 minutes loss of consciousness) 1-6 years prior to their inclusion. All patients experienced post concussion syndrome (PCS) and complained of impaired cognitive functions for over a year, yet brain damage was below the detection level of MRI or CT brain imaging. Only patients who reported no change in cognitive function during one month prior to the beginning of the study were included.

Exclusions. Exclusions were due to chest pathology incompatible with HBOT, inner ear disease, claustrophobia and inability to sign informed consent. Smoking was not allowed during the study.

Protocol and End Points

After signing an informed consent form, the patients were invited for baseline evaluation. Included patients were randomized into two groups (1:1 randomization): a treated group and a crossover group. The neuropsychological functions, evaluated by Mindstreams testing battery, and brain activity as visualized by SPECT (Single photon emission computed tomography), were the primary endpoints of the study. Secondary end point included quality of life evaluation by the EQ-5D questionnaire. Evaluations were made by medical and neuropsychological practitioners who were blinded to patients' inclusion in the control-crossed or the treated groups.

Patients in the treated group were evaluated twice – at baseline and after 2 months of HBOT. Patients in the crossover group were evaluated three times: baseline, after 2 months control period of no treatment, and after subsequent 2 months of HBOT (Figure 1). The post-HBOT neurological evaluations as well as the SPECT scans were performed more than 1 week (1–3 weeks) after the end of the HBOT protocol. The following HBOT protocol was practiced: 40 daily sessions, 5 days/week, 60 minutes each, 100% oxygen at 1.5ATA.

Patients were not involved in any other cognitive or rehabilitation intervention as part of the study protocol. The detailed clinical study protocol, copy of the informed consent, as well as CONSORT 2010 checklist of information are attached as supporting information (Protocol S1, Form S1, Checklist S1). We note that information regarding sample size, detectable change and power calculation parameters is included and addressed in the "statistical considerations" section in the SI1.

Evaluation of cognitive state

Cognitive Indices. The state of the patients' cognitive functions was assessed in terms of the following four cognitive indices, ordered from the index associated with most fundamental (basic) functions to that associated with the higher functions: 1. ***Information Processing Speed (IPS) index***. This index is associated with the basic ability to process and respond to stimuli at different levels of speed and complexity. 2. ***Attention-related index***. This index is associated primarily with the ability to remain concentrated and respond effectively throughout relatively extended periods of time. 3. ***Memory-related index***. This index is associated with the learning of verbal and visual new stimuli, and the immediate and delayed recognition of these learned stimuli. 4. ***Executive Functions (EF) index***. This index is associated with cognitive abilities involved in the initiation, planning, organization and regulation of behavior. Each of above cognitive indices was computed as a normalized combined score of 2–3 cognitive tests from the Mindstreams Computerized Cognitive Test Battery (Mindstreams; NeuroTrax Corp., NY).

Cognitive tests. The Mindstreams battery includes several cognitive tests devised to check various aspects of brain capabilities. In the current study we evaluated the cognitive indices based on the scores of the 6 cognitive tests listed below, which are expected to be relevant for mild TBI. For detailed description of all cognitive tests in Mindstreams battery see [39]. The tests are:

1. ***Verbal memory***. Ten pairs of words are presented, followed by a recognition test in which the first word of a previously presented pair appears together with a list of four words from which the patients choose the other member of the pair. There are four immediate repetitions and one delayed repetition after 10 min.

2. ***Non-verbal memory***. Eight pictures of simple geometric objects are presented, followed by a recognition test in which four versions of each object are presented, each oriented in a different direction. There are four immediate repetitions and one delayed repetition after 10 min.

3. ***Go–No-Go test***. In this continuous performance test, a colored square (red, green, white or blue) appears randomly on the center of the screen. The patient in then asked to respond quickly only for red squares by pressing the mouse button, and inhibit his reaction to any other colored square.

4. ***Stroop test***. Timed test of response inhibition modified from the Stroop paper-based test. In the first phase, patients choose a colored square matching the color of a general word (for example, the word "Cat" appears in red letters, the patient must choose the red square out of two colored squares in the following screen). In the next phase (termed the Choice Reaction Time test), the task is to choose the colored square matching the name of the color presented in white letter–color. In the final (Stroop interference) phase, patients are asked to choose the colored square matching the color and not the meaning of a former color-naming word, presented in an incongruent color (for example, the word "RED" appears in green letters, the patient is asked to choose the color green and not red, a task requiring the ability to inhibit an automatic response to the meaning of the word).

5. ***Staged information processing test***. Timed test requiring a reaction based on solving simple arithmetic problems (pressing right/left mouse button if the answer higher/lower than 4, respectively) with three levels of information processing load (single digit, two digits addition/subtraction and three digits addition/subtraction problems), each containing three speed levels (3, 2, and 1 second for the presentation of the stimuli).

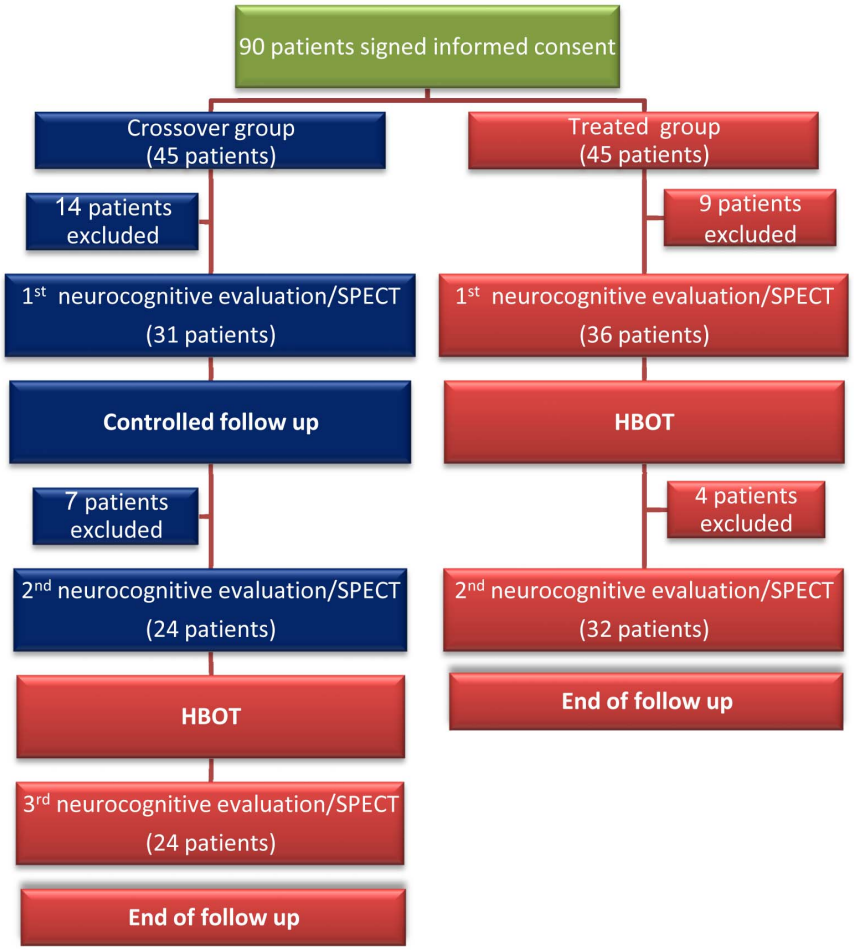

Figure 1. Flow chart of the patients in the study.
doi:10.1371/journal.pone.0079995.g001

6. *Catch game*. A test of motor planning that requires participants to catch a falling object on a computer screen by moving a paddle horizontally so that it can "catch" the falling object.

To assign scores, Mindstreams data was uploaded to the NeuroTrax central server. Outcome parameters were calculated using custom software blind to diagnosis or testing site. To minimize differences related to age and education, each outcome parameter was normalized and fit to an IQ-like scale (mean = 100, STD = 15) according to patient's age and education. We note that the score evaluation was based on normative data from cognitively healthy individuals collected in controlled research studies that were part of more than 10 clinical sites [40].

The cognitive indices' scores. The computation of the cognitive indices based on the scores of the cognitive tests was done as follows: 1. Information Processing Speed index was computed as the combined score for the low and medium-load stages of the staged information processing test. 2. Attention index was calculated as the mean score of reaction time for Go–No-Go test and choice reaction time of the Stroop test (at second phase), mean STD of reaction time for Go–No-Go test, mean reaction time for a low-load stage of staged information processing test and mean accuracy for a medium-load stage of information processing test. 3. Memory index was computed as the mean score for total learning score (after four repetitions) and delayed recognition phase of verbal and non-verbal memory tests. 4. Executive Functions index was computed based on the scores of the Stroop test and the Go–No-Go test and the mean weighted accuracy for catch game. For more information regarding the validity of the tests and the construction of the cognitive indices, see [41,42]. 5. In addition, we defined the individual's General Cognitive Score as the average of the scores of the four cognitive indices for each individual.

It is important to note that the above cognitive index scores were specifically designed to represent known impaired cognitive domains in mild TBI. In addition, the fact that each index is referred to more than one test-score ensures the index to be associated more with a cognitive domain score and less with a test-dependent score. We also utilized a computerized testing battery which supports the inclusion of more accurate measures such as reaction time and elimination of the bias effect of tests' administration and hand scoring. An important aspect of the tests is the inclusion of the cognitive domain of information processing speed, known to be impaired in mild TBI patients.

Quality of life evaluation

Quality of life (QOL) was evaluated by the EQ-5D questionnaire [43]. EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D descriptive system covers mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-VAS

records the respondent's self-rated health on a vertical, visual analogue scale [range: 0(worst)-100(best)].

Brain Functional Imaging- SPECT

Brain single photon emission computed tomography (SPECT) was conducted with 925–1,110 MBq (25–30 mCi) of technetium-99m-methyl-cysteinate-dimmer (Tc-99m-ECD) at 40–60 min post injection using a dual detector gamma camera (ECAM or Symbia T, Siemens Medical Systems) equipped with high resolution collimators. Data was acquired in 3-degree steps and reconstructed iteratively with Chang method (μ = 0.12/cm) attenuation correction [44].

Visual analysis was conducted by fusing pre- and post-treatment studies that were normalized to cerebellum brain activity. SPECT images were reoriented into Talairach space using NeuroGam (Segami Corporation) for identification (based on visual inspection) of Brodmann cortical areas and in order to compute the mean perfusion in each Brodmann area (BA). In addition volume rendered brain perfusion images normalized to cerebellum maximal activity were reconstructed. All SPECT analysis was done while blinded to the laboratory and clinical data. Change in perfusion in all Brodmann areas for each subject was determined by calculating the percentage difference between post-period and pre/baseline-period divided by the pre/baseline-period perfusion. An average of these perfusion changes for each Brodmann area was calculated.

Statistical analysis

The statistical analysis was done using SPSS software (version 16.0). Continuous data is expressed as means ± standard deviations and compared by one-tailed paired t-test for intra-group comparisons and two-tailed unpaired t-test for inter-group comparisons. Effect sizes for main comparisons were calculated using Cohen's d. Categorical data is expressed in numbers and percentages and compared by χ^2 test. P values<0.05 were considered statistically significant. All randomly allocated patients were included in the safety analysis and those with complete post-baseline assessment were included in efficacy analysis.

Scatter plot analysis of the clinical scores

The analysis aims to better quantify and compare changes in the clinical scores, while taking into consideration the high patient-to-patient variability following Efrati et al [3]. The idea was to inspect, for each patient at each time stage, the scaled relative differences in each of the clinical scores. More specifically, we calculated for a specific patient (j) the scaled relative difference SRD_j, defined as:

$$SRD_j \equiv \left[SF_j \check{S} < SF_j > \right] \Big/ \left[STD(SF_j)\right] \quad \check{S}\left[SI_j \check{S} < SI_j > \right] \Big/ \left[STD(SI_j)\right] + \left[< SF_j \check{S} SI_j > \right] \tag{1}$$

Where SF_j is the value of a clinical score at the end of the time stage (either treatment or control), and SI_j is the score at the beginning of the time stage. We note that the symbol $< >$ indicates average over the values of the patients in the group. For example, $<SF_j>$ means the average of SF_j over all patients (j) that belong to the group. The abbreviation STD means the standard deviation between the values of the patients in the group. This analysis enables quantitative inspection of the changes in the clinical scores as is further explained in [3].

Results

Participants Profiles

The study included 90 screened patients, aged 18 years or older, who signed an informed consent.

Pre-study exclusions. Nineteen patients had their consent withdrawn before the beginning of the control/treatment period (13 in the crossover group, 6 in the treated group).

In-study exclusions. Four patients decided to drop out during the treatment protocol, 3 due to personal reasons and 1 due to ear problem (1 in crossover group, 3 in treatment group). Seven patients (5 in crossover group, 2 in treatment group) were excluded due to technical performance problems in their cognitive tests and 4 patients due to inconsistent use of medications (such us methylphenidate) during the tests period (2 in crossover group, 2 in treated group).

Accordingly, 56 patients (32 in the treated group and 24 in crossover group) were included in the final analysis (Figure 1). Thirty two (57%) patients were females, the mean age was 44 years (range of 21–66 years) and the time elapsed since the acute traumatic event ranged from 1–6 years with 33 months average.

The most frequent etiology of the TBI was a vehicle accident (n = 38), with some other less common etiologies (falls = 7, object hit = 6, pedestrian accident = 3, assault = 2). Baseline patients' characteristics are summarized in Table 1. As seen from this table, there was no significant difference in the included measures between the groups except for years of education, where there was a minor advantage for the treated group.

The Effect on Cognitive Functions

Changes in cognitive indices. The effect of the hyperbaric oxygen treatment on the patients' cognitive functions, as assessed by the four cognitive indices, is summarized in Figure 2 and Table 2. The baseline mean cognitive scores of all four indices were close in the two groups (within the standard error) but with somewhat higher values in the treated group. The HBOT treatments of both groups led to statistically significant improvements in the mean scores of all four indices.

As is apparent in Figure 2 and detailed in Table 2, a significant improvement was observed in the treated group after HBOT in all cognitive measures: Information Processing Speed ($t_{(31)} = 4.20$, $p<0.0001$), Attention ($t_{(31)} = 3.26$, $p<0.005$), Memory ($t_{(31)} = 4.13$, $p<0.0005$) and Executive Functions ($t_{(31)} = 3.72$, $p<0.0005$). Effect sizes were medium to large: the Cohen's d measures [45] were 0.74, 0.57, 0.73 and 0.66, respectively.

No significant improvement was noticed in the crossover group during the control period: Information Processing Speed ($t_{(23)} = 0.53$, $p = 0.298$), Attention ($t_{(23)} = 0.33$, $p = 0.368$), Memory ($t_{(23)} = 0.74$, $p = 0.233$) and Executive Functions ($t_{(23)} = 0.54$, $p = 0.295$). However, a significant improvement following HBOT was noticed in the crossover group as well: Information Processing Speed ($t_{(23)} = 1.98$, $p<0.05$), Attention ($t_{(23)} = 2.29$, $p<0.05$), Memory ($t_{(23)} = 3.21$, $p<0.005$) and Executive Functions ($t_{(23)} = 2.26$, $p<0.05$). Effect sizes were medium to large, with Cohen's d measures of 0.40, 0.47, 0.65 and 0.46, respectively. Note that $t_{(31)}$ and $t_{(23)}$ correspond to N-1, where N = 32 and N = 24 are the number of patients in the treated and crossover group, respectively.

Assessment of a general cognitive score. The changes in the four cognitive indices presented in Figure 2 and in Table 2 show noticeable variability. For example, the mean values of the Information Processing Speed and Executive Functions indices decreased during the control period of the crossover group, while the corresponding mean values of the Attention and Memory

Table 1. Baseline patients' characteristics.

	Treated group (n = 32)	Crossover group (n = 24)	Comparison
Age (years)	42.5±12.6	45.7±10.9	p = 0.32
Gender – male	11 (34%)	13 (54%)	p = 0.07
Years of education	16.2±3.9	14.0±3.1	p<0.05
Time since injury (months)	34.6±16.7	31.7±16.3	p = 0.51
Loss of consciousness			p = 0.18
None	24 (75%)	14 (58%)	
<30 minutes	8 (25%)	10 (42%)	
Etiology			
Vehicle accident	20 (63%)	18 (75%)	
Fall	5 (16%)	2 (8%)	
Object hit	4 (12%)	2 (8%)	
Pedestrian accident	2 (6%)	1 (4%)	
Assault	1 (3%)	1 (4%)	
Background disease			
Hypertension (HTN)	5 (15%)	4 (16%)	
Diabetes Mellitus (DM)	2 (6%)	2 (8%)	
Hyperlipidemia	4 (12%)	3 (12%)	
Ischemic Heart Disease	0	1 (4%)	
Epileptic seizure	0	0	
Smoking	1 (3%)	0	
Medications			
Aspirin	2 (6%)	3 (12%)	
Glucose lowering drugs	2 (6%)	1 (4%)	
Anti-HTN	4 (12%)	3 (12%)	
Statins	3 (9%)	3 (12%)	
Anti-depressant	7 (22%)	4 (16%)	

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indices increased. Figure 3 shows the mean values of the individual general cognitive scores, with standard error, for the treated and crossover groups at each evaluation stage: baseline and post-HBOT for both groups, and after the control for the crossover group. It can be seen that the cross group had the same general score at baseline and after the control period. This value seems higher than the score of the treated group at baseline – ~88 vs. 85, and the post-HBOT general cognitive score of the treated group seems higher than that of the crossover group – ~96 vs. 94. While these differences are within the standard error, they still give rise to what appears to be significant differences in the level of changes (post- vs. pre-HBOT) between the crossover and the treated groups: 6 points for the crossover group vs. 11 for the treated group.

Examining the relative changes. There is a high patient-to-patient variability in the cognitive indices, with scores ranging from 20 to 120. The magnitude of the change in a cognitive score has different implications for patients at low or high base levels. Hence, we inspect the effect of the HBOT on the relative changes, i.e. the change relative to the base value. We calculated, for each person, the relative change in each of the cognitive indices for each period (control and HBOT for the crossover group and HBOT for the treated group). In Figure 4A we show the mean relative changes in all four cognitive indices for the crossover group following the control period and following HBOT, and for the treated group following HBOT. In Figure 4B we show the mean relative changes in the general cognitive score for the same three periods. We note that calculating the mean of the relative changes is more informative than calculating the changes in the mean values, especially for small groups with high patient-to-patient variability.

Looking at the relative changes elucidates the improvements after the HBOT period vs. the control period of the crossover group. However, it also amplifies the differences mentioned earlier between the crossover and treated groups: the bigger relative changes in the treated group vs. the crossover group reflect the fact that the baseline values of the treated group were lower and the post-HBOT values were higher in comparison to the corresponding values of the crossover group.

Scatter plot analysis of the cognitive indices. As mentioned in the methods section, the analysis aims to present the mean relative changes in cognitive indices while superimposing information regarding the patient-to-patient variability. For that we calculated, for each patient (i), the normalized relative change NRC(i). Next, we calculated for each group (control and HBOT in the crossover group and HBOT in the treated group) the locations of the mean departures from baseline. Finally, we marked the location of each patient (i) at a distance NRC(i) from the location of his/her group's mean difference (see methods section for details). Typical results are shown in Figure 5. More specifically, we show the scatter plots for Information Processing Speed vs. Executive Functions (Figure 5A), for Attention vs. Memory

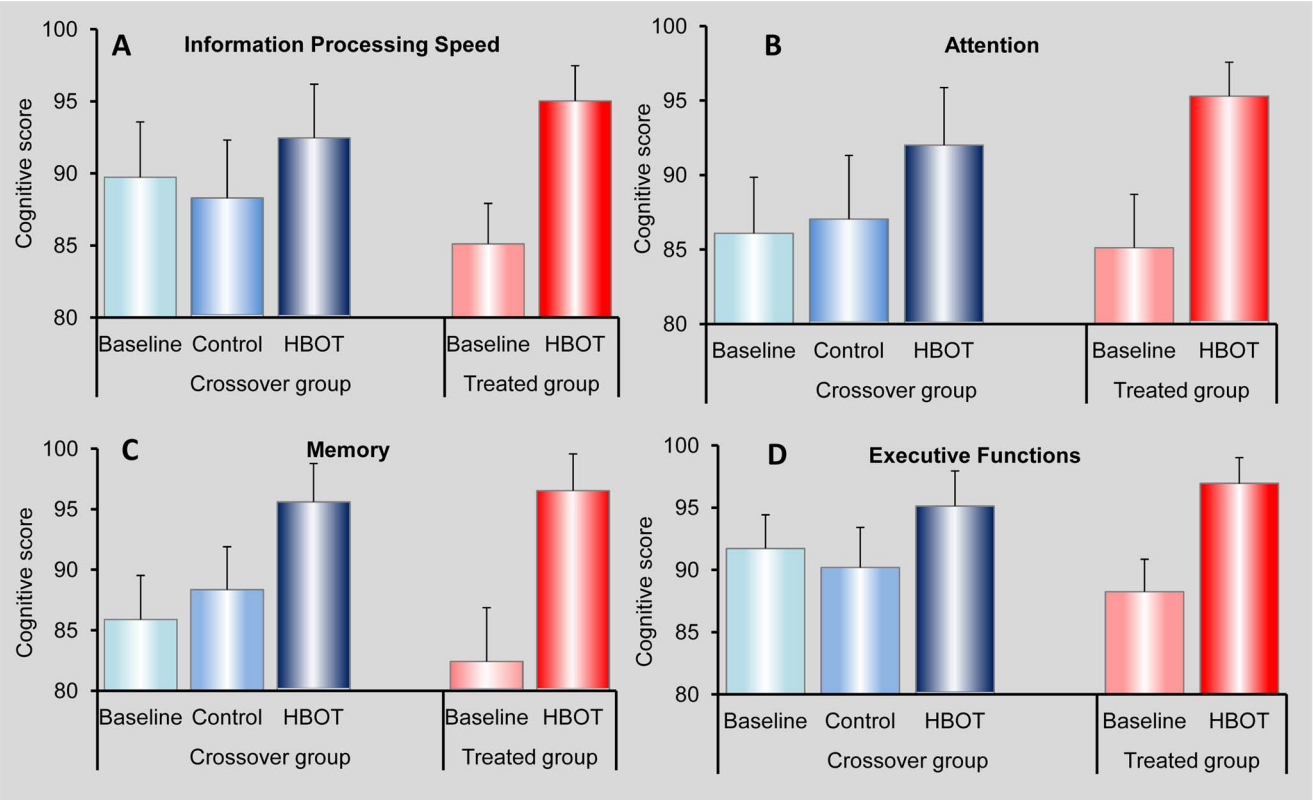

Figure 2. Assessment of the cognitive indices. Each patient in each group was assigned a score at baseline, after the control period (for patients in the crossover group) and after HBOT. The figures show the mean scores and standard errors for the two groups at each stage for the four cognitive indices - Information Processing Speed (A), Attention (B), Memory (C) and Executive Functions (D), as defined in the method section.
doi:10.1371/journal.pone.0079995.g002

(Figure 5B), for Attention vs. General cognitive score (Figure 5C), and for IPS vs. General cognitive score (Figure 5D). The results illustrate the differences between the three cases (control and HBOT for the crossover group, and HBOT for the treated group) which form three distinct clusters. Also clear in all the figures is the linear dependence between the changes in the different cognitive indices (similar results are also obtained for the other combinations, e.g. Memory-IPS, Attention-IPS, Memory-EF and Attention-EF). Interestingly, the scattering of the individual patients also follows the linear line for the scatter plots of the specific cognitive indices as function of the general cognitive score (Figures 5C and 5D). These linear dependences demonstrate high consistency between the changes of the different cognitive indices for each patient. As such, the analysis provides valuable test for the validity of the test performances and the validity of the general cognitive score.

Table 2. Summary of results for Mindstreams cognitive indices scores.

	Treated group (n = 32)				Crossover group (n = 24)					
	Baseline	HBOT	P1	P2	Baseline	Control -Pre HBOT	Post HBOT	P2	P3	P4
Memory	82.43±25.15	96.54±17.18	0.567	<.0005	85.90±17.80	88.36±17.34	95.61±15.54	0.233	<0.005	0.835
Executive function	88.26±14.74	96.96±11.69	0.367	<0.0005	91.73±13.26	90.20±15.77	95.13±13.84	0.295	<0.05	0.595
Attention	85.13±20.28	95.30±12.90	0.854	<0.005	86.10±18.42	87.05±20.98	92.02±18.95	0.368	<0.05	0.443
Information processing speed	85.12±15.88	95.04±13.75	0.324	<0.0001	89.74±18.81	88.30±19.68	92.47±18.25	0.298	<0.05	0.55

Abbreviations:
Values are presented as mean ± STD. P1 stands for the p values for baseline comparison of treated and crossover group; P2 stands for the p values for comparison of the second measurement to baseline in the same group; P3 stands for the p values for comparison of pre- and post-HBOT in the crossover group; P4 stands for the p values for endpoint scores comparison following treatment in both groups. The baseline mean cognitive scores of all four indices were close in the two groups, with no significant difference. The HBOT treatments of both groups led to statistically significant improvements in the mean scores of all four indices as oppose to no significant improvement after control period alone. The tables are discussed in details in the results section.
doi:10.1371/journal.pone.0079995.t002

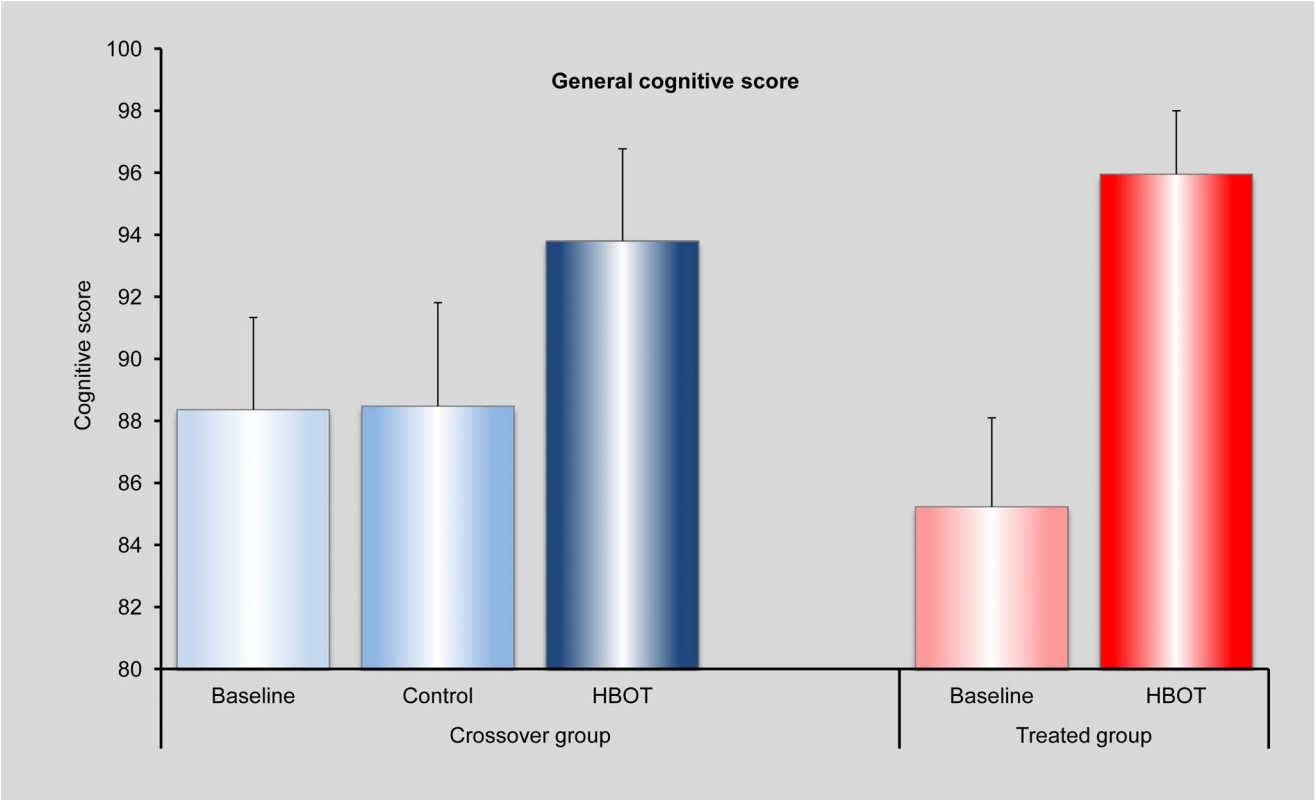

Figure 3. Assessments of the general cognitive score. The figure shows the level of the general cognitive score (defined in the text) for the crossover group at baseline, after the control period and after HBOT, and for the treated group at baseline and after HBOT.
doi:10.1371/journal.pone.0079995.g003

The Effect on quality of life

The effect on the QOL is summarized in Table 3. The EQ-5D score significantly improved following HBOT in the treated group ($t_{(31)} = 7.41$, $p<0.0001$) and in the crossover group after HBOT ($t_{(23)} = 6.17$, $p<0.0001$). As expected, there was no improvement in the EQ-5D score in the crossover group following the control period. During the control period, we have noticed some reduction in this group with respect to the patients' subjective perception of their quality of life ($t_{(23)} = 2.60$, $p<0.01$). Similar results were obtained for the EQ-VAS evaluations as summarized in Table 3. More specifically, the EQ-VAS score significantly improved following HBOT, both in the treated group ($t_{(31)} = 4.86$, $p<0.0001$) and in the crossover group following treatment ($t_{(23)} = 4.79$, $p<0.0001$), while there was no significant improvement following the control period ($t_{(23)} = 0.32$, $p = 0.373$). Details are presented in Table 3.

Examining the relative changes. Figure 6 presents the mean relative changes and standard errors in both measurements of quality of life for the treated group following HBOT and for the crossover group after the control period and after HBOT.

SPECT assessments of brain activity

Motivation. Since mTBI involves a diffuse structural and/or physiologic/metabolic derangement [46,47,48], patients with mTBI have more frequent and more extensive areas of brain damage than can be seen by anatomical imaging (conventional CT and MRI scans). The preferred brain imaging methods are thus functional/metabolic (SPECT, PET, CT perfusion, and functional MRI). In order to achieve greater validity of the results, cognitive function and SPECT analysis were done by a blinded evaluation and evaluator: the cognitive function tests were done by a computerized validated method and the SPECT analysis was blind to patients' participation in treated/crossover group.

Brain SPECT evaluations were completed for 31 patients in the treated group (one patient from the treated group did not complete two SPECT scans) and for 24 in the crossover group. In supporting information (Table S1) we present detailed statistics of the SPECT results for all Brodmann areas (BA) of all the tested patients. The results revealed a significant increase in brain activity (perfusion) following the hyperbaric oxygen treatments in both groups compared to the change during the control period of the crossover group. A summary of the results is presented in Figure 7. To construct the figure we calculated, for each patient, the relative change in the SPECT measured brain activity during each phase of the trial. The relative change was defined as the difference in normalized activity (relative to the cerebellum activity, see SI4) between the end point and the start point divided by the activity at the start. We calculated, for each BA, the average changes over all patients that underwent HBOT (both treated and cross groups). These results correspond to the red curve in Figure 7. The blue curve represents the results of similar calculations for the control period (averaging for each BA over all the results of all patients in the crossover group during the control period).

The results revealed significant improvement in brain perfusion following HBOT in the frontal and temporal areas, including: inferior frontal gyrus (BA 45), the middle frontal area (BA 46), parts of the orbito-frontal cortex (BA 47 and 11), most of the temporal cortex (BA 36, 37, 38, 20, 21, 22, 28), and parts of the Cingulate gyrus (BA 24, 25). These fronto-temporal regions, responsible for the cognitive functions, are the most affected in

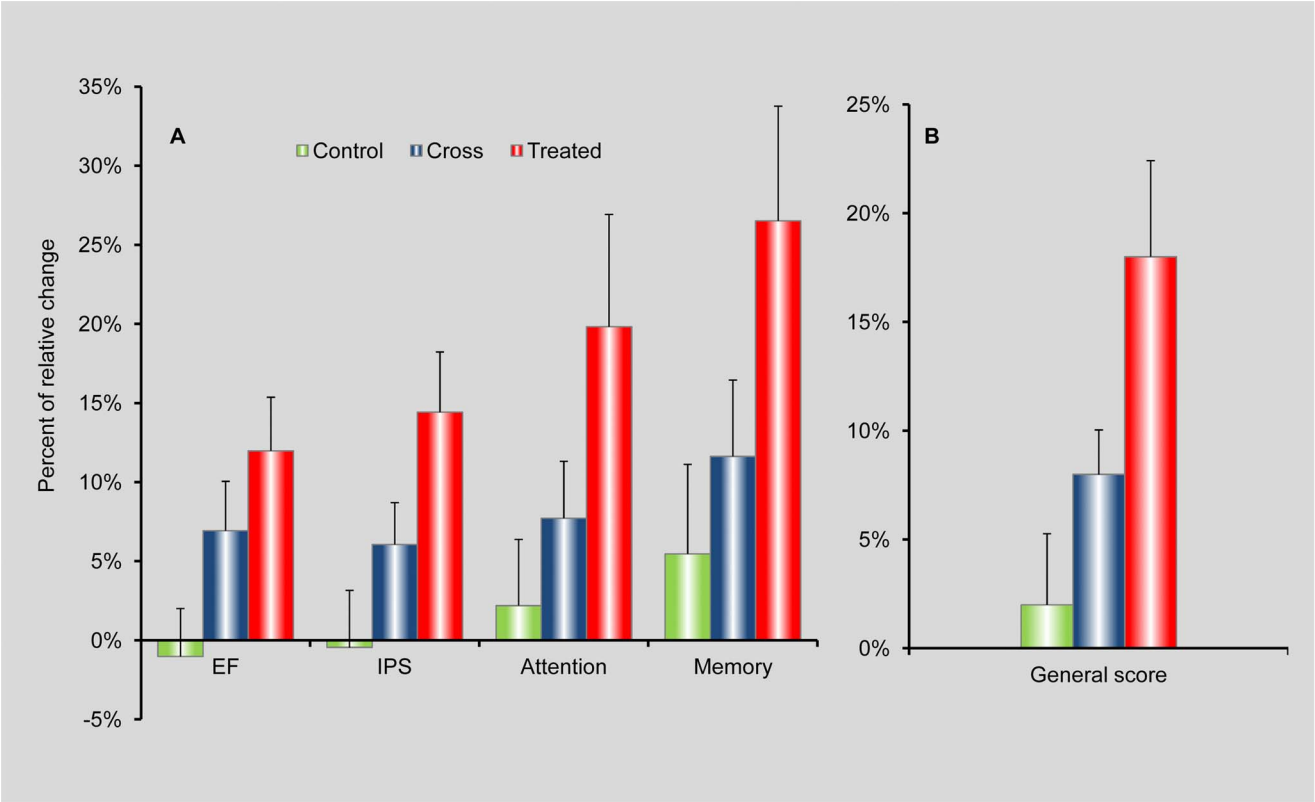

Figure 4. Assessment of the relative changes. A) The relative changes (as defined in the text) for the four cognitive indices. The changes are shown for the crossover group following the control period (green bars) and HBOT (blue bars), and for the treated group following HBOT (red bars). B) Relative changes in the general cognitive score for the same three cases as in (A).
doi:10.1371/journal.pone.0079995.g004

head trauma [12]. The temporal lobe plays a significant role in memory and learning skills [49,50,51]; the frontal lobe is associated with attention and executive functions [52,53], and the cingulate gyrus plays an important role in emotions and cognitive self regulation [54,55,56]. The SPECT results of elevated activity in these Brodmann areas are consistent with the improvement in cognitive indices following HBOT. Further below we show specific examples of SPECT results for four patients (two from the treated group and two from the crossover group).

Representative examples

Example 1. SPECT analysis of a 51-year-old woman from the treated group (Figure 8). The patient suffered from cognitive impairments due to mTBI as a result of a fall in a moving bus 2 years prior to inclusion in the study. The patient experienced no loss of consciousness and CT imaging did not reveal anatomic damage. The patient's main complaints included headaches, dizziness, memory and concentration problems, and random mood swings. The patient was a manager in a private business, and since the injury was having difficulties following and completing daily activities and routine. Following HBOT, the patient reported significant improvement in every aspect of daily functioning. The patient's cognitive indices demonstrated significant improvements following treatment: increase of 3.5 STD in Memory (56 pre-HBOT to 108 post-HBOT), 2 STD increase in Attention (47 to 81), 1.5 STD increase in Executive Functions (65 to 85) and a 0.7 STD increase in Information Processing Speed (85 to 95).

Example 2. SPECT analysis of a 46-year-old woman from the treated group, following mTBI as a result of a car accident 1 year prior to inclusion in the study. The patient's main complaints were related to her memory and concentration capabilities, as well as dizziness and tinnitus that interfered with her daily functioning. Following HBOT, the dizziness and tinnitus disappeared, in addition to significant improvement in all cognitive domains. The patient's cognitive indices demonstrated significant improvements following treatment: increase of 1.5 STD in Memory (57 pre-HBOT to 78 post-HBOT), 1 STD increase in Attention (88 to 104), 1.5 STD increase in Executive Functions (82 to 102) and 0.6 STD increase in Information Processing Speed (85 to 95). SPECT images of the patient at baseline and following HBOT are shown in Figure 9. The percentage of CBF change demonstrated significant improvements after HBOT in parts of the frontal and temporal lobes, in agreement with the improvements in neurological functions.

Example 3. SPECT analysis of a 44-year-old man from the cross group, suffering from cognitive impairments due to mild TBI as a result of a fall 2 years prior to treatments. The patient complained mainly on short and long term memory difficulties, attention and concentration problems, decline in naming abilities, as well as headaches, dizziness, anxiety and sleep problems. Following HBOT, the patient experienced significant improvements in most aspects, including concentration and memory, headaches, dizziness, mood and sleep. The patient's cognitive indices demonstrated significant improvements in Executive Functions after treatment: baseline 60, after control 63 and post-HBOT 74. SPECT images of the patient after the control period

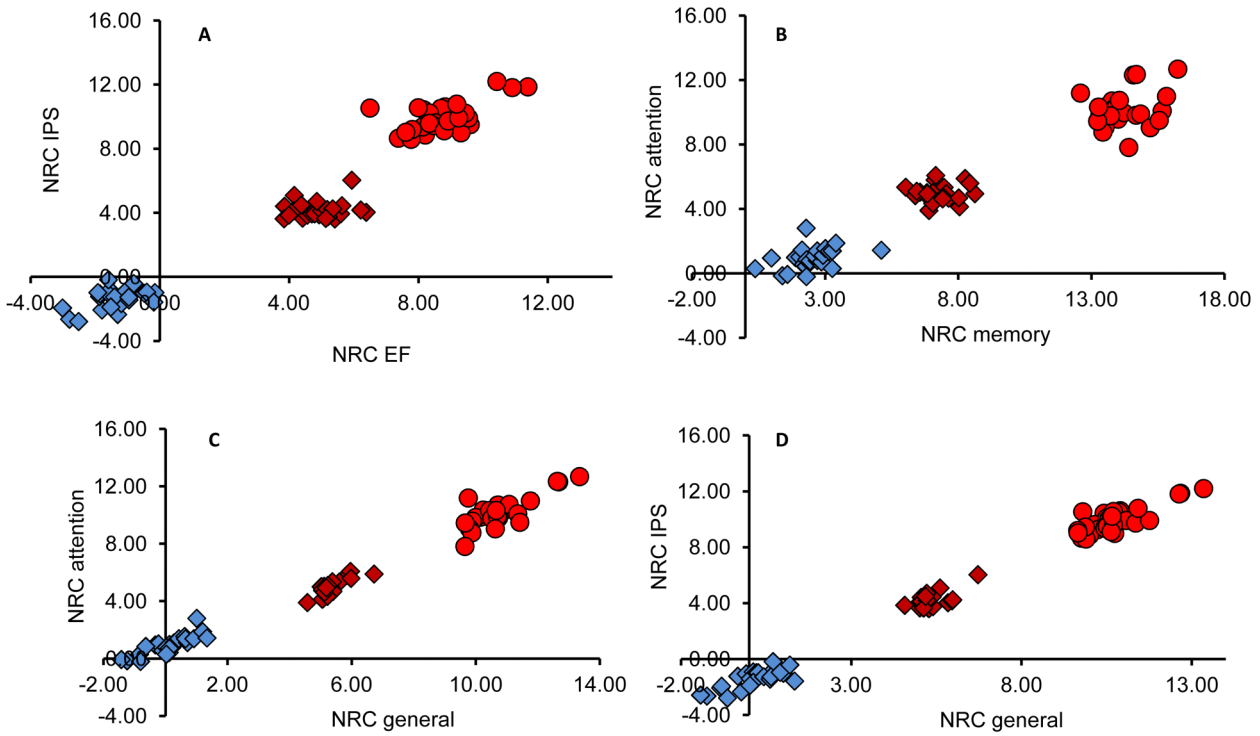

Figure 5. Scatter plot analysis of the changes in cognitive indices. The scatter plots show the normalized relative changes (NRC) as defined in the methods section and explained in the text above. A) Scatter plot for the changes in IPS as function of changes in EF. B) Scatter plot for changes in Attention as function of Memory. The changes in the Attention and in the IPS as function of the General cognitive score are shown in (C) and (D), respectively. Circles are for the treated group and diamonds are for the crossover group. The color code is: Red for changes during HBOT and blue for changes during control.
doi:10.1371/journal.pone.0079995.g005

and following HBOT are shown in Figure 10. The CBF change was not significant after the control period but substantial improvement after HBOT in most of bilateral frontal and temporal lobes and right parietal lobe.

Example 4. SPECT analysis of a 39-year-old woman from the cross group, suffering from cognitive impairments due to mild TBI as a result of a car hit as a pedestrian, 2 years prior to treatments. The patient's complaints included dizziness, nausea, fatigue and decrease in memory and concentration abilities. The patient also had troubles in performing every-day activities, such as attaining the grocery store, or reading the newspaper. The patient was working as a nurse and could not continue to perform her work after the accident, due to the impaired abilities. The patient's cognitive indices demonstrated significant improvements following treatment in comparison to the changes during the control period: Executive Functions at baseline, after control and post HBOT were 77, 71 and 88 respectively, and Attention scores were 62, 64 and 78 respectively. SPECT images of the patient, after the control period and following HBOT are shown in Figure 11. At first global look, the CBF changes after HBOT seem to be similar to the changes after the control period demonstrating no significant change. However, a closer inspection of the SPECT images reveal local improved perfusion in the right anterior temporal and right dorso-lateral frontal areas. This example is shown to demonstrate that even for patients with relatively mild cognitive improvements there is good correspondence between the change in the cognitive tests and the SPECT results.

Table 3. Summary of results of quality of life questionnaire (EQ-5D and EQ-VAS).

	Treated group (n = 32)				Crossover group (n = 24)					
	Baseline	HBOT	P1	P2	Baseline	Control-Pre HBOT	Post HBOT	P2	P3	P4
EQ-5D	7.87±1.36	6.48±1.07	0.615	<0.0001	7.70±1.11	8.06±1.05	6.75±1.06	<0.01	<0.0001	0.362
EQ- VAS	5.03±2.31	6.62±2.45	0.696	<0.0001	5.26±1.70	5.21±1.66	6.39±1.80	0.373	<0.0001	0.696

Abbreviations:
Values are presented as mean ± STD. P1 stands for the p values for baseline comparison of treated and crossover group; P2 stands for the p values for comparison of the second measurement to baseline in the same group; P3 stands for the p values for comparison of pre- and post-HBOT in the crossover group; P4 stands for the p values for endpoint scores comparison following treatment in both groups. EQ-5D as well as the EQ-VAS scores significantly improved following HBOT, both in the treated group and in the crossover group following treatment, while there was no significant improvement following the control period.
doi:10.1371/journal.pone.0079995.t003

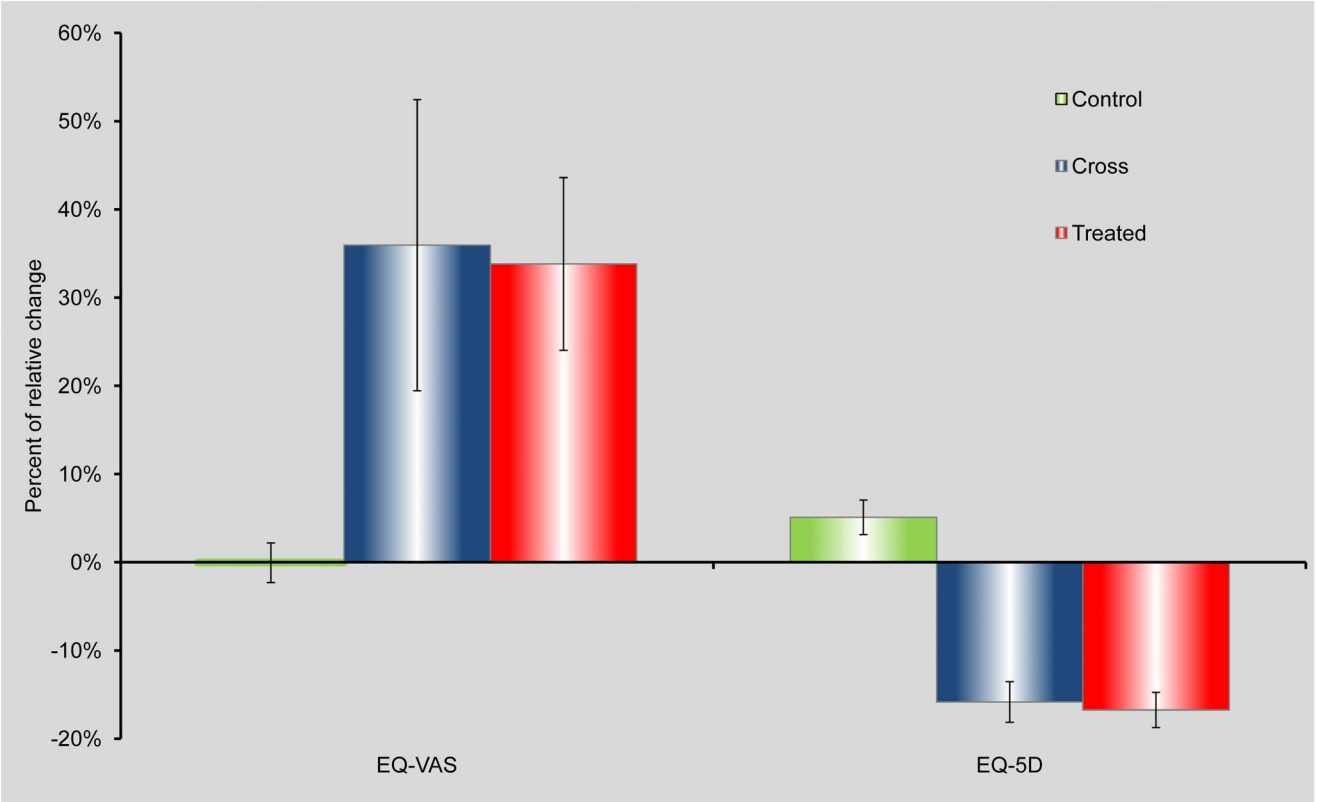

Figure 6. Assessments of the mean relative changes and standard errors in quality of life measurements. The changes are shown for the crossover group following control period (green bars) and following HBOT (blue bars), and for the treated group following HBOT (red bars). Note that, according to the questionnaire structure, in the EQ-5D measurement improvement is reflected as score decrease, hence the negative values of change.
doi:10.1371/journal.pone.0079995.g006

Discussion

We presented a prospective, randomized and controlled cross over study of the effect of HBOT with 100% oxygen at 1.5Atm on mTBI patients at late chronic stage. The results clearly demonstrate that HBOT can induce neuroplasticity and significant brain function improvement in mild TBI patients with prolonged Post-Concussion-Syndrome at late chronic stage, years after brain injury. Additional statistical validation using simulated randomizations is available as supporting information (Text S1).

Linking elevated oxygen, metabolism and brain activity to neuroplasticity

The changes in SPECT images after treatment indicate that HBOT led to reactivation of neuronal activity in stunned areas that seemed normal under CT and MRI imaging. While SPECT imaging has a limited spatial resolution (compared, for example, to fMRI), the changes in activity were sufficiently robust to be clearly detected by the SPECT images.

Recently, Kan et al. [57] discussed the need for potent interventions, such as elevated tissue oxygen, capable of repairing microenvironment alterations after mTBI (e.g impairments in vascular changes, in cerebral blood flow and in perfusion), leading to reduced oxygen availability followed by reduced metabolism, which in turn leads to reduced neuronal activity, loss of synapses and tampered neuronal connectivity.

The observed reactivation of neuronal activity in the stunned areas found here, along with similar results in post-stroke patients [3], imply that increasing the plasma oxygen concentration with hyperbaric oxygenation is a potent means of delivering to the brain sufficient oxygen for tissue repair. HBOT might initiate a cellular and vascular repair mechanism and improve cerebral vascular flow [34,58,59,60]. More specifically, HBOT induces regeneration of axonal white matter [61,62,63,64], has positive effect upon the myelinization and maturation of injured neural fibers [65], and can stimulate axonal growth and increase the ability of neurons to function and communicate with each other [66]. In addition, HBOT was found to have a role in initiation and/or facilitation of angiogenesis and cell proliferation processes needed for axonal regeneration [67].

At the cellular level, HBOT can improve cellular metabolism, reduce apoptosis, alleviate oxidative stress and increase levels of neurotrophins and nitric oxide through enhancement of mitochondrial function (in both neurons and glial cells). Moreover, the effects of HBOT on neurons can be mediated indirectly by glial cells, including astrocytes [23]. HBOT may promote the neurogenesis of endogenous neural stem cells [24]. With regard to secondary injury mechanisms in mTBI, HBOT can initiate vascular repair mechanism and improve cerebral vascular flow [58,59,68,69], promote blood brain barrier integrity and reduce inflammatory reactions [28] as well as brain edema [20,21,22,26,34,70]. A drawback to the above-mentioned findings is that the different effects have been tested at different experimental setups and while utilizing different protocols of HBOT. However, it is well noticed that there is at least one common denominator to all repair/regeneration mechanisms:

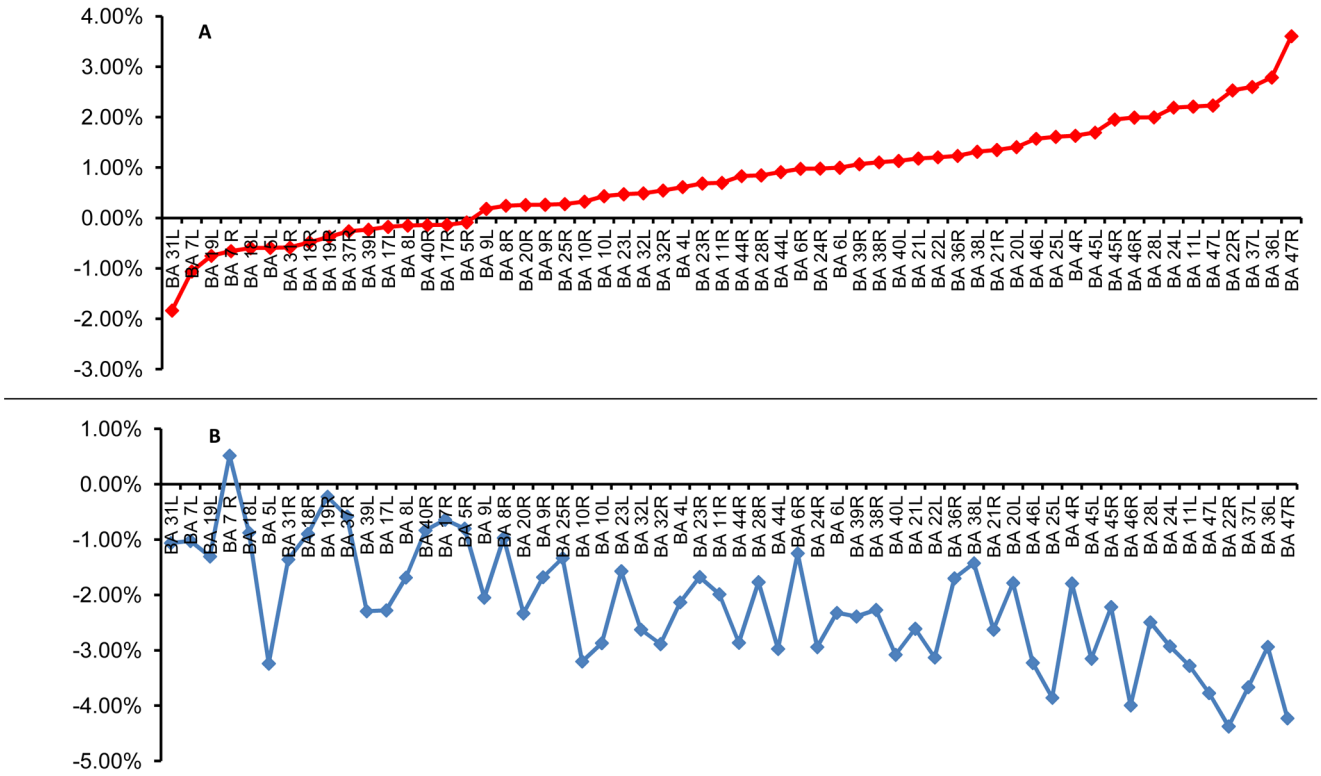

Figure 7. Distribution of the Brodmann areas relative SPECT CBF changes. The change for each BA represents and averaging of the relative changes of all the patients as explained in the text. The results show a clear difference between the control and the HBOT periods. We note that the higher variations for the control period are associated with the fact that the averaging in this case is over 24 patients (the crossover group), while for the HBOT period the averaging is over all 55 patients.
doi:10.1371/journal.pone.0079995.g007

they are all energy/oxygen dependent. It might be possible that HBOT enables the metabolic change simply by supplying the missing energy/oxygen needed for those regeneration processes.

Rationale for testing the HBOT effect on patients at late chronic stage

As stated in the introduction, the crossover approach is adopted in order to avoid the inherent difficulties associated with randomized HBOT trial while practicing standard placebo (see Text S1). The placebo dilemma and the rationale for a crossover approach are further discussed below following the rationale to selecting patients at late chronic stage. First, as explained in [3], applying hyperbaric oxygen in the acute or early phase after brain injury makes it almost impossible to signify and assess the HBOT effects vs. the effects of the spontaneous natural repair mechanism that are effective at this stage. Moreover, in some patients the elevated oxygen can inhibit natural regeneration or even cause toxicity. In [3] it was proposed that this might explain the contradictive results in studies using HBOT at early stage after stroke [71,72,73,74,75]. One can assume that any added energy during the degenerative stage, immediately after brain injury, could further increase the unwanted, post-injury damage. On the other hand, elevated oxygen supply during the regenerative stage would supply the energy needs for the innate brain repair processes. Second, as also explained in [3], patients at the chronic late stage demonstrate neurological stability with low probability of spontaneous changes unrelated to treatment. Third, typically, patients at this stage, years after injury, have already gone through rehabilitation programs. These programs, which attempt to attend mainly to the cognitive dysfunction following the injury, are commonly based on behavioral compensation methods (such as attention training drills, teaching memory, planning strategies and usage of external aids [16,76], and have limited patient-specific success in repair of mTBI impaired brain function [77]. Therefore, studies at the late chronic stage allow assessment of the power of the HBOT approach to achieve brain function improvements in addition to, rather than instead of, the standard rehabilitation programs.

The placebo dilemma and debate

There are inherent ethical and logistic difficulties in handling the sham control in HBOT trial according to the standard placebo definition: "*Medically ineffectual treatment for medical conditions intended to deceive the recipient from knowing which treatment is given*". First, the minimal pressure for the patients to sense pressure increase is 1.3Atm. Second, breathing regular air under hyperbaric conditions of 1.3Atm leads to more than 50% elevation in tissue oxygenation. There are many case reports illustrating significant effects due to small increases in air pressure, including effects on the brain [38,78,79,80]. Moreover, even a slight increase in partial pressure, such as to 1.05 ATM at altitude 402 m below sea level (the Dead Sea), can lead to noticeable physiological effects [81,82,83,84,85]. Since 50% elevation in tissue oxygen can have significant physiological effects, treatment with room air at 1.3Atm is not an "ineffectual treatment" as is required from a proper sham control. Yet, a recent randomized, controlled trial on mTBI patients by Wolf et al [36], used room air at 1.3Atm as sham control for treatment with 100% oxygen at 2.4Atm. Both groups

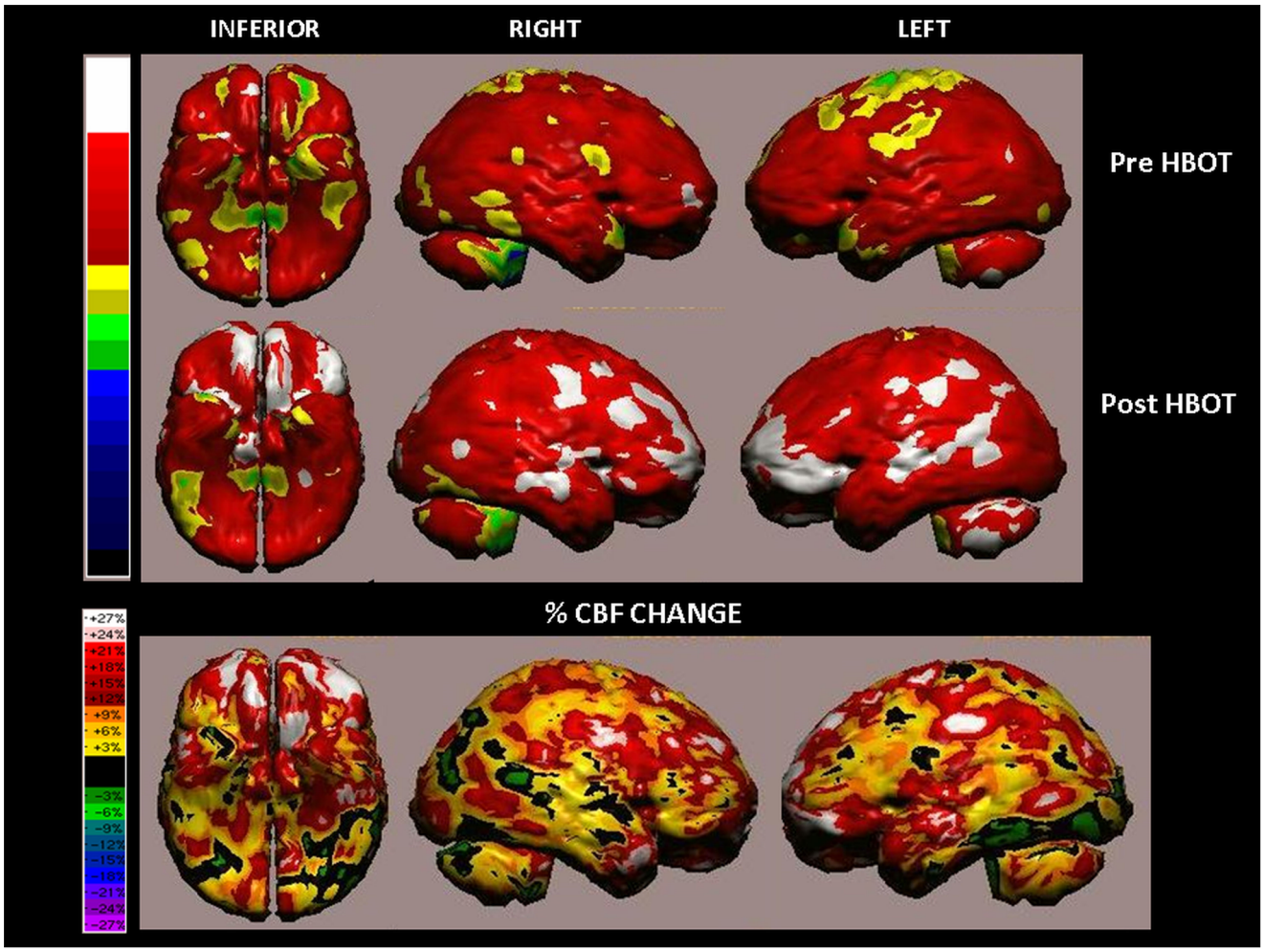

Figure 8. Volume rendered Brain SPECT perfusion maps of Example 1, a 51-year-old woman from the treated group suffering mTBI that had occurred 2 years prior to inclusion in the study. Comparison of the baseline activity (upper row) with the post HBOT activity (middle row) and the CBF changes (bottom row) demonstrated significant improvements after HBOT in bilateral orbito-frontal and lateral-parietal regions and left ventro-lateral-frontal region correlating to BAs 45, 47, and 11.
doi:10.1371/journal.pone.0079995.g008

revealed significant improvements in cognitive symptoms and in the measure of post traumatic stress disorder (PTSD). We find these results very important: they actually demonstrate that the significantly less expensive and logistically simpler treatment of mTBI patients with mild HBNO2 (mild hyperbaric pressure of 1.3Atm and regular air) can lead to meaningful improvements. Our interpretation is based on previous studies demonstrating that mild HBNO2 conditions can be effectual treatment. The authors of that study presented a very different interpretation. Overlooking the fact that mild HBNO2 can be an effectual treatment, they regarded it as sham control and concluded that the observed improvements must be due to placebo, and that HBOT has no therapeutic effect on mTBI patients. In other words, they implicitly assumed that bringing the patients many times to spend long duration in the hyperbaric chamber can trigger such a powerful placebo effect that it can lead to a significant repair of chronic brain damage due to mTBI. Remembering that for mTBI patients (with intact macro vascular bed), breathing 100% oxygen at 2.4ATA generate very high oxygen levels in tissues, which can cause an inhibitory effect or even focal toxicity, it is conceivable that HBOT using 2.4 ATA can be less effective than 1.3 ATA or other lower levels of pressure [86]. Future studies are needed to test this issue by evaluating the specific dose response in post mTBI patients.

A potential way to comply with standard placebo could be to expose the patients to normal pressure combined with falsifying stimulations (e.g., by increasing and decreasing the pressure), which generates a fictitious pressure sensation. This approach poses non trivial logistic difficulties. Some patients, especially in long-term repeated treatments, can detect pressure fluctuations. Another potential way to avoid the increase in tissue oxygen at 1.3Atm in order to attain a standard placebo is to let the patients breath air with lower than normal oxygen level. Obviously, this is an unsuitable approach, as it involves ethical issues and leaves an open question with regards to the pressure effect. Nevertheless, Cifu et al [35] conducted a randomized blinded clinical study in which 2.0 ATA with 10.5% oxygen was used as the sham control. More specifically, the patients were at 2.0 ATA but were randomly assigned to one of three groups breathing either 10.5%, 75% or 100% oxygen to mimic normal air at 1.0 ATA, 100% air at 1.5 ATA and 100% air at 2.0 ATA, respectively. The authors concluded that: "This study demonstrated that HBO2 at either 1.5 or 2.0 ATA equivalent had no effect on post-concussion symptoms after mild traumatic brain injury when compared with sham

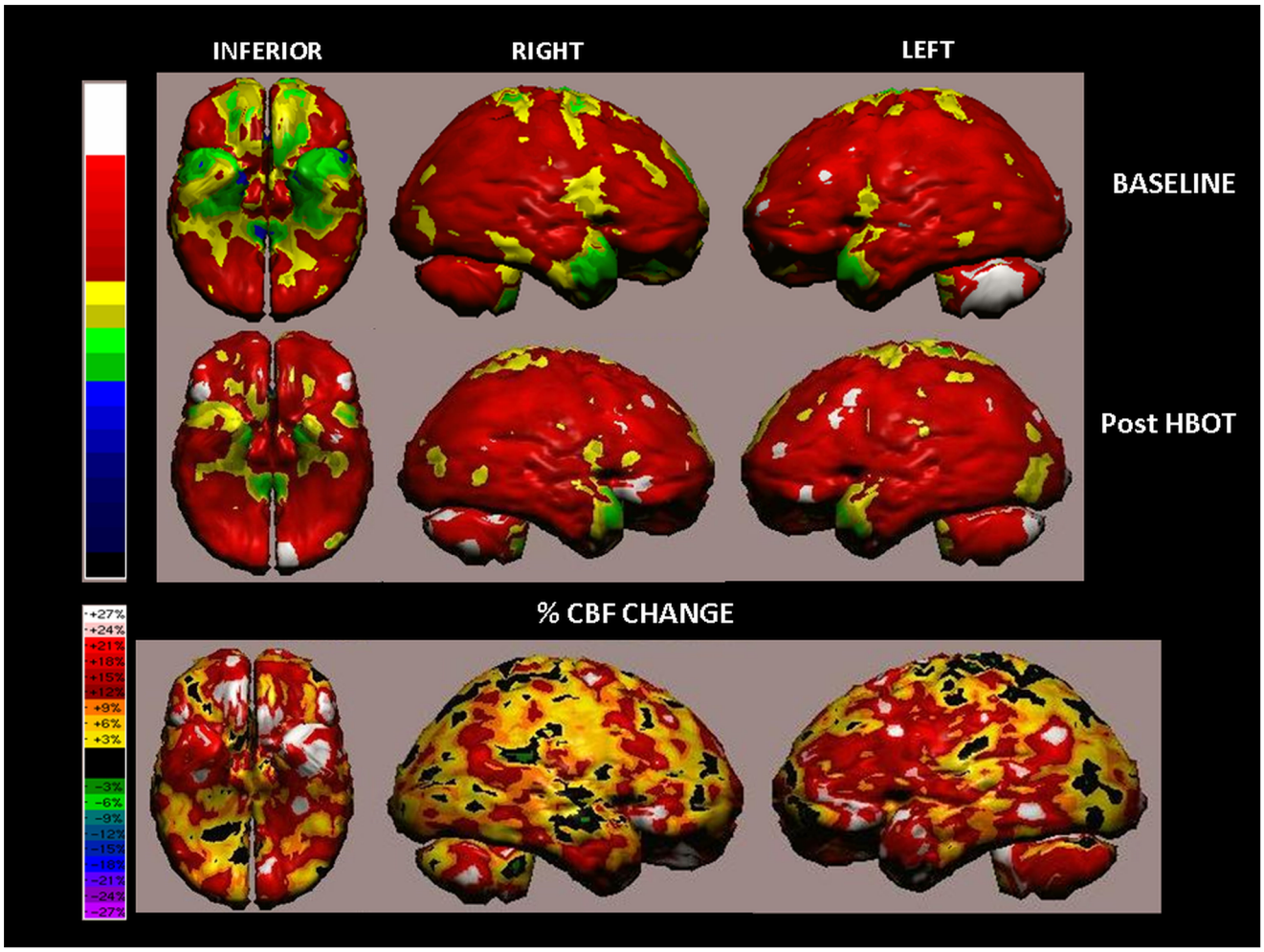

Figure 9. Volume rendered Brain SPECT perfusion maps of Example 2. The results are of a patient in the treated group, suffering mTBI that had occurred 1 year prior to inclusion in the study. Comparison of the baseline activity (upper row) with the post-HBOT activity (middle row) and the CBF changes (bottom row) demonstrated significant improvements after HBOT in bilateral orbito-frontal regions, the medial aspect of the temporal lobes and the temporal poles that correspond to BAs 11, 25, 27, 28 and 38.
doi:10.1371/journal.pone.0079995.g009

compression''. Unfortunately, the HBOT effect in this study was assessed merely based on the self-administered Rivermead Post-Concussion Symptoms Questionnaire (RPQ) which is known to display several flaws in implementation and in its ability to accurately reflect test-taker experience. Moreover, interpretation and accuracy of the RPQ can vary widely due to self-administration and the various confounding variables involved [87]. Put aside this weakness, the study suffers from a logical flaw: The authors mention that their study was motivated by the results of Wolf et al. [36], and they accepted the interpretation that any observed improvements should be a reflection of placebo effect and have nothing to do with the HBOT. If indeed, placebo can be so powerful in mTBI patients, one would expect that stress related to the idea of breathing half the normal level of air may trigger powerful negative placebo effect.

Rationale for the crossover approach

In the current study we tested the effect of 1.5 ATA using the crossover approach. As stated in the introduction, the approach is adopted in order to avoid the inherent difficulties associated with conducting HBOT trial while practicing standard placebo. The crossover approach involves two groups – a treated group in which the patients went through two months of 40 HBOT sessions, and a crossover group in which the patients first went through two month of no treatment followed by two months of HBOT sessions. The advantage of the crossover approach is the triple comparison – between treatments of two groups, between treatment and no treatment of the same group and between treatment and no treatment in different groups (see Text S1). For both groups, the HBOT sessions induced statistically significant improvement in cognitive functions (according to four cognitive indices: Information Processing Speed, Attention, Memory and Executive functions), in brain activity (according to SPECT imaging) and in quality of life (according to the EQ-5D and the EQ-VAS scores), compared to the control period of the crossover group. To gain better validity of the results, we used the scatter plot analysis of the changes of the cognitive indices in terms of the corresponding scaled relative changes. The scatter plots (figure 5) show correlations in the improvements of the different indices both for the group means and the individual patients. The good correspondence between the improvements in the cognitive indices, the quality of life scores and the elevated brain activity as revealed by the SPECT imaging, which was done in a

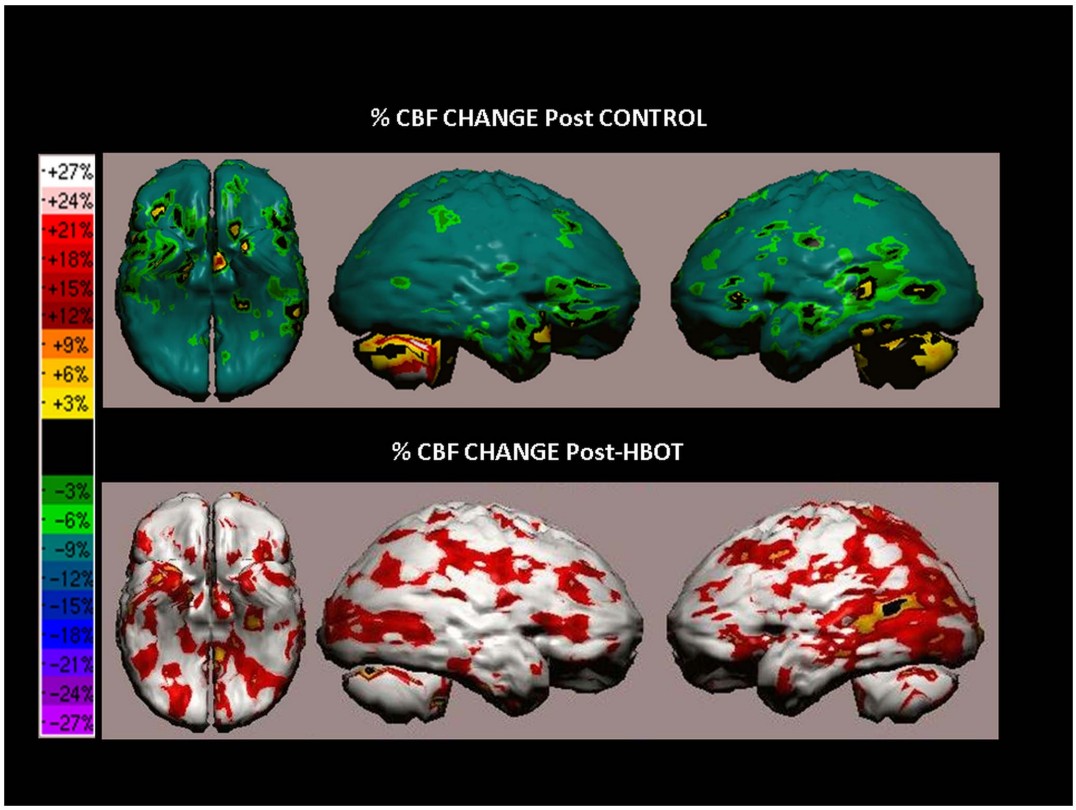

Figure 10. Volume rendered Brain SPECT images representing the percentage of CBF change post control period and post HBOT of the cross group patient described in example 3. As can be clearly seen, the improvement in perfusion following HBOT was significantly high in most areas of the brain as opposed to insignificant change following the control period. The most significant improvements were in both frontal and temporal lobes and right parietal lobe.
doi:10.1371/journal.pone.0079995.g010

completely blinded fashion, further substantiates the clinical findings.

Implications

Combined with previous studies of the HBOT effects on TBI and CVA patients, the results presented here show that treatment with hyperbaric oxygen can significantly repair the chronically impaired brain functions and dramatically improve the quality of life of these patients. Yet, HBOT did not become a common acceptable treatment for TBI and CVA, largely because of the debate regarding the placebo issue and the optimal time for administration. Additional larger scale clinical studies are required to asses if and to what extent placebo effects might be operative. However, since the improvements are significant with no significant side effects, it seems reasonable to let patients benefit from HBOT now rather than wait until future studies are completed.

We foresee that the future oxygen-pressure dose-response studies, described in the discussion section, will have significant therapeutic implications. In particular, we expect that HBOT treatment with room air at 1.3ATA will have significant brain repair effects, and its effect should be compared with the 1.5ATA protocol used in this study.

In the current study, the HBOT effects were assessed shortly after treatment ended. Future follow-up studies are needed in order to investigate the durability of the effect. It might be that some patients will need more than 40 HBOT sessions. The issue of how to optimize patient-specific protocol is important subject for future research.

In conclusion, this study provides, for the first time, convincing results based on a crossover study, demonstrating that HBOT can induce neuroplasticity and significant brain function improvements in mild TBI patients with prolonged Post-Concussion-Syndrome at late chronic stage, years after injury. The results call for better understanding of how to set the optimal HBOT protocol for the specific patients and how to determine which patients benefit the most from this treatment. The findings reported here bear the promises that HBOT can be effective in treating other brain impairments, like easing PTSD symptoms or repairing radiation damage. It is also reasonable to expect that HBOT can help slow down or even reverse metabolic disorders associated neurodegenerative diseases.

Supporting Information

Table S1 SPECT based measurements of changes in brain activity. This SI includes data regarding the SPECT imaging for all the patients (Table S1.1–S1.3). The data was normalized according to Cerebellum activity, and the relative change percentage from baseline was calculated for each subject for each Brodmann area. Average and STD of all subjects were then calculated for each BA. The data is available for all three groups of subjects - control group after waiting period, control group after HBOT (crossover), and treated group after HBOT.

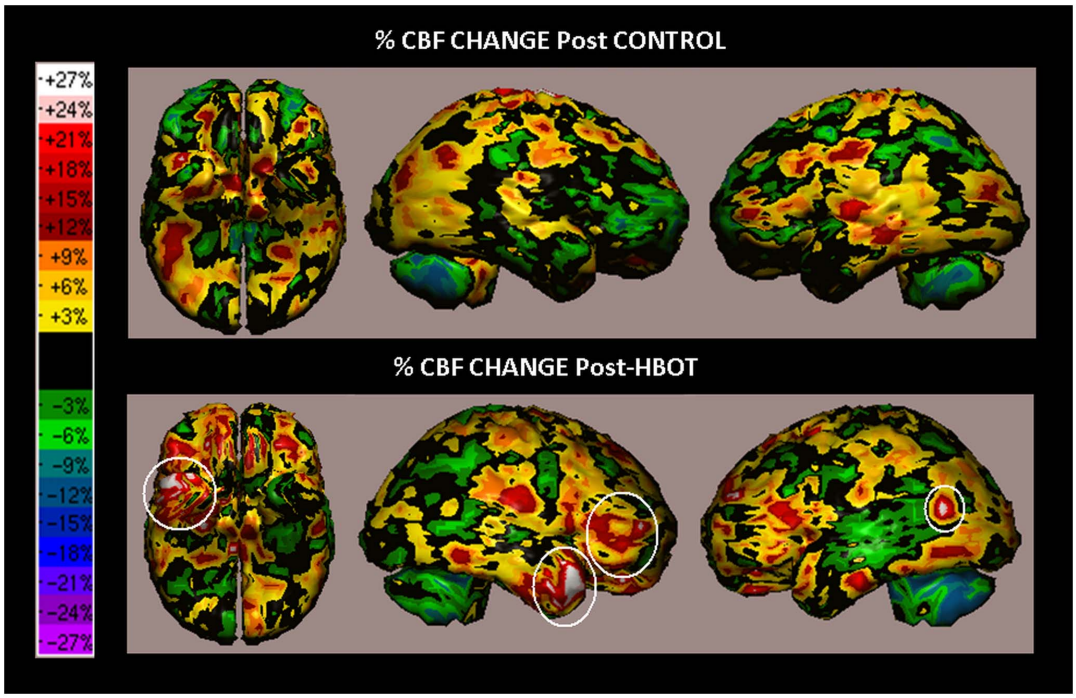

Figure 11. Volume rendered Brain SPECT images representing the CBF change (in percentage) post control period and post HBOT of the cross group patient described in example 4. The overall changes after the control period and the HBOT show normal variations of brain perfusion in the -10% to +10% range (from green to orange colors). However, close inspection reveals localized significant changes (white circles) in the in the right temporal pole and in the right dorso-lateral area. These changes in perfusion are in good agreement with the improvements in the cognitive indices as the SPECT detected changes correspond to Brodmann areas 45–46, 11, 38 and 39.
doi:10.1371/journal.pone.0079995.g011

Doing so ease associating the changes in SPECT measurements of brain activity with the assessed changes in the cognitive indices.
(PDF)

Protocol S1 Clinical study protocol.
(DOCX)

Form S1 Informed consent form (English translation).
(DOCX)

Checklist S1 CONSORT 2010 checklist.
(DOCX)

Text S1 Crossover approach and simulated randomization.
(DOC)

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Author Contributions

Conceived and designed the experiments: RB-G HG SE. Performed the experiments: HG GF YB OV NS. Analyzed the data: RB-G HG JB MF DH EB-J SE. Contributed reagents/materials/analysis tools: HG OV SE. Wrote the paper: RB-G HG EB-J SE.

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Evolution of neuronal and astroglial disruption in the peri-contusional cortex of mice revealed by *in vivo* two-photon imaging

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Summary

In traumatic brain injury mechanical forces applied to the cranium and brain cause irreversible primary neuronal and astroglial damage associated with terminal dendritic beading and spine loss representing acute damage to synaptic circuitry. Oedema develops quickly after trauma, raising intracranial pressure that results in a decrease of blood flow and consequently in cerebral ischaemia, which can cause secondary injury in the peri-contusional cortex. Spreading depolarizations have also been shown to occur after traumatic brain injury in humans and in animal models and are thought to accelerate and exacerbate secondary tissue injury in at-risk cortical territory. Yet, the mechanisms of acute secondary injury to fine synaptic circuitry within the peri-contusional cortex after mild traumatic brain injury remain unknown. A mild focal cortical contusion model in adult mouse sensory-motor cortex was implemented by the controlled cortical impact injury device. *In vivo* two-photon microscopy in the peri-contusional cortex was used to monitor via optical window yellow fluorescent protein expressing neurons, enhanced green fluorescent protein expressing astrocytes and capillary blood flow. Dendritic beading in the peri-contusional cortex developed slowly and the loss of capillary blood flow preceded terminal dendritic injury. Astrocytes were swollen indicating oedema and remained swollen during the next 24 h throughout the imaging session. There were no recurrent spontaneous spreading depolarizations in this mild traumatic brain injury model; however, when spreading depolarizations were repeatedly induced outside the peri-contusional cortex by pressure-injecting KCl, dendrites undergo rapid beading and recovery coinciding with passage of spreading depolarizations, as was confirmed with electrophysiological recordings in the vicinity of imaged dendrites. Yet, accumulating metabolic stress resulting from as few as four rounds of spreading depolarization significantly added to the fraction of beaded dendrites that were incapable to recover during repolarization, thus facilitating terminal injury. In contrast, similarly induced four rounds of spreading depolarization in another set of control healthy mice caused no accumulating dendritic injury as dendrites fully recovered from beading during repolarization.

the acute dendritic injury in the peri-contusional cortex is gated by the decline in the local blood flow, most probably as a result of developing oedema. Furthermore, spreading depolarization is a specific mechanism that could accelerate injury to synaptic circuitry in the metabolically compromised peri-contusional cortex, worsening secondary damage following traumatic brain injury.

Key words acute brain injury dendritic beading astroglial swelling cortical spreading depolarization *in vivo* two-photon microscopy

- Abbreviations

2PLSM
: two-photon laser scanning microscopy

EGFP
: enhanced green fluorescent protein

TBI
: traumatic brain injury

YFP
: yellow fluorescent protein

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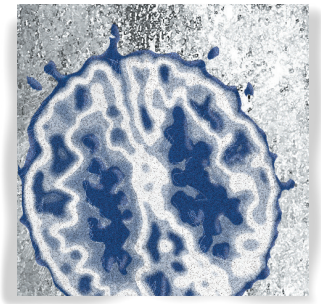
Neurobiological consequences of traumatic brain injury

Thomas W. McAllister, MD



Traumatic brain injury (TBI) is a worldwide public health problem typically caused by contact and inertial forces acting on the brain. Recent attention has also focused on the mechanisms of injury associated with exposure to blast events or explosions. Advances in the understanding of the neuropathophysiology of TBI suggest that these forces initiate an elaborate and complex array of cellular and subcellular events related to alterations in Ca^{++} homeostasis and signaling. Furthermore, there is a fairly predictable profile of brain regions that are impacted by neurotrauma and the related events. This profile of brain damage accurately predicts the acute and chronic sequelae that TBI survivors suffer from, although there is enough variation to suggest that individual differences such as genetic polymorphisms and factors governing resiliency play a role in modulating outcome. This paper reviews our current understanding of the neuropathophysiology of TBI and how this relates to the common clinical presentation of neurobehavioral difficulties seen after an injury.

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Keywords: *neurotrauma; neurobehavior; traumatic brain injury; neuropsychiatry of TBI*

Traumatic brain injury (TBI) may be the brain disorder that best illustrates the perils of the mind/brain dualism and that breaks down the remaining conceptual barriers between the clinical disciplines of neurology and psychiatry. The forces that create neurotrauma typically result in a profile of regional brain dysfunction that maps nicely onto the neuropsychiatric sequelae and functional distress encountered by survivors of such injury. In turn, the effects of living with these neurobehavioral sequelae, the meaning and the significance of being identified as "brain injured" greatly influence the quality of life of the individuals and their caregivers. Failure to appreciate these complex but predictable relationships impedes proper assessment and treatment of the individual with a TBI. This paper reviews the current knowledge of the neurobiological effects of TBI, with special emphasis on how these processes inform the understanding of the clinical presentation and treatment of a person with neurobehavioral complications of neurotrauma.

It is helpful to start with some clarification of the term "traumatic brain injury." A variety of definitions have been put forth by various groups including the American Congress of Rehabilitation Medicine,[1] the Centers for Disease Control, [2] and the World Health Organization.[3] The most recent consensus definition is that proposed by the Demographics and Clinical Assessment Working Group of the International and

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Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health.[4] They posit that TBI is "an alteration in brain function, or other evidence of brain pathology, caused by an external force"[4] (p 1637). As with previous definitions, alteration in brain function can be manifest by loss or decreased level of consciousness, alteration in mental state, incomplete memory for the event, or neurological deficits. Examples of external forces include the head striking or being struck by an object, rapid acceleration or deceleration of the brain, penetration of the brain by a foreign object, and exposure to forces associated with blasts. The external force requirement separates TBI from other acquired brain injuries due to cerebrovascular, neoplastic, or neurodegenerative conditions. Two additional points are worth noting. Most definitions have distinguished *brain* injury from *head* injury, which might be limited to damage to the face or scalp. In addition, most groups have emphasized that sustaining a brain injury at some point in time is different from attributing current symptoms to that event. Many of the symptoms associated with TBI are nonspecific.[5]

Using any of the common definitions, TBI is a global health concern. For example 1 to 2 million Americans are injured each year, with 290 000 hospitalized and over 50 000 dying from their injuries.[6] Other developed regions of the world have roughly similar rates,[7] and although figures are harder to come by in developing nations, it is generally thought that TBI is a significant public health problem in these regions as well.

Many individuals with TBI, particularly those with moderate and severe TBI, are left with significant long-term neurobehavioral sequelae.[8-10] The overarching theme of this article is that there is a clear relationship between these sequelae and the profile of brain injury seen in the typical TBI. Thus it is helpful to understand the forces involved in TBI, the brain regions at particular risk for damage from the forces, and the cascade of neurobiological changes precipitated by these forces in order to make sense of the clinical presentation of individuals with TBI and neurobehavioral difficulties. It is also helpful to distinguish between traumatic injuries involving penetration of the brain substance ("penetrating" injuries) and injuries that do not penetrate the brain (often referred to as "closed" head injuries). The main reasons for drawing this distinction is that the injury profiles can be quite different, and thus the associated neurobehavioral sequelae can be quite different. Broadly speaking, the profile of injury involving penetration of the brain substance will depend on the location and trajectory of the object that is involved, for example the entrance location, trajectory, and size of a bullet that enters the head will largely predict the neurobehavioral sequelae. In these injuries damage typically results from displacement or destruction of brain tissue by the projectile; fragmentation and deposition of bone or a projectile within brain tissue; or introduction of potential infectious material on the projectile.

Nonpenetrating or closed injuries are better understood based on how the typical biomechanical forces involved in causing injury interact with the material properties of the brain substance and its relationship to the bony structure (skull) in which it sits. The following discussion focuses primarily on the latter category of injury (closed or nonpenetrating). However, it is important to note that many injuries, particularly in the modern combat context, can be a combination of these different forces and injury types.

Mechanisms of injury

Contact forces

The biomechanical effects of nonpenetrating injuries may be divided broadly into two types, both of which are applicable across the spectrum of injury severity: contact and inertial. Contact injuries result when the brain, moving inside the skull, strikes the inner surface of skull. Movement of brain against the various ridges and bony protuberances of the anterior (frontal) and middle (temporal) fossae is particularly injurious to the temporal and frontal poles and the ventral anterior, medial, and lateral temporal cortices, and the frontal cortices.[11-14]

Inertial forces

Linear translation and rotational forces, which in combination produce angular acceleration or deceleration, can result in straining, shearing, and compression of brain tissue.[15-22] When these forces exceed the tolerances of brain tissue, injury results. These forces tend to be maximal in brain areas that experience the highest angular acceleration or deceleration forces (superficial > deep and anterior > posterior), at the planes between tissues of different densities and elasticities (eg, the junc-

tion between gray and white matter), and at the rotational center of mass in the intracranial space (rostral brain stem). The effects of high-speed, long-duration acceleration or deceleration injuries are maximal on axonal projections and small blood vessels within and from the brain stem, the parasagittal white matter of the cerebrum, the corpus callosum, the gray-white junctions of the cerebral cortex,[23] and especially at gray-white junctions in the ventral and anterior frontal and temporal lobes.[12] Although this type of inertial injury usually is described as diffuse axonal injury, the term is somewhat misleading in that the actual pattern of injury is more accurately characterized as multifocal.[23]

Cellular response to injury

The above-described forces, whether in and around focal injuries such as contusions, or remote from the focal injury and attributable to inertial forces, a complex set of events is set in motion at the cellular and subcellular level that is only partially understood *(Figure 1)*.[24] Two initiating events related to Ca^{++} homeostasis appear to be of particular importance. First, at the time of injury mechanical perturbation of neurons is associated with a significant release of a host of neurotransmitters. Of particular importance is the release of glutamate and other excitatory amino acids with a resultant influx of extra-

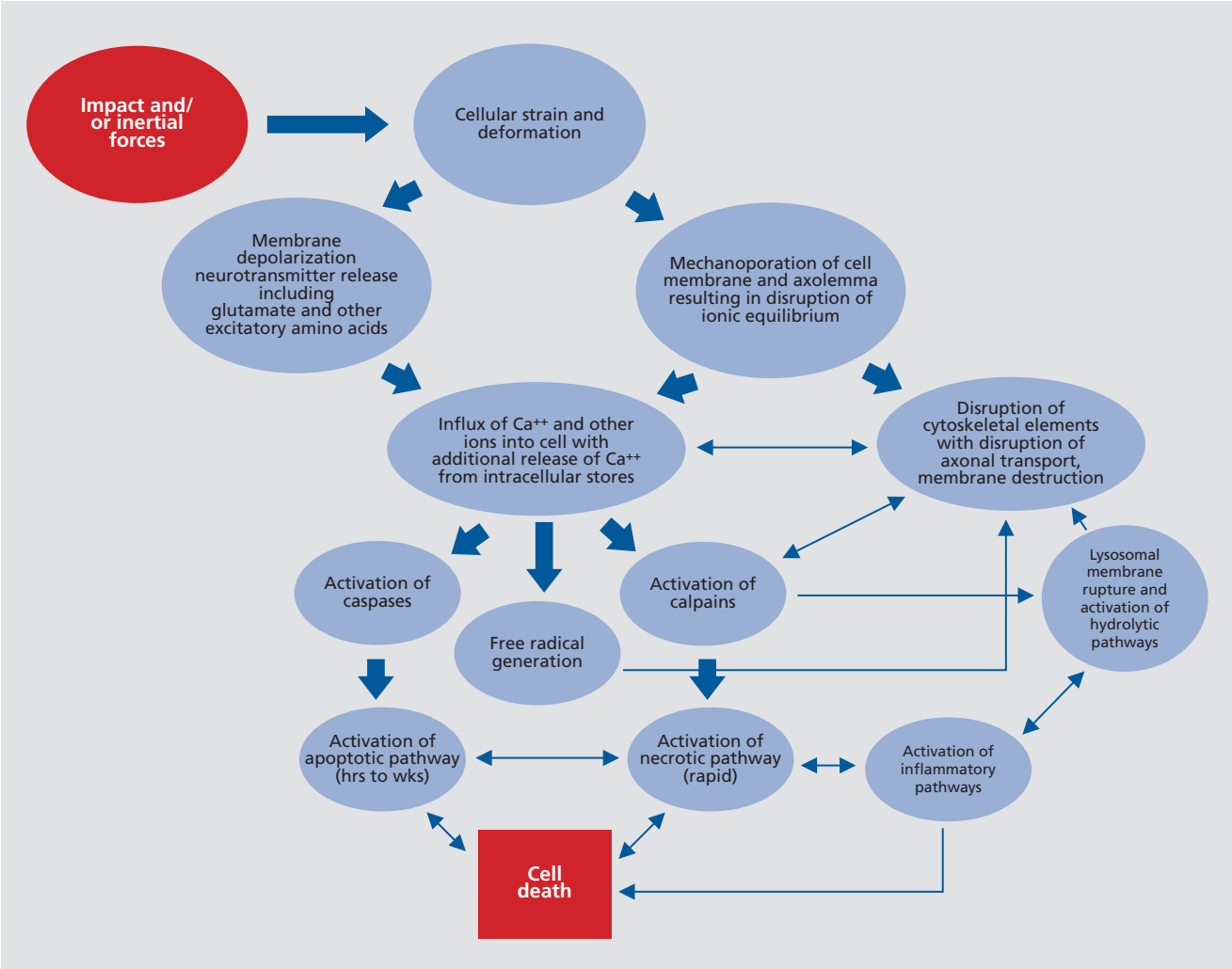

Figure 1. Simplified summary of traumatic brain injury (TBI)-associated cellular injury cascades. Of note is that events are triggered at the time of injury but the full evolution of the process plays out over hours to weeks after injury. For further details see ref 24.

cellular Ca^{++} into the cell. This in turn releases additional Ca^{++} from intracellular stores, thus producing sufficient quantities of free intracellular Ca^{++} to initiate a host of intracellular reactions that can result in cytotoxic injury and eventually cell death. Second, mechanical perturbation of the neuron and its axon can result in mechanoporation of the cell membrane and axolemma with subsequent influx of extracellular Ca^{++} and other ions into the cell and axon. The mechanical distortion of the membrane does not resolve immediately and the ultimate fate of the membrane and the neuron appears related to the degree of distortion and other factors, with some cells repairing and resealing, and others progressing on to further disruption and cell death.

A variety of intracellular events attributable to this altered Ca^{++} homeostasis are set in motion (see refs 24-26). Most emphasis has been on the activation of two groups of cysteine proteases, the caspases and the calpains, and their role in the initiation of necrosis and apoptosis. Both pathways can result in cell death, and there are important linkages between the two mechanisms. However the necrosis pathway occurs rapidly, is a "passive" event related to energy failure and subsequent inability to maintain cellular homeostasis, is more closely associated with the calpain proteases, and triggers an inflammatory response, whereas the apoptotic pathway evolves over hours to weeks after injury, is an active process requiring energy, is more closely associated with the caspase proteases, and is less clearly linked to inflammatory responses. A variety of cytoskeletal elements including neurofilaments and spectrin are primary substrates for the calpains and thus activation of these proteases can lead to disruption of cell transport, destruction of cytoarchitecture and cell membrane elements, disruption of cell transport, and ultimately cell death. The apoptotic pathway evolves over hours to weeks after injury, is an active process requiring energy, is more closely associated with the caspase proteases, and is less clearly linked to inflammatory responses. Primary substrates for the caspases also include cytoskeletal elements as well as the capacity to activate other processes that can be toxic to the cell.[25] Both families of proteases and hence both the necrotic and apoptotic pathways are under complex control of multiple modulators, the ultimate balance of which appear to determine cell survival.[25]

In addition to these processes, there is a growing appreciation for the role of other factors in the cytotoxic cascades such as the generation of free radicals, and the disruption of lysosomal membranes with the subsequent release of hydrolytic enzymes into the intracellular environment.[24] The excessive release of neurotransmitters other than glutamate may also play a role in the elaboration of neurotrauma. For example cholinergic excess may amplify the destructive effects of excitatory amino acid excesses, and may be particularly injurious to brain areas where acetylcholine and excitatory amino acids are densely colocated (ie, hippocampus and frontal cortices).[27] The effects of cerebral monoaminergic excesses in the cytotoxic cascade are not understood fully, although in experimental injury models traumatically induced elevations of cerebral serotonin seem to decrease cerebral glucose use,[28,29] and serotonin agonists are not particularly helpful in improving post-traumatic neurobehavioral status or TBI outcome.[30,31] Administration of catecholamine antagonists impedes recovery from brain injury[32-34] and delay emergence from post-traumatic amnesia in humans,[35] suggesting that blocking catecholamine excesses is not an effective means by which to mitigate the cytotoxic cascade after TBI.

Neurotransmitter excesses seem to wane over the first several weeks after TBI,[36,37] although the time course of their resolution is not characterized fully. TBI in humans produces chronic cerebral cholinergic deficit via injury to ventral forebrain cholinergic nuclei[38,39] and their cortical projections.[39-41] It is possible that TBI also results in primary or secondary disturbances in monoaminergic systems,[42] the effects of which may be amplified by individual genetically mediated variations in catecholamine metabolism.[43]

Role of secondary and systemic complications

In addition to the above primary effects of TBI, a variety of additional factors may complicate an injury including traumatic hematomas (eg, subdural, epidural, subarachnoid, and intraparenchymal hematomas), focal or diffuse cerebral edema, elevated intracranial pressure, obstructive hydrocephalus, hypoxic-ischemic injury, and infection. Because TBI frequently occurs in the context of other injuries (polytrauma) and medical complications such as volume depletion or blood loss, hypoperfusion, hypoxia, infection, and related problems can be seen and may increase post-traumatic mortality and morbidity.[44]

Blast injury

The emergence of explosive devices, particularly "improvised explosive devices" (IEDs), as a primary method of attack in recent conflicts, has called attention to "blast injury." Explosions generate a rapidly moving wave of overheated expanding gases that compress surrounding air. The ongoing expansion of the heated gases eventually results in a drop in pressure, with resulting reversal of the pressure wave. These fluctuations in pressure are associated with strain and shear forces (barotrauma) that can be particularly damaging to air- and fluid-filled organs and cavities.[45] For example the tympanic membrane can be ruptured with approximately a 30% increase in atmospheric pressure and is a useful, though not always reliable, indicator of blast exposure.[46] Blast can also be associated with significant brain injury.[47-51] At this time it is not clear if injury associated with blast is due to the high pressure wave with distortion of vascular tissue, neural tissue or both, the inertial effects of buffeting by the alternating high- and low-pressure events, or some other mechanism. Additional mechanisms often come into play, including impact mechanisms from the head coming into contact with an object or penetrating injuries from fragments and debris (referred to as secondary blast injury), and rapid acceleration or deceleration of the brain causing inertial injury (tertiary injury), and exposure to toxic gas or chemicals as a result of the explosion (quaternary injury).[46]

Animal models suggest that primary blast injury can be associated with neural injury, although the underlying mechanism is not clear.[52] For example Cernak et al[47,50] exposed rats to either whole-body blast or localized pulmonary blast in which the brain was protected from the pressure wave with a steel plate. Both groups of animals showed hippocampal injury with neuronal swelling, cytoplasmic vacuolization, and loss of myelin integrity. These changes were associated with poorer performance on an active avoidance response task learned prior to the injury. This group has postulated that one potential mechanism is transmission of the pressure wave through cerebral vasculature with subsequent injury to perivascular neural tissue, axonal stretching, release of neurotransmitters and precipitation of the usual excitotoxic cascades,[47,50,53] although this is not yet firmly established.

Summary of neuropathophysiology of TBI

Distilling the literature reviewed above, there are several points worth highlighting. The typical profile of injury involves a combination of focal and diffuse injury. Injury occurs at the time of the event (often referred to as "primary injury") and additional damage ("secondary injury") evolves over a variable period of time related to the elaborately choreographed injury cascades that play out at the cellular and subcellular level. Although each injury is necessarily unique, there are certain brain regions that are particularly vulnerable to damage including the frontal cortex and subfrontal white matter, the deeper midline structures including the basal ganglia and diencephalon, the rostral brain stem, and the temporal lobes including the hippocampi. Certain neurotransmitter systems, particularly the catecholaminergic[42] and cholinergic systems,[54] are altered in TBI. Both of these systems play critical roles in a variety of domains important in behavioral homeostasis including arousal, cognition, reward behavior, and mood regulation. This profile of structural injury and neurochemical dysregulation occurs along a spectrum of injury severity, including "mild" injury.[55] The correspondence between the neuropathophysiology of TBI and the common and disabling neurobehavioral sequelae associated with it is now reviewed.

Relationship of neurobiology of TBI to neurobehavioral sequelae of TBI

As noted, there are several high-risk regions vulnerable to the effects of neurotrauma, but it is important to note that these brain regions are important nodal points in frontal-subcortical circuits that subserve cognition and social behavior. In particular, three major frontal-subcortical circuits have significant roles in nonmotor forms of behavior[56] *(Figure 2)*. A circuit arising in the dorsolateral prefrontal cortex modulates executive functions, such as working memory, decision making, problem solving, and mental flexibility. Another, arising from cells in the orbitofrontal cortex, plays a critical role in intuitive reflexive social behaviors and the capacity to self-monitor and self-correct in real time within a social context. A third circuit starting in the anterior cingulate modulates motivated and reward-related behaviors. Although not a frontal subcortical circuit, per se, circuits traversing medial temporal regions play critical roles in episodic memory and new learning, as well as the smooth inte-

gration of emotional memory with current experience and real-time assessment of stimulus salience. Thus, the typical regions vulnerable to damage associated with TBI overlap significantly with key regions and nodal points in these frontal subcortical circuits, making it readily apparent that problems with cognition, social comportment, and executive function, as well as an increased relative risk of specific psychiatric disorders would be common after TBI *(Table I, Figure 3)*.

Changes in cognition

Initial and persistent cognitive deficits are the most common complaints after TBI[57,58] and can present significant challenges to independent living, social readaptation, family life, and return to work.[59,60] Frontal executive functions (problem solving, set shifting, impulse control, self-monitoring), attention, short-term memory and learning, speed of information processing, and speech and language functions are the cognitive domains typically impaired.[61-67] Injury to medial temporal regions, the dorsolateral prefrontal cortex, and subcortical white matter connecting these regions readily account for these difficulties.

Changes in personality

The term "personality change" is often used by survivors and family/caregivers to describe alterations in emotional and behavioral regulation after brain injury. In some individuals, this presents as exaggeration of preinjury traits (eg, irritability). It is important in this context to ask about changes in the frequency and/or intensity of behaviors or traits that may have been present before the injury took place. Alternatively, these behaviors can present as fundamental changes in response patterns. Several common clusters of symptoms that characterize the "personality changes" are recognizable.

Impulsivity

This may be manifest in verbal utterances, physical actions, snap decisions, and poor judgment flowing from

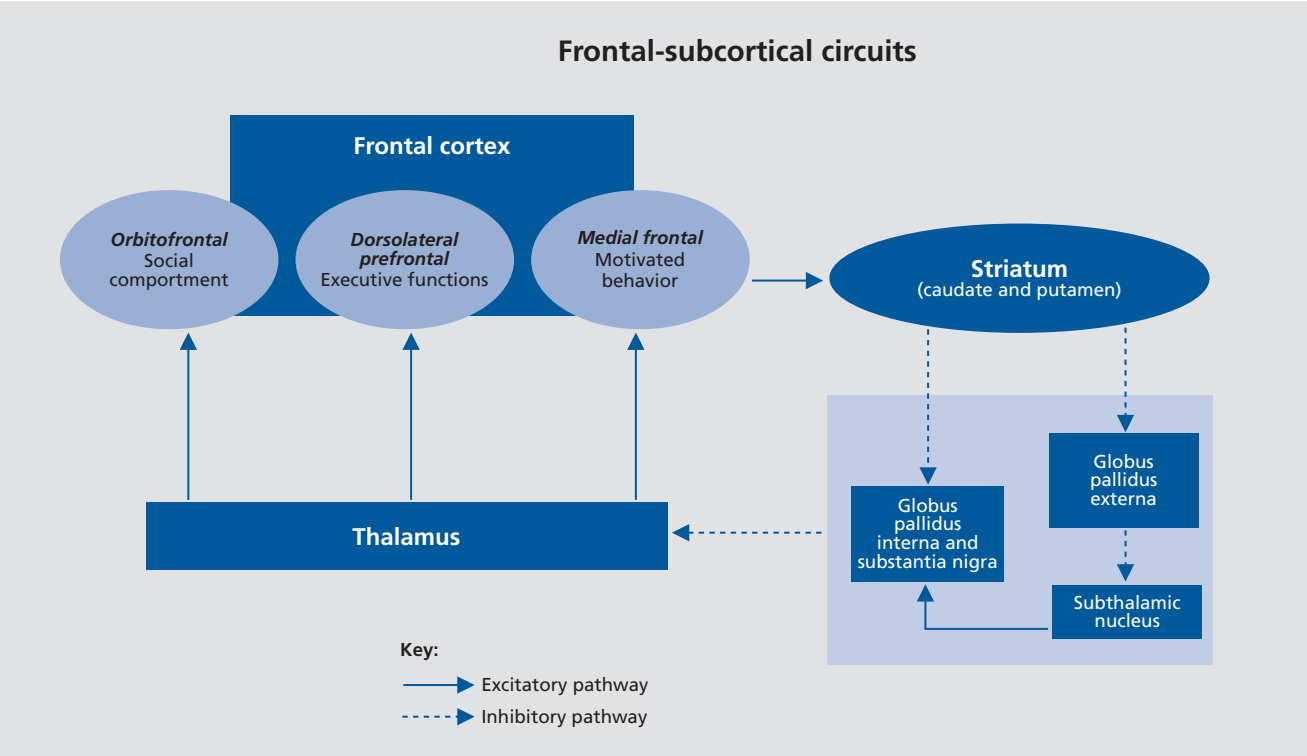

Figure 2. Outline of frontal subcortical circuits relevant to common neurobehavioral sequelae of traumatic brain injury (TBI).
Adapted from ref 111: Arciniegas DB, Beresford TP. *Neuropsychiatry: an Introductory Approach*. Cambridge, UK: Cambridge University Press; 2001:58.

the failure to fully consider the implications of a given action. This is closely related to the concept of stimulus boundedness, in which the individual responds to the most salient cue in the environment or attaches exaggerated salience to a particular cue, without regard to previously determined foci of attention or priorities, a syndrome commonly seen in individuals with frontal cortical damage or degeneration from a variety of disorders.

Irritability

Survivors are often described as more irritable or more easily angered. Responses can range from verbal outbursts to aggressive and assaultive behavior. Although a particular cue might be perceived as a legitimate aggravation, the response is characteristically out of proportion to the precipitating stimulus. This modulatory deficit differs in intensity, onset, and duration from the pre-injury pattern for many individuals. This behavioral disinhibition is most likely attributable to damage to orbital frontal regions and white matter connections along the orbitofrontal subcortical circuitry of social comportment.

Affective instability

Survivors and family/caregivers frequently describe exaggerated displays of emotional expression, out of proportion to the precipitating stimulus and the preinjury range of responses. Additional characteristics include a paroxysmal onset, brief duration, and subsequent remorse. This phenomenon occurs in other central nervous system disorders and has been called pathological affect, affective lability, pseudobulbar affect, and affective incontinence,[61] and is most likely related to disruption of "top-down" modulation of limbic responses to emotional stimuli by frontal cortex.[68]

Neurobehavioral sequelae	Predominant brain regions involved	Predominant neurotransmitter systems involved	Comment
Cognitive deficits			
Working memory	Dorsolateral prefrontal, parietal, and cerebellar cortices; subcortical white matter	Dopamine, norepinephrine, ?acetylcholine	Overlaps with attentional deficits
Short-term memory	Frontal and hippocampal cortices	acetylcholine	Remote memory typically intact
Attention	Frontal, cingulate and parietal cortices, subcortical white matter, reticular activating system	Dopamine, norepinephrine, acetylcholine	"Top-down" processing may be impaired in TBI of all severities, "bottom-up" (arousal) more often in severe TBI
Processing speed	Subcortical white matter tracts	Catecholamines, acetylcholine	Underlies complaints of "slowed thinking"
Dysexecutive syndromes			
Disinhibition/social comportment	Orbitofrontal subcortical circuit	Complex interaction of GABA, catecholamines, serotonin and others	Emotional responses including anger out of proportion to precipitant
Cognitive dysexecutive	Dorsolateral prefrontal cortex	Interaction of GABA, catecholamines, and others	Overlaps with cognitive deficits described above
Disorders of motivated behavior	Medial frontal cortex, anterior cingulate, related reward circuitry	Dopamine, norepinephrine	Often presents as apathy and can be confused with depression
Psychiatric disorders			
Depression	?left anterior frontal cortex, temporo-limbic circuitry	? dopamine, norepinephrine, serotonin	Associated with poor short and long-term outcome.
Substance abuse	Components of reward circuitry (nucleus accumbens, frontal cortex)	Dopamine, norepinephrine, opiod system?	Often present before injury but can arise *de novo*
PTSD	Medial and orbitofrontal cortices, amygdala, hippocampus	? serotonin, norepinephrine, dopamine	Cognitive deficits increase risk of PTSD

Table I. Neural substrates of common sequelae of TBI. TBI, traumatic brain injury; PTSD; post-traumatic stress disorder; GABA, γ-aminobutyric acid

Apathy

Disorders of motivated behavior can be of concern to family members and can be a barrier to progress in rehabilitation programs. It is often misinterpreted as laziness or depression and may be linked to aggression when attempts to engage the individual in activities in which they have little interest can precipitate assaultive behavior.[69] Kant et al[70] found that apathy (mixed with depression) occurred in 60% of their sample. Andersson et al[71] found that almost half of their individuals with TBI had significant degrees of apathy. Deficits in motivated behavior can occur in association with injury to the circuitry of "reward." [69,72] Key nodal points in this circuitry include the amygdala, hippocampus, caudate, entorhinal and cingulate cortices, the ventral tegmental area, and the medial forebrain bundle. Catecholaminergic systems, particularly the mesolimbic dopaminergic system, appear to play critical roles in the modulation of the reward system.[66,73]

Lack of awareness of deficits

The personality changes described above are often more difficult to address because the injured individual may be unable to appreciate that his or her behavior is different after the injury.[62,74] Of interest is that individuals with TBI are less likely to be aware of changes in behavior and executive function than changes in more concrete domains, such as motor function.[67] Furthermore,

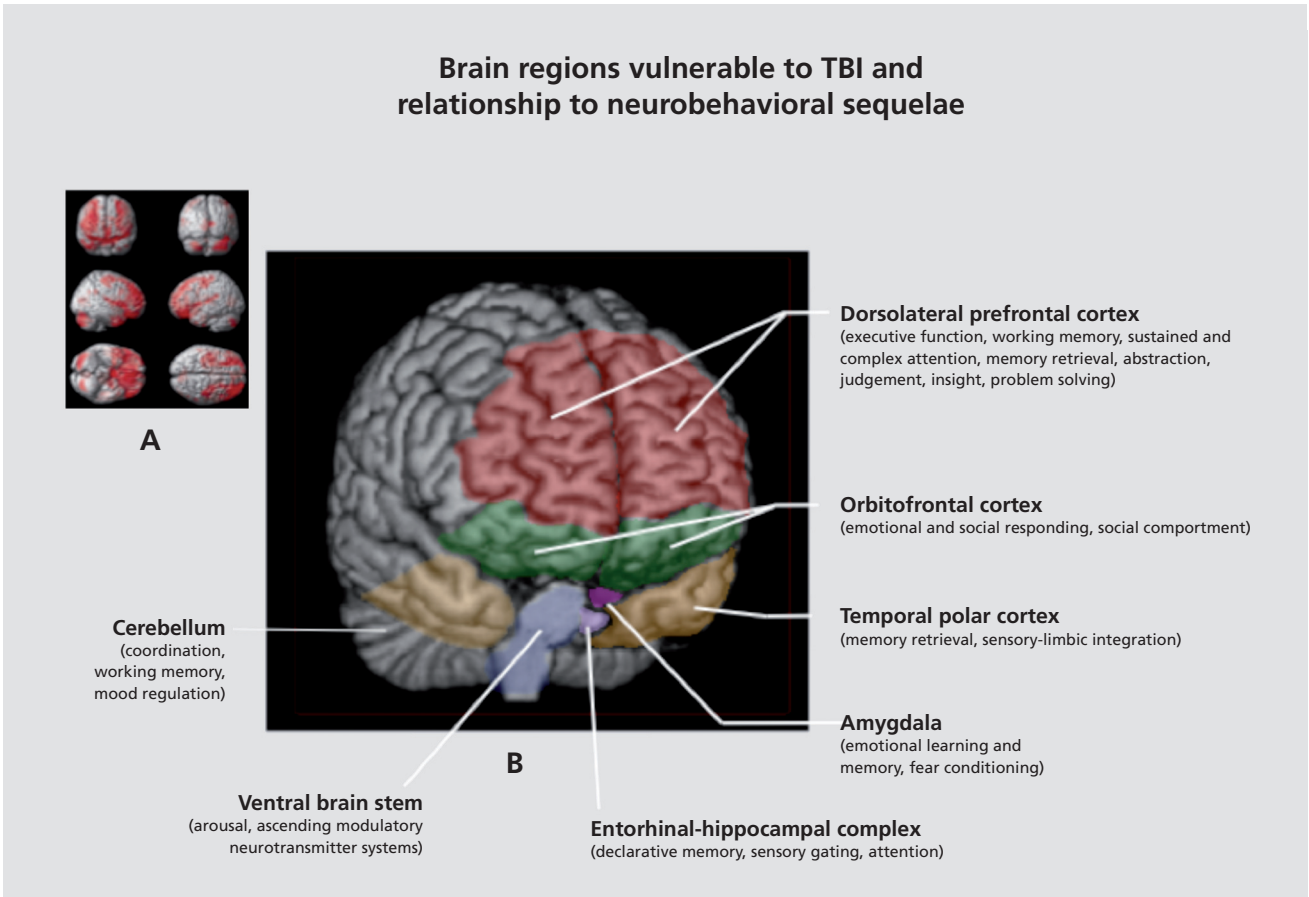

Figure 3. (A) Brain regions vulnerable to damage in a typical traumatic brain injury (TBI); (B) Relationship of vulnerable brain regions to common neurobehavioral sequelae associated with TBI.
(A) Adapted from ref 112: Bigler E. Structural imaging In: Silver J, McAllister T, Yudofsky S, eds. *Textbook of Traumatic Brain Injury*. Washington DC: American Psychiatric Press; 2005:87. Copyright © American Psychiatric Press, 2005. (B) Adapted from ref 111: Arciniegas DB, Beresford TP. *Neuropsychiatry: an Introductory Approach*. Cambridge, UK: Cambridge University Press; 2001:58. Copyright © Cambridge University Press, 2001

the degree of awareness has been found to correlate with functional and vocational outcome in many,[75-78] although not all,[79] studies.

Relationship of TBI to psychiatric disorders

In addition to the changes in cognition, behavior, and personality described above, a significant body of evidence suggests that TBI results in an increased risk of developing psychiatric disorders, including mood and anxiety disorders,[80] sleep disorders,[81] substance abuse, and psychotic syndromes.[82-85] For example, Kopenen et al[85] studied 60 individuals 30 years after their TBI and found that almost half (48%) developed a new Axis I psychiatric disorder[86] after their injury. The most common diagnoses were depression, substance abuse, and anxiety disorders. In individuals with a TBI, rates of lifetime and current depression (26%; 10%), panic disorder (8%; 6%), and psychotic disorders (8%; 8%), were significantly higher than base rates found in the Epidemiologic Catchment Area (ECA) study.[87] Hibbard et al[83] studied 100 adults on average 8 years after TBI. A significant number of individuals had Axis I disorders before injury. After TBI, the most frequent diagnoses were major depression and anxiety disorders (ie, posttraumatic stress disorder [PTSD], obsessive-compulsive disorder, and panic disorder). Almost half (44%) of individuals had two or more disorders. More recently, this group reported a longitudinal study of 188 individuals enrolled within 4 years of injury and assessed at yearly intervals on at least two occasions.[88] Once again, they found elevated rates of psychiatric disorders (depression and substance abuse) before injury and increased rates of depression, PTSD, and other anxiety disorders subsequent to injury. This was particularly true of those with preinjury psychiatric disorders. Furthermore, the rates were greatest at the initial assessment point after injury and stabilized or decreased over time. Others have also reported increased indicators of psychiatric illness after TBI and increased medical costs associated with those indicators.[89,90] More recently, Bryant et al[91] have shown that there are high rates of psychiatric illness in individuals hospitalized with traumatic injury of any sort (including mild TBI) 12 months after the event (31%). Twenty-two percent suffered psychiatric disorders that they had never had before. Having a mild TBI was associated with higher rates of PTSD and other anxiety disorders. The combination of mild TBI and psychiatric illness was associated with greater degrees of functional impairment. Whelan-Goodinson et al[92] also found a strong relationship between post-TBI depression, anxiety, and outcome. Furthermore, as with any potentially disabling condition, individuals with TBI report a variety of symptoms in different domains (discouragement, frustration, fatigue, anxiety, etc). Not all of these symptoms will rise to the level of a disorder. However, constellations of symptoms that are consistent and sustained over time (usually weeks), and that are of sufficient severity to interfere with social or occupational function or quality of life, are legitimately considered disorders. The consistent observation that individuals who sustain a TBI have higher base rates of psychopathology before injury also suggests that there is a reciprocal interaction: psychopathology predisposes to TBI, and TBI in turn predisposes the individual to develop psychiatric disorders. Although the link between TBI and psychiatric disorders holds for many conditions, the relationship of TBI to PTSD and dementia are worth additional comment.

Relationship to PTSD

Recent conflicts in Iraq and Afghanistan have focused attention on the relationship between psychological and biomechanical trauma particularly in military populations (eg, see refs 93-95). Several recent studies highlight their complex interaction. Hoge et al[96] found that higher rates of Iraq war returnees reporting a TBI with loss of consciousness met criteria for PTSD, relative to those reporting only altered mental status, other injuries, and or no injury. Much of the variance across these groups with respect to physical health outcomes and symptoms could be accounted for by the presence of PTSD and/or depression. It is important to point out that participants were assessed 3 to 4 months after deployment and thus reflect individuals with persistent symptoms. Schneiderman et al[97] found that combat-incurred mild TBI approximately doubled the risk for PTSD and that a PTSD diagnosis was the strongest factor associated with persistent post-concussive symptoms. Belanger et al[98] studied patients with mild and moderate-to-severe TBI and found, as expected, that mild TBI was associated with higher levels of postconcussion complaints approximately 2 years after injury. However, after adjusting for PTSD symptoms, these between-group differences were no longer significant. These studies are

consistent with the literature cited above that suggests that mild TBI may increase the relative risk for psychiatric disorders, and that these disorders can interfere with recovery from the TBI.

There is reason to believe that part of the explanation for the complex interaction between biomechanical and psychological trauma relates to overlap in the neural substrates of both conditions (see refs 93-95,99 for discussion). For example mesial temporal structures are vulnerable in TBI from both contact/impact forces, as well as increased sensitivity to excitotoxic injury. Hippocampal and amygdala injury are common. Both of these regions play key roles in PTSD as well, both in terms of contextual memory consolidation and fear conditioning. The hippocampus is also felt to be vulnerable to the effects of chronic stress presumably through the mediating effects of the HPA axis. Thus biomechanical and neurochemically mediated damage could conceivably interact with neurohumoral dysregulation to create a milieu that lends itself to the development of PTSD. Orbitofrontal cortex is also vulnerable to TBI through impact forces as well as frontal subcortical axonal injury.

Relationship to dementia

Several studies have raised a concern about the relationship of TBI to progressive dementia.[100] For example, TBI-associated disruption of axonal transport results in the rapid accumulation of amyloid precursor protein (APP) in animals[100,101] and humans.[102,103] APP, A-beta, and other proteins associated with Alzheimer's disease and other neurodegenerative disorders accumulate rapidly after a TBI.[104-106] Some (but not all) autopsy studies have shown increased amyloid plaques and neurofibrillary tangles in individuals with TBI.[106,107] This variation has prompted exploration of the role of genetic factors in modulating risk for Alzheimer's disease after TBI. For example, Mayeux et al[108] retrospectively studied 113 older adults with AD, comparing them with a control group of 123 healthy older individuals. They found that the combination of APOE-e4 and history of TBI increased the risk of AD by a factor of 10. However, not all studies have found such a relationship. A large, prospective population-based study of 6645 individuals 55 years and older and free of dementia at baseline found that mild brain trauma was not a major risk factor for the development of AD. Moreover, brain trauma did not appear to increase the risk of developing AD in people carrying the APOE-e4 allele.[109] One possibility is that diminished cognitive reserve associated with TBI facilitates earlier manifestation of dementia symptoms in individuals already at risk for AD.[110] Therefore, although there are some compelling scientific reasons to consider the relationship of TBI to Alzheimer's disease and other neurodegenerative disorders, and some strong evidence suggesting clinical associations, the relationship between TBI and dementia needs further study.

Although the relationships between profile of injury and neurobehavioral sequelae are generally seen, there is a surprising amount of variance in long-term outcome after TBI. Some individuals with apparently severe injuries have remarkably good functional outcomes, whereas some individuals with injuries that judged "mild" at the time of the event suffer longstanding significant disability. A full discussion of the factors involved in outcome variance is beyond the scope of this paper; however, such observations have raised the question of whether individual differences, for example, polymorphisms in genes that modulate response to neurotrauma (for instance at key points in the excitotoxic injury cascades), efficiency and extent of neural repair and plasticity, or baseline cognitive and behavioral functions might play a role in modulating outcome after TBI. Although this field is relatively new, several promising candidate polymorphic alleles in genes such as *APOE*, *BDNF*, *DRD2/ANKK1*, and others, suggest that this is in fact the case (see ref 86 for recent review) and may prove a fruitful line of inquiry.

Conclusions

TBI is a significant public health problem both because of the high incidence of injury events and because of the high prevalence of chronic neuropsychiatric sequelae that can devastate the lives of survivors and their family caregivers. Related to the common mechanisms of injury such as motor vehicle crashes, falls, and assaults, there are two broad types of force that results in neurotrauma—contact and inertial. Both of these forces are associated with damage to predictable brain regions and both are also associated with damage that occurs at the time of the event and that precipitates a complex set of potentially excitotoxic cascades that evolves in the minutes to days after the event. In addition to these factors, other event-related processes such as hemorrhage, cerebral edema, and cerebral anoxia may further complicate

the injury profile. Blast injury is an incompletely understood event that may have additional neuropathological processes, further complicated by the fact that inertial and contact mechanisms are also typically involved in explosion-related injuries.

Related to the profile of brain damage associated with these forces and related events, there is an equally predictable profile of neurobehavioral sequelae that survivors of brain injury often suffer from including cognitive deficits (memory, attention, executive function, speed of information processing), personality changes (best characterized as dysexecutive syndromes involving social comportment, cognition, and motivated behavior), and increased relative rates of psychiatric disorders, particularly depression, anxiety, and PTSD both in civilian and military populations. Our understanding of the neuropathophysiology of TBI has outpaced advances in our ability to mitigate and treat the effects of neurotrauma both acutely (eg, neuroprotection trials) and chronically. Furthermore, although the patterns described are the norm, there are surprising variations in outcome that suggest that individual factors such as genetic differences and factors modulating resiliency are worthy of much more study. ❑

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Consecuencias neurobiológicas del daño cerebral traumático

El daño cerebral traumático (DCT) es un problema de salud pública mundial causado característicamente por fuerzas de contacto o de inercia que actúan sobre el cerebro. La preocupación reciente se ha centrado en los mecanismos de daño asociado con la exposición al efecto de ráfagas o explosiones. Los avances en la comprensión de la neurofisiopatología del DCT sugieren que estas fuerzas inician y producen una serie compleja de acontecimientos celulares y subcelulares relacionados con alteraciones en la homeostasis y mecanismos de señales del Ca^{++}. Además, hay un perfil bastante predecible de regiones cerebrales que son afectadas por el neurotrauma y los acontecimientos relacionados. Este perfil de daño cerebral predice con precisión las secuelas agudas y crónicas que sufren los supervivientes de un DCT, aunque existe bastante variación que sugiere que las diferencias individuales -como los polimorfismos genéticos y los factores que regulan la resiliencia- tienen un papel en la modulación de los resultados. Este artículo revisa la comprensión actual de la neurofisiopatología del DCT y cómo se relaciona ésta con la presentación clínica habitual de las dificultades neuroconductuales que se observan después de una lesión.

Conséquences neurobiologiques d'une lésion cérébrale traumatique

La lésion cérébrale traumatique (LCT), problème de santé publique mondial, est provoquée par un contact et des forces d'inertie agissant sur le cerveau. Récemment, l'intérêt s'est porté aussi sur les mécanismes des lésions associées aux explosions ou aux phénomènes de souffle. Les avancées dans la compréhension de la neurophysiopathologie de la LCT laissent supposer que ces forces sont à l'origine d'une série élaborée et complexe d'événements cellulaires et sous-cellulaires liés aux altérations de l'homéostasie et du signal calciques. De plus, le profil des régions cérébrales touchées par les neurotraumatismes et les événements liés est assez prévisible. Le profil de la lésion cérébrale prédit précisément les séquelles aiguës et chroniques des survivants aux LCT, les variations étant néanmoins suffisantes pour suggérer que des différences individuelles (polymorphismes génétiques et facteurs de résilience) jouent un rôle dans la modulation de l'évolution. Cet article fait une mise au point sur notre compréhension actuelle de la neurophysiopathologie de la LCT et sur la façon dont on peut la rattacher aux problèmes neurocomportementaux observés après une lésion.

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Health Issues

Sleep Apnea

Overview and Facts

Sleep apnea, a disruption of breathing while asleep, is a deceiving sleep disorder - 90% of people who have sleep apnea don't know that they have it! Although episodes of choking or gasping for air might occur hundreds of times throughout the night, you may not have any recollection of struggling for breath.

Usually it is the bed partner who first notices that the person is struggling to breathe. If left untreated, this common disorder can be life-threatening.

What happens when you have an episode of sleep apnea?

When you stop breathing during sleep due to sleep apnea, the balance of oxygen and carbon dioxide in the blood is upset. This imbalance stimulates the brain to restart the breathing process. The brain signals you to wake up so that the muscles of the tongue and throat can increase the size of the airway. Then, carbon dioxide can escape, and oxygen can enter the airway. These waking episodes are necessary to restart breathing (and to save your life), and you may not remember them, but they do disrupt your sleep and cause daytime exhaustion.

Obstructive Sleep Apnea (OSA)

OSA is the most common type of sleep apnea. It is caused by a breathing obstruction, which stops the air flow in the nose and mouth. The rest of this article discusses the causes, symptoms and treatments for OSA.

Central Sleep Apnea (CSA)

Central sleep apnea (CSA), less common than OSA, is a central nervous system disorder that occurs when the brain signal telling the body to breathe is delayed. CSA can be caused by disease or injury involving the brainstem, such as a stroke, a brain tumor, a viral brain infection, or a chronic respiratory disease. People with CSA seldom snore. However, while the causes of apnea are different in CSA and OSA, the symptoms and results are much the same – a deprivation of oxygen and poor sleep. The treatments for CSA include medications that stimulate the need to breathe and administration of oxygen.

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SEPTEMBER 21, 2004 4:01 PM POSTED BY

Chiari malformation (4)

Questions & Comments 21

Today will be my fourth and final post on Chiari malformation.

While it is generally believed that Chiari malformation occurs at birth, recent scientific research has shown that this condition, which may be asymptomatic, can become symptomatic due to trauma. Also, there is a body of literature that recognizes that Chiari malformation may become acquired as opposed to congenital.

The leading study on the effects of trauma and Chiari malformation was published by Thomas H. Milhorat, M.D. et al in a study of 364 symptomatic patients.3 In this study, 364 symptomatic patients were evaluated (275 female and 89 male). The study found that Chiari malformation I is a disorder of the para-axial mesoderm that is characterized by underdevelopment of the posterior cranial fossa and overcrowding of the normally developed hindbrain. Clinical manifestations of Chiari malformation I were related to cerebrospinal fluid disturbances which were responsible for headaches, pseudo tumor-like episodes, endolymphatic hydrops, syringomyelia, hydrocephalus and direct compression of nervous tissue.

In this study, 25 percent of the patients cited trauma as the precipitating factor. The most common mechanisms were whiplash injuries and direct blows to the head and neck, which raised the possibility that certain types of trauma accentuate tonsillar impaction or result in subarachanoid hemorrhage that destabilizes a marginally compensated CSF system.

Dr. Milhorat and his colleagues can be located at North Shore University Hospital in Manhasset, New York.

This study is increasingly important as patients with traumatically symptomatic Chiari I malformation have found it exceedingly difficult to obtain reimbursement from their automobile insurance

companies and find it difficult, in attempting to obtain compensation, to convince adjusters, judges and juries that a specific traumatic event was the cause of their symptomtology.

Giving weight to the argument that Chiari malformation may be acquired as well as simply congenital are various published studies. The reader is directed to the following published articles:

1. J Neurosurg 1995 Sep;83(3):556-558 Acquired Chiari malformation and syrin associated with bilateral chronic subdural hematoma. Case report. Morioka T, Sho Nishio S, Yoshida K, Hasuo K, Fukui M. Department of Neurosurgery, Kyushu University, Fukuoka, Japan.

2. J Neurosurg 1998 Feb;88(2):237-242 Acquired Chiari I malformation secondary to spontaneous spinal cerebrospinal fluid leakage and chronic intracranial hypotension syndrome in seven cases. Atkinson JL, Weinshenker BG, Miller GM, Piepgras DG, Mokri B. Department of Neurological Surgery, Mayo Clinic, Rochestert, Minnesota 55905.

3. Pediatr Neurosurg 1995;22(5):251-254 Acquired Chiari-I malformation and hydromyelia secondary to a giant craniopharyngio. Lee M, Rezai AR, Wisoff JH. Division of Pediatric Neurosurgery, New York University Medical Center, NY 10016.

4. "Acquired" Chiari I malformation. Case report. Huang PP, Constantini S. Department of Neurosurgery, New York University Medical Center, New York.

5. Acta Neurochir (Wien) 1998;140(5):417-27; discussion 427-8. The acquired Chiari malformation and syringomyelia following spinal CSF drainage: a incidence and management. Johnston I, Jacobson E, Besser M. Department of Neurosurgery, New Children's Hospital, Australia.

6. A Case of a Temporary ACM/Syrinx, 28 year old female with a car accident head injury - when the injury healed the ACM/syrinx disappeared. Source - W.C. Clivero and D.H. Dinh, Neurology, v.30, #5, 758 (1992).4

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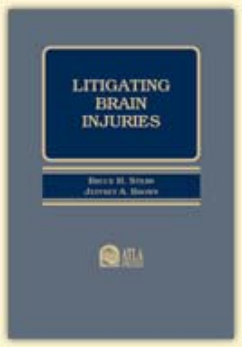
Written By: Mrs. Scott



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BioEthics & Law

On November 1, 2004 6:33 PM

I was in an auto accident in Sept.1998. I have had nothing but problems since. I just recently found out that I may have Chiari Malformation. My life has been a downhill battle since the accident. Pain constantly, diagnosis of fybromyalgia and chronic pain syndrome. I have syringomyelia from my T5-T10 area w/widening at T7. I know the problems I've been having were caused from that accident. The attorneys that represented me only got me $10,000 and that was including my totalled car. 1 yr. after my settlement I had surgery for a herniated disc in my L4-5. I found out that I had a $300,000. underinsured policy on my auto insurance yet the attorney told me to settle because I wasn't going to get any more money as the driver of the vehicle that hit me only had a $25,000. policy and with my medical bills and what they're fee was I should take what they were offering. Unfortunatly the chiropractor I was seeing at the time released me saying there was nothing more they could do for me. I knew there was still something wrong. It took 9 doctors and 3 yrs. of walking around in severe pain to find out about the disc. It has now been 6 yrs. since the accident and 3yrs. since my disc surgery. I have had to quit my job of 4 yrs. with the college and am on long term disability fighting my SS disability. I really feel I got screwed royally and am afraid theres nothing I can do about it now. I called the attorney after my surgery and they never returned my calls. Is there any recourse for me, I have suffered so much. Please e-mail me at - - - - -.

Written By: Bruce H. Stern
On November 3, 2004 6:31 PM

Mrs. Scott - Thank you for your comment. I have emailed you as requested and await your response. I look forward to speaking with you soon.

Written By: Cathy Babcock
On January 26, 2005 3:16 PM

Our daughter became ill after an MMR immunization. Six years later, she was ultimately diagnosed with Chiari Malformation, with a large Syringomyelia cyst within the spinal cord. She had brain surgery in 2000. Her neurosurgeon testified that the Chiari and Syrinx was aggravated by encephalitis following immunization.

Brain Ethics

Beyond Structured Settlements

Illinois Trial Practice Weblog (Evan Schaeffer)

Brain Blog (Anthony Risser)

We filed Vaccine Injury Compensation Fund claim in 1998, which we won in 2001. The first portion of the case is entitlement; the second portion is damages.

The Department of Justice hired psych doctors to pose the claim that it is Somatoform. The Judge appears to believe that she has somatoform, despite the fact she has a serious spinal cord injury.

We need someone who understands spinal cord injury, proof of damages, psychological aspect, etc. The lawyer with whom we've worked understands the Vaccine Injury Compensation Fund and procedures for that system. However, we really are lacking in our argument of damages, and I wonder about the benefit of hiring a lawyer who understands spinal cord injury.

Please advise your thoughts on this matter. Thank you very much.

Written By: Stephen Reese
On February 14, 2005 2:44 AM

Hi! My wife (Janice) was a passenger in a car that was t-boned where she was sitting (July 4th 2004). Since the car accident Janice's neurosurgeon has diagnosed her with ACM based on her10/21&22/2004 MRI's and her many associated symptoms. Janice had an MRI of the brain on October 10th 2001 that Stated, "Tonsils are in satisfactory position" and "IMPRESSION: MRI of brain is normal". The reason Janice had the earlier MRI was because her job at that time (Visual Therapist) strained her eyes and caused her to have headaches in her forehead. Shortly after she quit her job the headaches went away. Isn't possible/probable many of ACM's were caused from trauma not congenitally they just didn't have a prior MRI (like Janice) to prove it?
The Insurance companies want the congenital link to reduce there liability.
Janice's insurance agency picked Neursurgeon has yet to directly tell her she has ACM. We found out his (Neurosurgeon) diagnosis and why from his correspondence with Janice's Psychiatrist. We ordered the Psychiatrist to give us copies of Janice's record, after we found out that our insurance assigned caseworker was telling all the different Dr.'s Janice's was seeing that there was no need to send copies to her primary care physician. We went and got copies from Janice's primary care physician and he didn't have any information from the Neurosurgeon, Neuropsychologist, Vascular, or Psychiatrist. We also found out that the Neurosurgeon didn't have a copy of the old (normal) MRI. Our next appointment on the 16th will

probably be the last with him. We almost went to a Chiropractor to help relieve some of Janice's pain. Now that we know she has ACM we know that is the last thing she needs.
If you know of a Neurosurgeon, who puts the patient's health care first and specializes with ACM, please inform us of who and how we can contact him/her.

Written By: Terrie Clarkson
On March 10, 2005 4:49 PM

Ihave recently diagnosed with c1m and all my doctors are trying to tell me tat it happens at birth. I have been reading information tht tells me otherwise. Do you have any suggstions as to how I can change their mind so that I can get this fixed? It is getting worse. Also, my doctor also said that there are treatments that can also take care of this. Is this true? thank ou. Terrie Clarkson

Written By: Regina Goodwin
On April 7, 2005 4:19 PM

I have recently been diagnosed with Chiari Malformation. I have appointments with 2 nuerosurgeons. What are some questions I should ask in seeking treatment? THank you.

Written By: shelly
On April 20, 2005 5:35 AM

Where can I get information to show that chiari malformations can be acquried or symptoms can be md worse by injury.

Written By: Angie H.
On April 20, 2005 8:23 PM

what is the possibility that my symptoms may be worse after having surgery?

Written By: Karen
On May 22, 2005 2:05 PM

I developed a chronic subdural hematoma after epidural anesthesia. Previous to the hematoma, I underwent two blood patches to stop the spinal fluid from leaking. Is this a common occurence??

Written By: sheila richardson
On June 5, 2005 1:10 PM

I am seeding an attorney out of state who has access to a neurosurgeon. My 13 year old was called dead after a VP shunt surgery and 30 minutes after I received the news a consulting doctor that didn't work for the hospital brought her back on line. The 30 minutes that passed between him leaving her dead caused severe brain stem damage. Children's Hospital did and autopsy and found a hole in her intestine and determined it happened while she was under the first doctors care. I am from Minnesota and having trouble obtaining an attorney because they do more auto injuries. I have all the medical records the attorney collected after her death, but not only were out privacy rights violated, but he left her to die. The doctor at Children's said he knew her perforation of the stomach caused her to go into shock, and the shunt failed because it was put in the wrong place. Any assistance you could give me would be greatly appreciated. I am wondering if an out of state lawyer could get me justice for my daughter.

Written By: Lori
On June 7, 2005 10:45 AM

My 10-year-old son was diagnosed in February 2005 with Chiari malformation type I. He has been suffering from headaches for five years now. In May 2005 we were involved in an auto accident, since the accident he has developed worsening of his headaches along with dizziness, gait disturbances, elevated reflexes, severe eye pain and he complains of his legs feeling heavy all the time. He has excellent doctors right now. He just recently went for another MRI because his doctor said it was possible to develop a syrinx after a car accident (even if it was a minor one). Our accident was not major, but it was not a minor one either. What I would like to know is it possible to develop a syrinx or make the chiari worse because of a car addident and whiplash? Also, my attorney feels that we should not settle my sons case right away. How long do I actually have to settle his case? I appreciate any help that you can give me.

Thank you,

Lori

Written By: Keith
On July 20, 2005 12:21 PM

Hi there, I came accross your site here and found it interesting. I am not in the US, but I am a member of a support site for folks with Syringomyelia and ACM. When I posted my story, I got quite a response from people who have had a similar experience to me. Basically, I was in a near head on accident, suffered severe back and leg pain on the day and was diagnosed with whiplash several days later - fully expected to get better but after 2 years didn't and asked to see a doctor to properly diagnose me. I was found to have a syrinx and the neurosurgeon I consulted said "the accident caused the problem" and he diagnosed me with Post-traumatic Syringomyelia. The problem many folks face with this situation is that insurers will try and connect a congenital factor to the disorder, which I find incredible since they don't even know the mechanics of the disorder yet! I am desperately searching out literature to support my claim, and I'm thinking that if you have any expertise in this it may be worth you having a look at the support group site as there are a few folks struggling with their cases. As it happens, I am a registered psychologist, ironically specialising in the area of disabilities, and do a fair share of medico-legal assessments and reports, so I guess I am a little more equiped to deal with this aspect of the process, however, most folks I know are not and are floundering with their own legal situations. I'd be really interested in chatting to you if you would care to email me, I'm sure that if you have any experience dealing with similar situations to mine that it might be worthwhile having a look at the support group. Kind regards, I will look forward to hearing from you. Keith.

Written By: MS. HORSTMAN
On July 29, 2005 3:14 PM

I was involved in an auto accident on 7/15/05 where in the car went airborne and finally hit large dirt piles. I wnt for an MRI and it was found that I have Chiari I Malformation with 7mm herniation. Since the accident I have severe headaches, pain in my shoulder generating into my arm and loss of strength in my hand. I also have pain and tingling and numbness in my hip and leg which generates doen to my

feet. I feel absolutely awful anymore is there anything that can be done. The accident was not my fault a tanker truck ran me off the road are there any attorneys in Southern New Jersey area that you could recommend for my case. Thank you.

Written By: Lisa
On November 17, 2005 4:29 PM

Wow, I'm a 34 year old that was involved in a T-bone accident w/me traveling @ 62mph as was the 21 year old that ran the stop sign. The accident occured on 05/05/04 the kid hit me on each side of my car, my head took out the drivers door window, before spinning me around hitting me on every other side of my vehicle before decending off a 13 foot embankment full of water. I was in physical therapy on and off for approx. a year. Then my insurance company had me see their doctor for evaulation which he then sent me for an MRI and has since said that I have chiaril one malformation which the insurance claim lady said is an issue from birth & they are not respossible financially to pay any further medical claim to neck and shoulders. So, basically I'm going to be suffering the rest of my life I guess, my health insurance went up $2000.00 last year with zero claims on it for me, and I can't afford for it to go up again. If anyone has any suggestions on whom could help me or lead me in the right direction. Like I stated before I have never been seen for any type of headaches, neck,back or shoulders problems ever, prior to this accident. My e-mail address is lcornwell@michiganchiefsales.com

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Written By: Kathy Adams
On December 7, 2005 11:01 PM

I was involved in a car accident in December 1993. I was misdiagnosed with pseudo tumor cerebi. In January 2004 was told on an MRI I actually had Chiari. In July 2004 was told by Dr. Bolognese I had Chiari and never had PTC. Basically I had surgery Nov 2004 and only recently felt up to checking into my misdiagnosis and trying to find out if I could do anything about the poor car settlement. I know that Ky and Ohio has a 1 year limit on time but did not know if they also have time extensions due to the disability of the person that is ill. Thank you,

Written By: Kane
On January 25, 2006 7:40 AM

I've read all the previous three blog enteries by you and I must say you have made your point outstandingly. As you said this being your final post but I hope you will come up with more interesting articles sooner or latter. One can hope.

Written By: Monique Soucy
On May 3, 2006 9:28 AM

I was dx with Chiari Type I in 1998 following a auto accident in which I was rear ended. I suffered from a mild case of headaches, low back pain and tingling in my left arm. That case was settled much to my dismay with an amount that I felt was insulting. At the time my attorney stated that I should settle and that I would never win if I brought it to court. So I settled. In June of 2005 I was once again rear ended. Now I suffer unbearable at times from headaches, facial pain, low back, mid back, neck pain, shoulder pain, dizziness, and at times even nausau. My MD feels that I have cervical radiculopathy and that cervical traction would be helpful for me. I have had one appt with the traction. My physical therapist has ceased all treatment after studying my malformity. She is concerned with the traction and the affect that it may be having with my condition. At this time I am deeply questioning whether or not this may be aquired from my accident. As a child I did not present any of these symptoms and lead a very normal childhood. When I was 18 and was in the accident in 98 I seemed to have recovered rather quickly, but now that I have had two children (vaginal births) and have been in the second car accident I am having a much harder time recovering. I am looking for anyone that would be willing to share some information on a medical level that would pertain to acquired CHiari Malformation Type I. I am trying everything in my power to avoid surgery!! Please email me at mnq_soucy@yahoo.com

Written By: kimberly dommasch
On July 6, 2006 4:49 PM

I WROTE A BLOG EARLIER TODAY AND AM HOPING THAT YOU WILL STILL HAVE TIME TO READ IT. I AM DESPERATE FOR ADVICE FROM ANYONE WHOM CAN RELATE TO MY STORY THANK YOU

KIMBERLY

EMAIL kdommasch@msn.com

Written By: Beverly
On July 27, 2006 4:31 AM

Upright MRI info type in CHIARI in the site search box

http://tinyurl.com/9s5hu or click my name

Written By: KEVIN
On August 10, 2006 7:24 PM

Hi everyone, i will try and make this short as possible. I was involved in a rearend MVA by a DRUNK DRIVER in 2001, before the accident i had no problems, after the accident i had lower back pain and neck pain. In 2003 i started to lose sensation in my right hand,i had an MRI done and thats when they found fluid in my spine (SYRINX) the insurance companys doctor says i was born with it. Could this be true? I think not because i had no problems before the accident. If anyone has any info to help me PLEASE E-MAIL me at sixfoot@telus.net THANK YOU.

Written By: alicia
On September 25, 2006 6:29 PM

Iwas diagnosed with acm at 12 years old I am now 27. last november i was involved in a little car accident which caused whiplash. within 2 days of sustaining my injury my eyes started getting all out of focus my head felt like it was going to explode. i know that the car accident triggered my acm but who do i get to prove this? dr. say that i now have intercranial brain pressure with optic nerve swelling. am i just supposed to live with this my head hurts constantly somedays i can see some i can't will the pain ever stop i can't even hold a job to support my 2 small kids if somebody can help please contact me. the accident was not my fault, but now i am paying for it with my health.

Post A Comment / Question

NAME: REMEMBER PERSONAL INFO?

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Preview Post

Brain Injury Lawyer & Attorney : Bruce H. Stern
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Bright light therapy may improve sleep and promote recovery in patients with mild TBI

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American Academy of Sleep Medicine
Thursday, May 30, 2013

FOR IMMEDIATE RELEASE

CONTACT: Lynn Celmer, 630-737-9700, ext. 9364, lcelmer@aasmnet.org

DARIEN, IL – A new study suggests that bright light therapy may improve sleep, cognition, emotion and brain function following mild traumatic brain injury (TBI).

Results show that six weeks of morning bright light therapy resulted in a marked decrease in subjective daytime sleepiness. This improvement was further associated with improvements in the propensity to fall asleep and nighttime sleep quality. Bright light therapy also affected depressive symptoms.

“Our preliminary data suggests that morning bright light therapy might be helpful to reduce subjective daytime sleepiness and to improve nighttime sleep,” said investigator Mareen Weber, PhD, instructor in psychiatry at McLean Hospital/Harvard Medical School in Belmont, Mass. “Importantly, the research also shows changes in brain activation during a demanding cognitive task, suggesting that bright light treatment might yield changes in brain functioning.”

The research abstract was published recently in an online supplement of the journal *SLEEP*, and Weber will present the findings Monday, June 3, in Baltimore, Md., at SLEEP 2013, the 27th annual meeting of the Associated Professional Sleep Societies LLC.

The study group comprised 18 individuals with a documented history of at least one mild TBI and sleep disturbance that either emerged or was aggravated with the most recent injury. Data were gathered using Multiple Sleep Latency Tests (MSLT), actigraphy and sleep diaries, and all participants underwent magnetic resonance imaging (MRI) and comprehensive psychiatric and neuropsychological assessments before and after the intervention.

According to the authors, it has been estimated that at least 50 percent of individuals with TBI experience some kind of sleep disturbance at some point following their injury, and sleep has been demonstrated to be essential for brain plasticity and may be important for recovery.

“Improving sleep following mild traumatic brain injury could prove critical to maximizing recovery from the injury,” said Weber. “Furthermore, bright light therapy is easy and minimally invasive, requiring no medication, and has no known serious side effects.”

For a copy of the abstract, or to arrange an interview with Dr. Weber or an AASM spokesperson, please contact AASM Communications Coordinator Lynn Celmer at lcelmer@aasmnet.org.

A joint venture of the American Academy of Sleep Medicine and the Sleep Research Society, the annual SLEEP meeting brings together an international body of more than 5,500 leading clinicians and scientists in the fields of sleep medicine and sleep research. At SLEEP 2013 (www.sleepmeeting.org) more than 1,300 research abstract presentations will showcase new findings that contribute to the understanding of sleep and the effective diagnosis and treatment of sleep disorders such as insomnia, narcolepsy and sleep apnea.

The American Academy of Sleep Medicine considers sleep disorders an illness that has reached epidemic proportions. Board-certified sleep medicine physicians in an AASM-accredited sleep center provide effective treatment. AASM encourages patients to talk to their doctors about sleep problems or visit www.sleepeducation.com for a searchable directory of sleep centers.

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Bright light therapy may improve sleep and promote recovery in patients with mild TBI

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American Academy of Sleep Medicine
Thursday, May 30, 2013

FOR IMMEDIATE RELEASE

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DARIEN, IL – A new study suggests that bright light therapy may improve sleep, cognition, emotion and brain function following mild traumatic brain injury (TBI).

Results show that six weeks of morning bright light therapy resulted in a marked decrease in subjective daytime sleepiness. This improvement was further associated with improvements in the propensity to fall asleep and nighttime sleep quality. Bright light therapy also affected depressive symptoms.

“Our preliminary data suggests that morning bright light therapy might be helpful to reduce subjective daytime sleepiness and to improve nighttime sleep,” said investigator Mareen Weber, PhD, instructor in psychiatry at McLean Hospital/Harvard Medical School in Belmont, Mass. “Importantly, the research also shows changes in brain activation during a demanding cognitive task, suggesting that bright light treatment might yield changes in brain functioning.”

The research abstract was published recently in an online supplement of the journal *SLEEP*, and Weber will present the findings Monday, June 3, in Baltimore, Md., at SLEEP 2013, the 27th annual meeting of the Associated Professional Sleep Societies LLC.

The study group comprised 18 individuals with a documented history of at least one mild TBI and sleep disturbance that either emerged or was aggravated with the most recent injury. Data were gathered using Multiple Sleep Latency Tests (MSLT), actigraphy and sleep diaries, and all participants underwent magnetic resonance imaging (MRI) and comprehensive psychiatric and neuropsychological assessments before and after the intervention.

According to the authors, it has been estimated that at least 50 percent of individuals with TBI experience some kind of sleep disturbance at some point following their injury, and sleep has been demonstrated to be essential for brain plasticity and may be important for recovery.

“Improving sleep following mild traumatic brain injury could prove critical to maximizing recovery from the injury,” said Weber. “Furthermore, bright light therapy is easy and minimally invasive, requiring no medication, and has no known serious side effects.”

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