Chronic post-traumatic headache: clinical findings and possible mechanisms

Ruth Defrin

Department of Physical Therapy, School of Allied Health Professions, Sackler Faculty of Medicine, Tel-Aviv University, Israel

Chronic post-traumatic headache (CPTH), the most frequent complaint after traumatic brain injury (TBI), dramatically affects quality of life and function. Despite its high prevalence and persistence, the mechanism of CPTH is poorly understood. This literature review aimed to analyze the results of studies assessing the characteristics and sensory profile of CPTH in order to shed light on its possible underlying mechanisms. The search for English language articles published between 1960 and 2013 was conducted in MEDLINE, CINAHL, and PubMed. Studies assessing clinical features of headache after TBI as well as studies conducting quantitative somatosensory testing (QST) in individuals with CPTH and in individuals suffering from other types of pain were included. Studies on animal models of pain following damage to peripheral tissues and to the peripheral and central nervous system were also included.

The clinical features of CPTH resembled those of primary headache, especially tension-type and migraine headache. Positive and negative signs were prevalent among individuals with CPTH, in both the head and in other body regions, suggesting the presence of local (cranial) mechanical hypersensitivity, together with generalized thermal hypoesthesia and hypoalgesia. Evidence of dysfunctional pain modulation was also observed. Chronic post-traumatic headache can result from damage to intra- and pericranial tissues that caused chronic sensitization of these tissues. Alternatively, although not mutually exclusive, CPTH might possibly be a form of central pain due to damage to brain structures involved in pain processing. These, other possibilities, as well as risk factors for CPTH are discussed at length.

Keywords: Chronic pain, Traumatic brain injury, Headache, Mechanisms

Chronic Pain after Traumatic Brain Injury (TBI) – the Scope of the Problem

Traumatic brain injury (TBI) is a non-degenerative, non-congenital insult to the brain from an external mechanical force, leading to permanent or temporary impairment of cognitive, physical, and/or psychosocial functions, with an associated diminished or altered state of consciousness. About 1.7 million people sustain a TBI each year in the United States mainly due to falls, motor vehicle-traffic crashes, and direct strikes to the head.¹ Blasts are the main cause of TBI among military personnel in active duty. Traumatic brain injury can be classified based on severity (mild, moderate, severe), mechanism (closed/penetrating head injury), or other features. Its outcome can range from complete recovery to permanent disability or death.

Chronic pain is one of the known consequences of a TBI, with prevalence rates varying between 10 and 95%, depending on the type of pain and the severity of the TBI.^{2–4} Chronic pain in patients with TBI can

originate from a number of sources. In some instances, the pain is a direct result of tissue injuries inflicted during the event causing the TBI, such as bone fractures and dislocations, cervical injuries, soft tissue trauma, and peripheral nerve or plexus damage. Chronic pain can also originate from secondary consequences of the trauma e.g. pressure palsies, peri-articular new bone formation, spasticity, deep venous thrombosis, and abnormal posture.^{6,7} In most of these instances, the chronic pain is located in body regions that are associated with known tissue damage or abnormality.

Chronic Post-Traumatic Headache (CPTH) – Definition and Prevalence

Perhaps, the most frequent type of chronic pain after TBI is headache.^{8,9} Post-traumatic headache (PTH) is defined as a secondary headache that develops within 7 days after head trauma (or after regaining consciousness following head trauma).¹⁰ Post-traumatic headache is regarded as chronic (CPTH) when it continues for more than 2 months after incurrence of the injury, although duration of 6 months has also been suggested.¹¹

Correspondence to: Ruth Defrin, Department of Physical Therapy, Sackler Faculty of Medicine, Tel-Aviv University, 69978, Israel. Email: rutidef@post.tau.ac.il

Figure 1 The location of pain in individuals with CPTH.

Chronic post-traumatic headache is perhaps the most prevalent type of pain after mild TBI, with a prevalence rate of 47–95%, compared to about 20–38% in moderate–severe TBI^{2,4,8,12–15} (however see Ref. 16). It is noteworthy that the wide prevalence of CPTH after mild TBI might stem from differences among studies in its diagnosis, the time lapsed from the injury to the evaluation, and the population tested (e.g. civilians or veterans). Recently, Hoffman *et al.*¹⁶ examined the rate of headache longitudinally among a large cohort during the first year after TBI.¹⁶ The incidence at baseline was 44% and the cumulative incidence of headache at 12 months was 71%, with a 20% incidence of new headaches from 3 to 12 months after injury.

Despite the high prevalence and chronicity, the mechanism of CPTH, and hence its treatment, remains yet unclear. Information on the mechanism of CPTH might be drawn from its clinical characteristics and from the results of sensory and other diagnostic tests assessing the neurological

profile of individuals with CPTH. Unfortunately, only a few studies have systematically characterized the features of CPTH, and even fewer have conducted diagnostic tests with regard to pain. The following chapters provide this information.

Clinical Characteristics of CPTH

There is no single major characteristic for CPTH; rather, it often shows clinical features characteristic of various types of primary headache, mainly tension-type and migraine headaches (each in about one third of individuals). Figure 1 presents the distribution of the painful regions as reported by individuals with CPTH.¹⁷ The most frequent painful region was the temple (82% of individuals), followed by the forehead (76.5%), neck (76%), back of head (53%), eyes (47%), and vertex (29%).

Table 1 summarizes the clinical features of the most common CPTH subtypes.

Individuals with tension-type like CPTH suffer from bilateral pain of mild to moderate intensity, which is described as pressing and dull in quality, and is aggravated by emotional stress and tension.^{8,11,15,17–21} Individuals with migraine type like CPTH suffer from unilateral pain of moderate to severe intensity, pounding, throbbing, drilling, and piercing in quality, which is aggravated by physical activity. These individuals may complain of sensitivity to bright light or noise.^{8,11,15,17–21}

Less than one third of individuals with CPTH suffer from ‘mixed headache’, i.e. overlapping symptoms from the above-mentioned types, from cluster-like headache characterized by excruciating unilateral pain mostly behind the eyes or from unclassified headache.^{8,11,20} It is noteworthy that the events causing TBI might also induce whiplash injuries, which often lead to headache. Individuals with whiplash injuries also present with headache features similar to tension-type and migraine-type headaches; however, cervicogenic and other headache subtypes are also reported.^{22–24}

Regardless of the subtype of CPTH, pain intensity tends to stabilize with time after the injury in the majority of individuals.^{8,17} It might, however, increase

Table 1 Clinical characteristics of the more common types of CPTH

	Tension-type like	Migraine like	Cluster like	Cervicogenic like
Sidedness	Bilateral	Unilateral	Unilateral	Mainly unilateral
Intensity	Mild-moderate	Moderate-severe	Severe-very severe	Mild-severe
Quality	Pressing, dull, squeezing	Pounding, throbbing, drilling, piercing	Boring, throbbing	Dull, aching
Location	Vary	Vary	Retro/peri-orbital but may spread	Starts in the neck and spreads to anterior regions
Aggravated by	Emotional stress, tension	Physical activity,	Alcohol (during the cluster)	Neck movement/posture
Other features	Can be episodic or continuous	Photophobia/phonophobia	Cranial autonomic activation (e.g. lacrimation, rhinorrhoe)	Often a history of whiplash
		Nausea/vomiting		
		With/without aura		

with time after the injury.¹⁷ Frequency of headache can vary with the majority of individuals experiencing daily or weekly headaches, and the minority experiencing headaches monthly or less frequently.^{8,17} Headache episodes were reported to last from a few minutes to a few hours each time. During the episode, the headache was reported to gradually increase, rising to very high intensities (VAS=8–10) and described as a misery.¹⁷ In addition to headache, individuals with CPTHa may report neck pain, which is described as a feeling of muscle spasm and/or muscle tension in the neck, mainly in the posterior aspect.^{17,20}

Sensory Testing in Individuals with CPTHa

As mentioned above, the studies assessing the sensory profile of individuals with CPTHa are scarce. Our group has conducted systematic quantitative somatosensory testing (QST) among individuals with chronic mild-moderate TBI with and without CPTHa, and healthy controls.¹⁷ Quantitative somatosensory testing included the measurement of thresholds to various stimuli applied to the skin, in order to detect abnormalities in the sensory systems that convey these stimuli. On one hand, increased thresholds or absence of sensations indicates partial or complete damage (deafferentation), respectively to the relevant system. On the other hand, decreased thresholds usually indicate that abnormal processes have developed within the relevant system. Testing was conducted over the temples and forehead (representing painful regions in all the individuals with CPTHa), over additional non-painful head regions, and also over the dorsal surface of the hands (which represented remote, intact pain-free regions).

Testing on the head revealed that the thresholds for thermal sensations, including warm, cold, and heat-pain sensation, were higher in both groups of individuals with TBI compared with controls. This suggests an impairment of the spinothalamic system after TBI, as this system conveys innocuous and noxious thermal information from the periphery to the brain.²⁵ However, the heat-pain threshold among individuals with CPTHa was significantly higher than in individuals with TBI without CPTHa, suggesting an even greater impairment in the former group. Furthermore, the heat-pain threshold among individuals with CPTHa was also significantly higher in the hand compared to individuals with TBI without CPTHa, suggesting a generalized rather than local impairment of the spinothalamic system. The threshold of light touch and graphesthesia on the head and hands was similar in all the groups, suggesting intact function of the dorsal column system conveying tactile sensations.²⁵

Testing on the head further revealed that the threshold of pressure-pain was lower among individuals with

CPTHa compared to individuals with TBI without CPTHa, indicative of the presence of hyperalgesia in the former. Furthermore, the threshold of pressure-pain was even lower in the painful regions compared to non-painful regions in the head among individuals with CPTHa. However, the threshold of pressure-pain in the hands was normal, suggesting that the hyperalgesia was local and not generalized. In addition, individuals with CPTHa had allodynia i.e. pain resulting from a normally innocuous stimulus, which was present on the head only and mainly in the painful regions.¹⁷

In a recent study, our group tested the function of the pain-inhibition systems among other groups of individuals after TBI with and without CPTHa.²⁶ We used the experimental paradigm termed 'Conditioned Pain Modulation' (CPM). This paradigm tests the ability of a painful stimulus applied to one body region, to inhibit another painful stimulus applied simultaneously, to a remote body region. It is accepted that this test reflects the function of spino-bulbo-spinal loops underlying the 'pain inhibiting pain' phenomenon termed 'Diffuse Noxious Inhibitory Control' (DNIC).^{27,28} We found that the magnitude of CPM was significantly lower in individuals with CPTHa compared with controls and essentially absent, suggesting a dysfunctional DNIC in these individuals.

Possible Mechanisms of CPTHa

The mechanism of CPTHa is currently unknown, yet hypotheses may be inferred from results of clinical and diagnostic tests done on individuals suffering from CPTHa. Chronic post-traumatic headache can be of peripheral or central origin. Figure 2 summarized three mechanisms that may contribute to the development of CPTHa.

Peripheral origin

Many peripheral tissues have the potential to generate headache after TBI. These may include intracranial arteries, the dura mater and dural arteries, as well as extracranial structures such as bone, muscle, skin, ligament, and deep fascia. These structures are innervated by pain receptors i.e. nociceptors, which are connected to C and A-delta fibers. These fibers convey impulses from the nociceptors to the nociceptive neurons in the dorsal horn of the spinal cord. These neurons then convey impulses via the spinothalamic tracts onto brain regions that process various aspects of the pain experience.²⁵

Damage to any of these cranial tissues during the event causing TBI can generate a chain of events leading to 'neurogenic inflammation'. These events include the release of cytokines and chemokines (e.g. interleukins and tumor necrosis factor-alpha) in the vicinity of the injured tissue that result in monocyte cellular activation and infiltration, glial cell activation, and release of nociceptive neuropeptides.^{29–32}

Figure 2 Summary of possible mechanisms for CPTHA.

Consequently, vascular disruption develops and in addition, nociceptors adjacent to the injury region are activated and sensitized, and become hyper responsive to stimuli.^{31,33–35} This in turn results in spontaneous pain, as well as hypersensitivity to noxious and innocuous stimuli i.e. hyperalgesia and allodynia, respectively (Figure 2 left flowchart), as is characteristic in individuals with CPTHA¹⁷ and as found in animals after controlled cortical impact.³¹

Although sensitization of intra- and extracranial nociceptors may be resolved spontaneously, it may become chronic and may underlie chronic headache. Evidence for chronic sensitization was also reported in tension-type headache,^{36,37} migraine,^{38,39} and cluster headache.⁴⁰ As CPTHA clinically resembles these primary headache types, it is possible that they share a common mechanism i.e. chronic sensitization due to peripheral tissue damage.

Injury to the neck region may also contribute to CPTHA. Neck pain is a common complaint after TBI.^{2,4,17,41} The association between neck pain and CPTHA was previously attributed to the presence of whiplash injury.^{41,42} If cervical damage occurs during the TBI, then nociceptive input from cervical segments reaching the trigeminal nucleus might be a source of referred pain,⁴³ and might also contribute to cranial mechanical hyperalgesia in individuals with CPTHA (Fig. 2 left flowchart).

The cranial nerves may be another source of CPTHA. Damage to nerve fibers provokes a cascade

of cellular events in the vicinity of the damaged site that leads to spontaneous ectopic discharge of primary afferents and cell bodies, which also propagate to uninjured afferents.^{44,45} This ectopic activity, in turn, induces and maintains sensitization of nociceptive neurons, accompanied by reduced inhibition, in the dorsal horn. These changes underlie spontaneous pain, as well as symptoms of hypersensitivity and hyper reactivity that are characteristic of neuropathic pain of peripheral origin.

Similar mechanisms can occur on cranial nerves following TBI. For example, direct damage to the trigeminal nerve during the trauma causing the TBI, or trauma to the trigeminal vascular system, may lead to neuropathic pain. Another factor contributing to the pathogenesis of trigeminal neuropathic pain is an abnormal compression of the trigeminal nerve by a vein or artery, leading to deterioration of myelin sheaths.^{46,47} Mechanical hypersensitivity accompanying trigeminal neuropathic pain involves spontaneous and low-threshold activity in injured myelinated fibers.⁴⁸ Animal models of trigeminal neuropathic pain consistently produce facial mechanical allodynia and central sensitization manifested by a reduced activation threshold and increased response to noxious and innocuous stimuli of medullary dorsal horn nociceptive neurons.⁴⁹ Thus, the spontaneous headache episodes, as well as the cranial allodynia and hyperalgesia seen in individuals with CPTHA,¹⁷ may result from pathological changes in the cranial nerves.

In summary, CPTHa can result from chronic sensitization of nociceptors in intra- and/or extra-cranial peripheral tissues, from damage to cranial nerves, or from both.

Central origin

The generalized thermal hypoalgesia seen in the head and hands (intact regions remote from the injury site) of individuals with CPTHa¹⁷ indicates the existence of central damage to the pain and temperature system, either at the spinothalamic or thalamocortical level, or both. The damage to the brain matter during a TBI may include diffuse axonal injury⁵⁰ alteration in cerebral blood flow,⁵¹ widespread neuronal depolarization, and increased glutamate release.⁵² These processes may, in turn, induce damage to brain tissue, including cell death. Distinct brain damage was observed even after mild TBI,^{53,54} and this might underlie the dysfunctional spinothalamic/thalamocortical system seen in individuals with CPTHa.¹⁷

Damage to the spinothalamic/thalamocortical pathways is the most prominent feature in individuals suffering from 'central pain' i.e. pain caused by a lesion or disease of the central somatosensory nervous system⁵⁵ such as following spinal cord injury (SCI),^{56,57} stroke,^{58,59} or severe traumatic brain injury.⁶⁰ Additional clinical features that characterize individuals with CPTHa such as mechanical allodynia in the painful regions, aggravation of pain by stress/tension, and sharp and pressing pain are also characteristic of central pain patients.^{56–59} It may, thus, be possible that CPTHa is a form of central pain that develops following TBI. We have previously reported the existence of central pain after severe TBI, which was diffusely located in the hemi body contralateral to the TBI site including the head and face.⁶⁰ It is possible that the extent of the pain in individuals with mild-moderate TBI is less, and proportional to the extent of the brain damage.

The pathophysiology of central pain is not fully established; however, it is agreed that damage to the spinothalamic/thalamocortical system is a necessary condition for its development.^{56–60} As ascending nociceptive input triggers descending pain inhibition,⁶¹ deafferentation of the pain pathways may induce reactive reduction in the inhibitory control. Residual neurons within the pain system are thus released from inhibitory control, and may become spontaneously active and hypersensitive (Fig. 2 middle flowchart).^{62,63} Electrophysiological recordings^{62,64} and brain scans^{65,66} of individuals with central pain indeed show that deafferented neurons in the thalamus and somatosensory cortex undergo plastic changes and become hyper-excitable and hyper-reactive. These neurons burst spontaneously with an epileptiform discharge, coinciding with complaints of pain. The epileptiform

and slow-wave abnormalities in individuals with TBI and chronic psychiatric, somatic, or cognitive complaints revealed by magnetoencephalography⁶⁷ may support this type of underlying mechanism for spontaneous pain in CPTHa.

A state of hyper-excitability and hyper-responsiveness drives nociceptive neurons susceptible to various external and internal stimuli. Consequently, noxious stimuli induce a stronger and more extended reaction than under normal conditions (hyperalgesia), and innocuous stimuli such as touch, physical activity, and stress may induce pain (allodynia), symptoms characteristic of CPTHa (Fig. 2 middle flowchart). This state can also underlie the photo- and phono-phobia reported by individuals with migraine-like CPTHa.⁶⁸ Animal models of central pain after damage to spinothalamic neurons indeed reveal shifts in the proportions of neurons responding to noxious stimulation, increased and irregular spontaneous background activity, increased evoked activity to innocuous and noxious stimuli, and alterations in sodium currents.^{69,70}

Animal models of TBI (although not of pain following TBI) showing increases in pro-inflammatory factors and macrophage/microglial and astrocytic activation,^{30,32} and similar finding in humans after TBI,⁷¹ suggest that abnormalities in glial function contribute to conditions that initiate and ensure persistence of neuronal dysfunction. Similarly, dysfunctional glial cells in the vicinity of damaged neurons in animal models of central pain were suggested to secrete pro-inflammatory cytokines and other sensitizing agents, creating persistent glial inflammation and continual sensitization of neurons.^{72–74} Perhaps, similar processes occurring in the brain after TBI underlie CPTHa.

Additional central causes may underlie CPTHa, one of which is the function of the endogenous pain-inhibitory systems. Alterations in the endogenous opioidergic system were observed in animal models of central pain⁷⁵ and in animals with TBI.⁷⁶ Such alterations may result from direct damage to structures involved in opioidergic control occurring during the TBI. Interestingly, subjects with acute PTHa exhibited transient functional alteration in the structures involved in the antinociceptive reflex arc,⁴² indicating altered central pain control.

It is noteworthy that the hyperalgesia and allodynia found in individuals with CPTHa might also result from impairment in supraspinal modulation of nociceptive inputs occurring after prolonged peripheral nociceptor activation.^{36,76} Our recent finding of lack of DNIC in individuals with CPTHa²⁶ might support this proposition. Similarly, lack of DNIC was demonstrated in individuals with migraine and tension-type headache,^{77–80} supporting the possibility of dysfunctional pain modulation in headache

patients. Recently, reduced connectivity between the periaqueductal gray and modulatory structures, such as the prefrontal cortex and anterior cingulate, which was associated with deficient pain modulation, has been observed in migraine patients.⁸¹ As many individuals with TBI present with damage to the frontal cortex,⁸² it is possible that CPTH is a manifestation of altered central modulation of pain.

In summary, CPTH may result from damage to spinothalamic/thalamocortical pathways and its consequences, as in central pain, from alteration to the central modulatory control over nociceptive input, or from both.

Additional Factors That May Contribute to the Pathophysiology of CPTH

Individuals after TBI present with various comorbidities that may contribute to and/or maintain the CPTH. For example, TBI and post-traumatic stress disorder (PTSD), an anxiety disorder that develops following the exposure to a potentially life-threatening event, are known to co-occur.^{83,84} We, and others, found that PTSD symptomatology was significantly higher in individuals with CPTH compared to controls.^{83–85} Co-occurrence can also exist between PTSD and chronic pain;^{85,86} therefore, PTSD might be associated with CPTH. Several studies report high rates of headache among individuals with PTSD even without related injury,^{83,85} supporting an association between the two. The reported correlation between PTSD symptomatology and chronic pain intensity,^{83,87} and the reported aggravation of CPTH by tension and emotional stress,¹⁷ support the involvement of PTSD in CPTH pathophysiology (Fig. 2 right flowchart).

Post-traumatic stress disorder may also affect CPTH via increased levels of depression, as has recently been found in individuals with TBI.⁸⁶ In a longitudinal study, Walker *et al.*⁸ found that at 6 months post rehabilitation discharge, the level of depression and anxiety in individuals after TBI correlated highly with headache density. At 12 months post rehabilitation discharge, the correlation between depression and headache density remained constant. Bryant *et al.*⁸³ found that chronic pain severity among individuals after TBI was associated with increased depression, low satisfaction with life, increased psychological morbidity, and poor community functioning. This relationship was mediated by PTSD. The above-mentioned results suggest that psychological processes may mediate chronic pain after TBI (Fig. 2 right flowchart).

Other symptoms might contribute to the maintenance of CPTH, including sleep disturbances, memory and concentration disturbances, and nervousness and hyper-vigilance. Distress and personality

changes documented in TBI subjects might also intensify CPTH,^{88,89} which may, in turn, perpetuate emotional problems that further exacerbate the pain. It is worth noting that symptoms reported by TBI subjects may be consciously or unconsciously influenced by factors motivated by litigation. Although CPTH may, at times, reflect malingering,⁸⁸ this possibility should be cautiously considered only after all other factors have been eliminated.

Risk Factors for CPTH

In a longitudinal study assessing potential risk factors for the development of headache 12 months after TBI, Hoffman *et al.*¹⁶ found that sex and a history of headache is significantly related to higher rates of headache over time. Females were more likely to report any headaches over a time period of 12 months after injury than males (74 vs 63%), and individuals with a history of headache were significantly more likely to report headache compared to those without a history of headache (45 vs 19%).¹⁶ Another study also found that women were more likely to develop CPTH than males (odd ratio of 2.6), but not other post-traumatic symptoms.⁹⁰ However, in another longitudinal study, Walker *et al.*⁸ did not find an association between sex and headache density. In addition, there was no association between headache density or recovery with time (12-month period), and race, marital status, education level, pre-injury employment status, and alcohol use at the time of injury or injury-related factors such as TBI etiology and Glasgow Coma Scale. Recently, Lucas *et al.*¹⁵ found that age (≤ 60) is a risk factor for CPTH. Thus, pre-injury headache, sex, and age might increase the risk for CPTH.

Clinical Implications

Individuals after TBI may suffer from an array of pathological conditions that may limit functional capability. The coexistence of these conditions and chronic pain further presents a challenge for practitioners as it may significantly hamper successful rehabilitation. Given the multiplicity of clinical symptoms characteristic of CPTH and of mechanisms that may underlie CPTH, a comprehensive examination of signs and symptoms from the head and neck regions is advised. A psychological evaluation is important as well. Accordingly, treatment strategies for CPTH should be matched for the type of headache and the clinical findings. An individually tailored, multidisciplinary treatment seems to be the optimal approach for individuals who suffer from CPTH. Early identification of symptoms and early intervention may help prevent headache chronicity and secondary pathological conditions. Randomized, double-blind, controlled studies assessing the efficacy

of current therapeutic means including manual techniques are called for.

Summary

Chronic post-traumatic headache is frequent after TBI, especially after minimal TBI. Its clinical features vary and may resemble those of tension-type and/or migraine headache. The mechanism of CPTH is poorly understood; however, evidence suggests that it may develop as a result of injury to intra/pericranial tissue that induced chronic local sensitization. An additional, not mutually exclusive option is that CPTH develops as a result of central sensitization and dysfunctional inhibitory control consequent to damage to structures of the pain system. Psychological factors may contribute to and/or maintain CPTH, and pre-injury sex, headache, and age might increase the risk for CPTH. Additional studies are needed to elucidate the pathophysiology of CPTH.

References

- Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalization and deaths 2002–2006. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
- Uomoto JM, Esselman PC. Traumatic brain injury and chronic pain: differential types and rates by head injury severity. *Arch Phys Med Rehabil*. 1993;74:61–4.
- Beetar JT, Guilmette TJ, Sparadeo FR. Sleep and pain complaints in symptomatic traumatic brain injury and neurological populations. *Arch Phys Med Rehabil*. 1996;77:1298–302.
- Lahz S, Bryant RA. Incidence of chronic pain following traumatic brain injury. *Arch Phys Med Rehabil*. 1996;77:889–91.
- Nampiarampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA*. 2000;300:711–9.
- Cooper PR. Head injury, 3rd edn. Baltimore, MD, USA: Williams & Wilkins; 1993. p. 1–27.
- Ivanhoe CB, Hartman ET. Clinical caveats on medical assessment and treatment of pain after TBI. *J Head Trauma Rehabil*. 2004;19:29–39.
- Walker WC, Seel RT, Curtiss G, Warden DL. Headache after moderate and severe traumatic brain injury: a longitudinal analysis. *Arch Phys Med Rehabil*. 2005;86:1793–800.
- Lew HL, Lin PH, Fuh JL, Wang SJ, Clark DJ, Walker WC. Characteristics and treatment of headache after traumatic brain injury: a focused review. *Am J Phys Med Rehabil*. 2006;85:619–27.
- ICHD-2. The International Classification of Headache Disorders. Headache Classification Committee of the International Headache Society. *Cephalalgia*. 2004;24:1–160.
- Baandrup L, Jensen R. Chronic post-traumatic headache – a clinical analysis in relation to the International Headache Classification 2nd Edition. *Cephalalgia*. 2005;25:132–8.
- Faux S, Sheedy J. A prospective controlled study in the prevalence of posttraumatic headache following mild traumatic brain injury. *Pain Med*. 2008;9(8):1001–11.
- Theeler BJ, Erickson JC. Mild head trauma and chronic headaches in returning US soldiers. *Headache*. 2009;49:529–34.
- Dikmen S, Machamer J, Fann JR, Temkin NR. Rates of symptom reporting following traumatic brain injury. *J Int Neuropsychol Soc*. 2010;16:401–11.
- Lucas S, Hoffman JM, Bell KR, Dikmen S. A prospective study of prevalence and characterization of headache following mild traumatic brain injury. *Cephalalgia*. 2013. [Epub ahead of print].
- Hoffman JM, Lucas S, Dikmen S, Braden CA, Brown AW, Brunner R, *et al*. Natural history of headache after traumatic brain injury. *J Neurotrauma*. 2011;28:1719–25.
- Defrin R, Gruener H, Schreiber S, Pick CG. Quantitative somatosensory testing of subjects with chronic post-traumatic headache: implications on its mechanisms. *Eur J Pain*. 2010;14:924–31.
- Haas DC. Characteristics of chronic posttraumatic headache. *Headache*. 2002;42:162–3.
- Bettucci D, Aguggia M, Bolamperti L, Riccio A, Mutani R. Chronic posttraumatic headache associated with minor cranial trauma: a description of cephalalgic patterns. *Ital J Neurol Sci*. 1998;19:20–4.
- Radanov BP, Di Stefano G, Augustiny KF. Symptomatic approach to posttraumatic headache and its possible implications for treatment. *Eur Spine J*. 2001;10:403–7.
- Bekkelund SI, Salvesen R. Prevalence of head trauma in patients with difficult headache: the North Norway Headache Study. *Headache*. 2003;43:59–62.
- Pearce JM. Headaches in the whiplash syndrome. *Spinal Cord*. 2001;39:228–33.
- Bring G, Westman G. Chronic posttraumatic syndrome after whiplash injury. A pilot study of 22 patients. *Scand J Prim Health Care*. 1991;9:135–41.
- Obelieniene D. Headache after whiplash: a historical cohort study outside the medico-legal context. *Cephalalgia*. 1998;18:559–64.
- Basbaum AI, Jessell TM. The perception of pain. In: Kandel ER, Schwartz JH, Jessell TM, editors. *Principles of neural sciences*, 4th edn. New York, McGraw-Hill; 2000. p. 472–91.
- Defrin R, Schreiber S, Feingold Y, Riabinin M, Pick CG. Reduced pain modulation in patients with chronic post traumatic headache. *Eur J Pain Suppl*. 2011;5:138.
- Le Bars D. The whole body receptive field of dorsal horn multireceptive neurons. *Brain Res Brain Res Rev*. 2002;40:29–44.
- Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, *et al*. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain*. 2010;14:339.
- Shohami E, Ginis I, Hallenbeck JM. Dual role of tumor necrosis factor alpha in brain injury. *Cytokines Growth Factor Rev*. 1999;10:119–30.
- Baratz R, Tweedie D, Rubovitch V, Luo W, Yoon JS, Hoffer BJ, *et al*. Tumor necrosis factor- α synthesis inhibitor, 3,6'-dithiothalidomide, reverses behavioral impairments induced by minimal traumatic brain injury in mice. *J Neurochem*. 2011;118:1032–42.
- Elliott MB, Oshinsky ML, Amenta PS, Awe OO, Jallo JI. Nociceptive neuropeptide increases and periorbital allodynia in a model of traumatic brain injury. *Headache*. 2012;52:966–84.
- Perez-Polo JR, Rea HC, Johnson KM, Parsley MA, Unabia GC, Xu GJ, *et al*. Inflammatory consequences in a rodent model of mild traumatic brain injury. *J Neurotrauma*. 2013;30:727–40.
- Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature*. 1983;306:686–8.
- McMahon SB, Lewin GR, Wall PD. Central hyperexcitability triggered by noxious inputs. *Curr Opin Neurobiol*. 1993;3:602–10.
- Bendtsen L. Central sensitization in tension-type headache: possible patho-physiological mechanisms. *Cephalalgia*. 2000;29:486–508.
- Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: a population study. *Pain*. 2006;123:19–27.
- Fernández-de-las-Peñas C, Cuadrado ML, Arendt-Nielsen L, Simons DG, Pareja JA. Myofascial trigger points and sensitization: an updated pain model for tension-type headache. *Cephalalgia*. 2007;27:383–93.
- Burstein R, Yaminsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. *Ann Neurol*. 2000;47:614–24.
- Sandrini G, ProiettiCecchini A, Milanov I, Tassorelli C, Buzzi MG, Nappi G. Electrophysiological evidence for trigeminal neuron sensitization in patients with migraine. *Neurosci Lett*. 2002;317:135–8.
- Fernández-de-Las-Peñas C, Ortega-Santiago R, Cuadrado ML, López-de-Silanes C, Pareja JA. Bilateral widespread mechanical pain hypersensitivity as sign of central sensitization in patients with cluster headache. *Headache*. 2011;51:384–91.
- Packard RC. The relationship of neck injury and post-traumatic headache. *Curr Pain Headache Rep*. 2002;6:301–7.
- Keidel M, Rieschke P, Stude P, Eisentraut R, van Schayck R, Diener H. Antinociceptive reflex alteration in acute posttraumatic headache following whiplash injury. *Pain*. 2001;92:319–26.
- Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. *Brain*. 2002;125:1496–509.
- Devor M. Sodium channels and mechanisms of neuropathic pain. *J Pain*. 2006;7(Suppl 1):S3–12.

- 45 Wu G, Ringkamp M, Murinson BB, Pogatzki EM, Hartke TV, Weerahandi HM, *et al.* Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents. *J Neurosci.* 2002;22:7746–53.
- 46 Devor M, Govrin-Lippmann R, Rappaport ZH. Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. *J Neurosurg.* 2002;96:532–43.
- 47 Luo DS, Zhang T, Zuo CX, Zuo ZF, Li H, Wu SX, *et al.* An animal model for trigeminal neuralgia by compression of the trigeminal nerve root. *Pain Physician.* 2012;15:187–96.
- 48 Nakagawa K, Takeda M, Tsuboi Y, Kondo M, Kitagawa J, Matsumoto S, *et al.* Alteration of primary afferent activity following inferior alveolar nerve transection in rats. *Mol Pain.* 2010;6:9.
- 49 Cao Y, Wang H, Chiang CY, Dostrovsky JO, Sessle BJ. Pregabalin suppresses nociceptive behavior and central sensitization in a rat trigeminal neuropathic pain model. *J Pain.* 2013;14:193–204.
- 50 Moen KG, Skandsen T, Folvik M, Brezova V, Kvistad KA, Rydland J, *et al.* A longitudinal MRI study of traumatic axonal injury in patients with moderate and severe traumatic brain injury. *J Neurol Neurosurg Psychiatry.* 2012;83:1193–200.
- 51 Gilkey SJ, Ramadan NM, Aurora TK, Welch KM. Cerebral blood flow in chronic posttraumatic headache. *Headache.* 1997;37:583–7.
- 52 Yi JH, Hazell AS. Excitotoxic mechanisms and the role of astrocytic glutamate transporters in traumatic brain injury. *Neurochem Int.* 2006;48:394–403.
- 53 Lewine JD, Davis JT, Bigler ED, Thoma R, Hill D, Funke M, *et al.* Objective documentation of traumatic brain injury subsequent to mild head trauma: multimodal brain imaging with MEG, SPECT, and MRI. *J Head Trauma Rehabil.* 2007;22:141–55.
- 54 Tashlykov V, Katz Y, Gazit V, Zohar O, Schreiber S, Pick CG. Apoptotic changes in the cortex and hippocampus following minimal brain trauma in mice. *Brain Res.* 2007;1130:197–205.
- 55 Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, *et al.* Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology.* 2008;70(18):1630–5.
- 56 Finnerup NB, Johannesen IL, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory function in spinal cord injury patients with and without central pain. *Brain.* 2003;126(Pt 1):57–70.
- 57 Zeilig G, Enosh S, Rubin-Asher D, Lehr B, Defrin R. The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. *Brain.* 2012;135(Pt 2):418–30.
- 58 Hansson P. Post-stroke pain case study: clinical characteristics, therapeutic options and long-term follow-up. *Eur J Neurol.* 2004;Suppl 1:22–30.
- 59 Krause T, Brunecker P, Pittl S, Taskin B, Laubisch D, Winter B, *et al.* Thalamic sensory strokes with and without pain: differences in lesion patterns in the ventral posterior thalamus. *J Neurol Neurosurg Psychiatry.* 2012;83(8):776–84.
- 60 Ofek H, Defrin R. Chronic pain following traumatic brain injury. *Pain.* 2007;131:330–40.
- 61 Fields HL, Basbaum AL, Heinricher MM. Central nervous system mechanisms of pain modulation. In: Wall PD, Melzack R, editors. *Textbook of pain*, 5th edn. Edinburgh, UK: Churchill Livingstone; 2006. p. 125–42.
- 62 Lenz FA, Tasker RR, Dostrovsky JO, Kwan HC, Gorecki J, Hirayama T, *et al.* Abnormal single-unit activity recorded in the somatosensory thalamus of a quadriplegic patient with central pain. *Pain.* 1987;31:225–36.
- 63 Wasner G, Lee BB, Engel S, McLachlan E. Residual spinothalamic tract pathways predict development of central pain after spinal cord injury. *Brain.* 2008;131(Pt 9):2387–400.
- 64 Masri R, Quinon RL, Lucas JM, Murray PD, Thompson SM, Keller A. Zona incerta: a role in central pain. *J Neurophysiol.* 2009;102:181–91.
- 65 Pattany PM, Yezielski RP, Widerström-Noga EG, Bowen BC, Martinez-Arizala A, Garcia BR, *et al.* Proton magnetic resonance spectroscopy of the thalamus in patients with chronic neuropathic pain after spinal cord injury. *Am J Neuroradiol.* 2002;23:901–5.
- 66 Peyron R, Schneider F, Faillenot I, Convers P, Barral FG, Garcia-Larrea L, *et al.* An fMRI study of cortical representation of mechanical allodynia in patients with neuropathic pain. *Neurology.* 2004;63:1838–46.
- 67 Nuwer MR, Hovda DA, Schrader LM, Vespa PM. Routine and quantitative EEG in mild traumatic brain injury. *Clin Neurophysiol.* 2005;116:2001–25.
- 68 Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. *Headache.* 1997;37:492–5.
- 69 Hains BC, Waxman SG. Sodium channel expression and the molecular pathophysiology of pain after SCI. *Prog Brain Res.* 2007;161:195–203.
- 70 Boroujerdi A, Zeng J, Sharp K, Kim D, Steward O, Luo ZD. Calcium channel alpha-2-delta-1 protein upregulation in dorsal spinal cord mediates spinal cord injury-induced neuropathic pain states. *Pain.* 2011;152:649–55.
- 71 Helmy A, Carpenter KL, Menon DK, Pickard JD, Hutchinson PJ. The cytokine response to human traumatic brain injury: temporal profiles and evidence for cerebral parenchymal production. *J Cereb Blood Flow Metab.* 2011;31:658–70.
- 72 Nestic O, Svrakic N, Xu GY, McAdoo D, Westlund KN, Hulsebosch CE, *et al.* DNA microarray analysis of the contused spinal cord: effect of NMDA receptor inhibition. *J Neurosci Res.* 2002;68:406–23.
- 73 Hulsebosch CE, Hains BC, Crown ED, Carlton SM. Mechanisms of chronic central neuropathic pain after spinal cord injury. *Brain Res Rev.* 2009;60:202–13.
- 74 Sandhir R, Gregory E, He YY, Berman NE. Upregulation of inflammatory mediators in a model of chronic pain after spinal cord injury. *Neurochem Res.* 2011;36:856–62.
- 75 Hao JX, Yu W, Xu XJ. Evidence that spinal endogenous opioidergic systems control the expression of chronic pain-related behaviors in spinally injured rats. *Exp Brain Res.* 1998;118:259–68.
- 76 McIntosh TK, Head VA, Faden AI. Alterations in regional concentrations of endogenous opioids following traumatic brain injury in the cat. *Brain Res.* 1987;425:225–33.
- 77 Jensen R. Pathophysiological mechanisms of tension-type headache: a review of epidemiological and experimental studies. *Cephalalgia.* 1999;19:602–21.
- 78 Sandrini G, Rossi P, Milanov I, Serrao M, Cecchini AP, Nappi G. Abnormal modulatory influence of diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. *Cephalalgia.* 2006;26:782–9.
- 79 Pielsticker A, Haag G, Zaudic M, Lautenbacher S. Impairment of pain inhibition in chronic tension-type headache. *Pain.* 2005;118:215–23.
- 80 Bezov D, Ashina S, Jensen V, Bendtsen L. Pain perception studies in tension-type headache. *Headache.* 2011;51:262–71.
- 81 Mainiero C, Boshyan J, Hadjikhani N. Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. *Ann Neurol.* 2011;70:838–45.
- 82 Kennedy JE, Jaffee FS, Leskin GA, Stokes JW, Leal FO, Fitzpatrick PJ. Posttraumatic stress disorder and posttraumatic stress disorder-like symptoms and mild-traumatic brain injury. *J Rehabil Res Dev.* 2007;44:895–920.
- 83 Bryant RA, Marosszeky JE, Crooks J, Baguley IJ, Gurka JA. Interaction of posttraumatic stress disorder and chronic pain following traumatic brain injury. *J Head Trauma Rehabil.* 1999;14:588–94.
- 84 Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med.* 2008;358:453–63.
- 85 Defrin R, Ginzburg K, Solomon Z, Polad E, Bloch M, Govezensky M, *et al.* Quantitative somatosensory testing of pain perception in patients with PTSD-relation to chronic pain. *Pain.* 2008;138:450–9.
- 86 Asmundson GJG, Coons MJ, Taylor S, Katz J. PTSD and the experience of pain: research and clinical implications of shared vulnerability and mutual maintenance models. *Can J Psychiat.* 2002;47:930–7.
- 87 Ruff RL, Riechers RG 2nd, Wang XF, Piero T, Ruff SS. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. *J Rehabil Res Dev.* 2012;49:1305–20.
- 88 Carroll LJ, Cassidy JD, Peloso PM, Borg J, von Holst H, Holm L, *et al.* Prognosis for mild traumatic brain injury: results of the WHO collaborating centre task force on mild traumatic brain injury. *J Rehabil Med.* 2004;43(Suppl):84–105.
- 89 Packard RC. Current concepts in chronic post-traumatic headache. *Curr Pain Headache Rep.* 2005;9:59–64.
- 90 Jensen OK, Thulstrup AM. Gender differences of post-traumatic headache and other post-commotio symptoms. A follow-up study after a period of 9–12 months. *Ugeskr Laeger* 2001;163:5029–33.