Aches and Trauma: Understanding Post-Traumatic Headache, Part 1 of 2: Diagnosis and Pathophysiology

Findings increasingly suggest a pathophysiological link between concussion and headache, with implications for how neurologists approach both conditions.

By Francis X. Conidi, DO, MS

Headache is the most common symptom of both traumatic (71 percent) and mild (91 percention) traumatic brain injury (TBI). One year after initial injury, 44 percent of patients with TBI and 54 percent of patients with concussion will continue to experience headache,[1] with many meeting the International Headache Society (IHS) criteria for chronic post-traumatic headache (PTH).[1] Recent studies have shown the prevalence of headache to be as high as 94 percent in athletes with concussion,[2] 90 percent in individuals with TBI,[3] and 98 percent in soldiers with head trauma during the final three months of deployment; one third meet the criteria for chronic post-traumatic headache.[4] In fact, among the 350-plus plus retired National Football League (NFL) players that we have evaluated to date, a large number suffer from daily headaches, with almost half showing objective evidence on neuroimaging studies of TBI.

This article will examine the links between headache/migraine and concussion more closely and consider the future implications of recent data and discoveries.

Classification and Pathophysiology

The International Headache Society Classification, third edition (beta version) divides post-traumatic headache into two major categories: acute and persistent. Each category is divided into two subcategories based on the head injury phenotype, e.g., TBI or mild TBI. While the committee does an admirable job in their classification, given the lack of available evidence-based studies, some significant flaws are worth noting. One is the reliance on loss of consciousness as criteria in all categories. Loss of consciousness has no bearing on the severity of concussion, the development of headache, or concussion outcome/recovery time. The major driver for update to the American Academy of Neurology (AAN) sports concussion guidelines was that the old classification was based on a grading system, which itself was based on loss of consciousness. However, data now and at that time support the opposite; fewer than 10 percent of individuals with concussion sustain loss of consciousness.

Another flaw in the current classification is the use of the Glascow Coma Scale (GCS). The major purpose of the GCS is the acute evaluation of head injury and prognosis for survival. Higher GCS scores do not rule out TBI, and lower scores (i.e., above a six) do not rule it in. For example, we have many retired professional athletes in our practice with objective evidence of TBI who never had a GCS of less than 13. Moreover, an extensive PubMed search failed to support any objective evidence regarding the correlation between GCS and headache.

Another important consideration is that the criteria do not rely on neurological exam findings that would be extremely important in evaluating individuals with suspected concussion and TBI. Finally, for headaches related to

mild trauma to the head, too much emphasis is placed on post-traumatic amnesia, and there is a lack of emphasis on vestibular issues, which are the second most common symptom after headache.

Phases of Concussion

In addition to the flaws in classification of post-traumatic headache, the pathophysiology of concussion is poorly understood; what we know is based on rat percussion models[5,6] and a few neuroimaging studies.

There are three phases of concussion: acute, intermediate, and late. Post-concussive deficits are based on temporary neuronal dysfunction and not cell death. Alterations in cerebral blood flow (CBF) also likely play a factor.[7]

The acute phase is characterized by metabolic and ion derangements, disruption of neural membranes, and axonal stretching. The latter results in abrupt and indiscriminant release of neurotransmitters and unchecked ion fluxes. Excitatory neurotransmitters, such as N-methyl-D-aspartate (NMDA) and glutamate, trigger neuronal depolarization with an efflux of potassium and influx of calcium. Increased extracellular calcium triggers further neuronal depolarization, further release of excitatory neurotransmitters, and still further release of potassium into the extracellular space. Normally, excessive extracellular calcium is taken up by surrounding glial cells, however, this mechanism is overcome in concussion. The massive excitation is followed by a wave of neuronal suppression (i.e., spreading depression). Early loss of consciousness, amnesia, and other cognitive deficits may be a result of post-traumatic spreading depression. Membrane pumps become activated in an effort to restore homeostasis, which results in increased glucose utilization. Increased glycolysis leads to increased lactate production, which results in neuronal dysfunction through processes such as metabolic acidosis, membrane damage, alterations in blood brain barrier permeability, and cerebral edema.

The intermediate phase is characterized by uncoupling of glucose metabolism and cerebral blood flow. Calcium influx, mitochondrial dysfunction, and delayed glucose hypometabolism also occur.[5,6] Uncoupling causes a 50 percent reduction of blood flow, which creates an energy mismatch.[5,6] There is a biphasic recovery of oxidative metabolism with a reduction on day one, recovery by day two, bottom-out by day five, and complete recovery by day 10.[5,6] Calcium accumulation can persist for two to four days, and the excess calcium is sequestered in mitochondria resulting in impaired metabolism and energy failure.[5,6] Cerebral glucose use is diminished by 24 hours and can last up to four weeks post-injury, with an average recovery of 10 days. Cerebral glucose metabolism and oxidative metabolism correlate with the average concussion recovery time of 10 days.[5,6] Intracellular magnesium levels are immediately reduced and remain so for up to four days, and magnesium level recovery is correlated with improvement in motor function.[5,6]

Hallmarks of the late phase include delayed cell death, persistent calcium accumulation, and neurotransmitter alteration.[5,6] Persistent elevations in intracellular calcium can lead to overactivation of enzymes and free radical production resulting in cell death.[5,6] Alterations in NMDA, adrenergic, cholinergic, and GABA neurotransmission also occur. In addition to ion fluctuations and neurotransmitter dysfunction, CBF is known to decrease immediately following both TBI and mild TBI and can remain lowered for extended periods of time. It has been hypothesized that alterations in CO_2 levels may play a significant role in the regulation of CBF.[7] Following severe TBI, cerebral autoregulation is either lost or impaired, and younger patients may have issues in cerebral reactivity, which in itself is likely mediated by alterations in the brain's metabolic activity. Moreover, cerebral oxygenation is significantly reduced (by up to 35 percent) on day one following mild TBI, and appears to be unresolved up to seven days following the injury.[8] Finally, it has been proposed that neuro-autonomic cardiovascular dysregulation, i.e., an uncoupling between the autonomic nervous system and the cardiovascular system, follows mild TBI. This, in turn, could result in alterations in CBF.

Migraine and Concussion: A Common Link in Pathophysiology?

Migraine pathophysiology has evolved considerably since Wolf proposed the "vascular theory" in the 1940s. It has been suggested that migraine represents a highly choreographed interaction between major inputs from both the peripheral and central nervous systems in genetically susceptible individuals.[9] Or, in lay terms, *migraine is a genetic disorder of triggers*. This is quite relevant to PTH, as head trauma could easily serve as the trigger of migraine, and migraine could serve to potentiate and prolong the symptoms of concussion. In fact, there are numerous epidemiological studies demonstrating a link between migraine and the duration of concussion symptoms.[10] One study looking at more than 50,000 Canadian individuals reported that, along with younger age and male sex, migraine may be an independent risk factor for concussion.[11]

The specific mechanisms underlying the development of migraine remain to be fully elucidated.[12] Current consensus is that the headache phase depends on the activation and sensitization of trigeminal sensory afferents that innervate cranial tissues, particularly the meninges and their large blood vessels.[13-15] This results in sequential activation and probable sensitization of second and third order neurons

in the brainstem, forebrain, and cortex.[13-14] However, recent evidence suggests that vasodilatation may not be necessary to trigger a migraine attack.[13,14] The innervation of intracranial vasculature and the meninges occurs via nonmyelinated (C fibers) and thinly myelinated (Aδ fibers) axons containing vasoactive neuropeptides, such as substance P (SP) and calcitonin gene–related peptide (CGRP). These fibers originate in the trigeminal ganglion and reach the dura primarily through the ophthalmic branch of the trigeminal nerve (V1), with additional innervation provided by neurons in the upper cervical dorsal root ganglia.[14,15] Central projections from trigeminal sensory afferents terminate in the trigeminocervical complex (TCC), comprising the C1 and C2 dorsal horns of the cervical spinal cord and the caudal division of the spinal trigeminal nucleus.[13,14] Almost all dural afferents are mechanoreceptors, which are sensitive to changes in vascular diameter and which may provide a mechanism for the throbbing character of migraine pain.[13] It also provides a possible mechanism by which concussion could trigger headache, i.e., through changes in cerebral blood flow or via a cervical mediated process.

The trigeminal nucleus complex (TNC) has ascending connections with the brainstem, thalamus, and hypothalamus, which may be related to migraine symptoms such as fatigue, loss of appetite, memory loss, irritability, and certain autonomic symptoms, many of which are also involved in concussion.[13,14] Thalamic projections (i.e., dural sensitive neurons) to visual and auditory association cortices contribute to associated migraine symptoms, such as visual and memory loss and motor and limbic abnormalities.[13,14] In addition, photosensitivity (also a common symptom of concussion) appears to be mediated at various levels of the thalamus.[13,14] The TNC also receives descending (inhibitory) input from the cortex, brainstem, and hypothalamus.[14,15] Increasing evidence suggests that alterations in cortical excitability play a significant role in migraine pathophysiology via direct cortico-trigeminal projections from the contralateral primary somatosensory and insula to the TCC.[14,15]

Perhaps more relevant is the finding that electrophysiological activity such as that seen in epilepsy can activate overlying meningeal nociceptors and generate ipsilateral headache.[13] Although somewhat controversial, some preliminary evidence indicates that cortical spreading depression (CSD) can trigger headache by activating dural nociceptors and central trigeminovascular neurons in the TCC.[13,14] As is the case in the physiology of concussion, CSD is triggered by increases in extracellular potassium. In migraine, this is felt to be mediated by nociceptors (peptide) with axons extending to the pia.[13,14] The resultant wave of CSD leads to the release of nitric oxide, glutamate, and serotonin, which in turn (through somewhat poorly understood mechanisms) activate meningeal afferents causing the release of inflammatory neuropeptides, such as CGRP and Substance P, which promote neurogenic inflammation in the dura and sustained activation and sensitization of meningeal nociceptors.[13,14] CSD can also result in gene activation in the TCC, as well as dilatation and increased blood flow in the middle meningeal artery, which may act as a "driver" of headache pain.

Migraine pathophysiology is similar to concussion pathophysiology, given that both conditions render the cerebral cortex hyper-excitable through abnormal excitatory/inhibitory balance, i.e., CSD or a similar process. A large body of evidence supports the role of CSD as a key event in migraine with aura, however further research is needed to determine if CSD-like events occur in migraine without aura.[14] Recently, the concept of the "hyper-excitable inter-ictal brain" has been proposed.[13] According to the theory, the migraineur's cortex is in a hyper-excitable state between attacks. This could result from either enhanced excitation or reduced inhibition.[13] Possible mechanisms include alterations in circuits that maintain excitatory and inhibitory balance, and/or alterations of cortical neuro-modulation by serotonergic, noradrenergic or cholinergic inputs originating in the brainstem, both resulting facilitation and propagation of CSD.[13] The latter concept provides a possible direct link to the physiology of concussion, given that the late phase of concussion also involves abnormalities in cholinergic, adrenergic, as well as NMDA and GABA neurotransmission.

The maintenance of a migraine attack appears to involve both peripheral and central sensitization. Peripheral sensitization mediates the throbbing perception of headache and involves an increase in sensitivity to noxious or non-noxious sensory stimuli caused by hyper responsiveness within primary afferent fibers.[13] It appears to be mediated by meningeal inflammation caused by the release of pro-inflammatory neuropeptides such as CGRP and substance P.[13]

The maintenance of peripheral sensitization is not fully understood, however, cortical spreading depression has been proposed as playing a major factor.[13] This raises the question of whether the biomechanics of concussion could cause peripheral sensitization via dural stretching, changes in dural blood flow, or activation of peripheral nerves, i.e., supra-orbital, occipital and auriculotemporal. Central sensitization is the increased sensitivity to noxious or non-noxious sensory stimulation (known as allodynia) and is caused by hyper responsiveness of neurons in the TCC and thalamus.[13,14] It appears to be mediated by activation of the descending pathways. Approximately two thirds of migraine patients experience allodynia in the periorbital and extracephalic regions.[15] Facial allodynia likely results

from sensitization of neurons in the TCC via meningeal nociceptors, whereas extracephallic allodynia reflects sensitization of thalamic neurons receiving input from the cranial meninges and extracephalic skin.[13] Moreover, the initiation of central sensitization depends on afferent input from previously sensitized meningeal nociceptors, once established central sensitization becomes independent of afferent input.

Finally, both concussion and post-traumatic headache are influenced by the cervical spine. The biomechanics of concussion are both directly and indirectly related to the cervical spine and its associated structures. In addition to the lateral and rotational forces the individual experiences on their head, they also experience axial loading on the spine itself as well as flexion, extension, and rotation of the neck, which is almost identical to what is seen in whiplash injuries. This results in damage to underlying structures, including the facets, ligaments, dorsal root ganglion, cervical muscles, and spinal/peripheral nerves. All of the aforementioned cervical structures can play a role in triggering and/or maintaining migraine/post traumatic headache.[16-18] After sustaining a blow to the head or body, a cascade of events including brain activation and cervical dysfunction are triggered to deactivate brainstem structures involved in the descending pathways. Compression of the DRG (especially C2) can result in activated afferent pain fibers that project to the neck and scalp as well as spinal and peripheral nerves, especially the third occipital and the greater occipital nerve (GON), which play a direct role in transmitting migraine pain. Furthermore, a likely lowering of the voltage threshold results in prolonged and persistent hyper-sensitization of the DRG, which in turn can contribute to the development of chronic cervical pain and chronic post traumatic headache. Perhaps more important are the direct and indirect effects on the upper spinal nerves, especially C2 and the GON, which receive a high convergence of input from the deep cervical muscles and skin and mediates afferent flow from the deep paraspinal neck muscles, zygapophyseal joints, and ligaments.[19] Nociceptive afferents from the C1, 2, and 3 spinal and the GON converge onto second-order neurons that also receive afferents from adjacent cervical nerves and from the first division of the trigeminal nerve via the trigeminal nerve spinal tract.[19] Additionally, trigeminocervical neurons can also receive convergent input from the supratentorial dura mater and contralateral GON.[19]

The concussed individual can experience damage and/or activation (i.e., secondary to biomechanical forces on the cervical spine) to the upper spinal nerves. The GON and to some extent the lesser occipital nerve, can be directly compressed by trauma (i.e., helmet to helmet) or via irritation or compression from the semispinalis muscle and/or occipital artery pulsations. Activation of either the GON or upper spinal nerve afferents can trigger migraine through their projections to the trigeminocervical complex and can result in referred pain to the cervical, occipital, and supraorbital regions.

Questions Remain

Despite the underlying similarities between migraine and concussion, several questions remain unanswered and require further exploration, such as how post-traumatic migraine develops after concussion, as well as the specific role of the cervical spine in trigger, maintenance, and chronification of PTH. It is unlikely that a single mechanism is involved, and multiple interrelated processes are likely occurring simultaneously.

The next entry in this two-part series (to appear in the September edition of *Practical Neurology*®) will explore various treatment options for PTH and tailored therapy. ■

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