Narrative Review of the Pathophysiology of Headaches and Photosensitivity in Mild Traumatic Brain Injury and Concussion

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ABSTRACT: The most common symptom of post-concussive syndrome (PCS) is post-traumatic headache (PTH) accompanied by photophobia. Post-traumatic headache is currently categorized as a secondary headache disorder with a clinical phenotype described by its main features and resembling one of the primary headache disorders: tension, migraine, migraine-like cluster. Although PTH is often treated with medication used for primary headache disorders, the underlying mechanism for PTH has yet to be elucidated. The goal of this narrative literature review is to determine the current level of knowledge of these PTHs and photophobia in mild traumatic brain injury (mTBI) in order to guide further research and attempt to discover the underlying mechanism to both symptoms. The ultimate purpose is to better understand the pathophysiology of these symptoms in order to provide better and more targeted care to afflicted patients. A review of the literature was conducted using the databases CINAHL, EMBASE, PubMed. All papers were screened for sections on pathophysiology of PTH or photophobia in mTBI patients. Our paper summarizes current hypotheses. Although the exact pathophysiology of PTH and photophobia in mTBI remains to be determined, we highlight several interesting findings and avenues for future research, including central and peripheral explanations for PTH, neuroinflammation, cortical spreading depolarization and the role of glutamate excitotoxicity. We discuss the possible neuroanatomical pathways for photophobia and hypothesize a possible common pathophysiological basis between PTH and photophobia.

RÉSUMÉ: Revue non systématique de la pathophysiologie des céphalées et de la photosensibilité dans le cas de traumatismes crânio-cérébraux légers. Les symptômes les plus courants du syndrome post-commotionnel (SPC) sont des céphalées post-traumatiques (CPT) accompagnées de photophobie. Ce type de céphalée est à l'heure actuelle considéré comme un trouble de nature secondaire dont le phénotype clinique et les caractéristiques ressemblent à ceux des céphalées dites primaires: tensions, migraines, maux de tête qui ressemblent à des migraines, algies vasculaires du visage, etc. Bien que les CPT soient souvent traitées par une médication utilisée dans le cas des céphalées dites primaires, il nous reste encore à élucider le mécanisme sous-jacent des CPT. L'objectif de cette revue non-systématique est de déterminer, chez des patients victimes de traumatismes crânio-cérébraux (TCC) légers, l'état actuel des connaissances concernant ce type de maux de tête et la photophobie qui y est associée, et ce, afin d'orienter les recherches ultérieures et de pouvoir découvrir les mécanismes qui président à l'apparition de ces deux symptômes. L'objectif ultime qui est le nôtre est de mieux comprendre la pathophysiologie de ces symptômes en vue de pouvoir offrir aux patients qui en sont atteints des soins mieux ciblés et de meilleure qualité. Nous avons ainsi mené une revue de la littérature au moyen des bases de données suivantes: CINAHL, Embase et PubMed. Tous les articles ont été passés au peigne fin en vue d'identifier, dans le cas de patients victimes de TCC légers, des passages portant sur la pathophysiologie des CPT ou sur la photophobie. Notre article entend aussi résumer les hypothèses actuelles qui portent sur cette question. Quoique la pathophysiologie précise des CPT et de la photophobie associée aux TCC légers restent à déterminer, nous avons mis en lumière plusieurs pistes et constats intéressants en vue d'activités de recherche futures, ce qui inclut des facteurs explicatifs d'origine centrale et périphérique, de la neuro-inflammation, des ondes lentes de dépolarisation (OLD) et le rôle de l'excitotoxicité du glutamate. Nous avons aussi abordé les possibles voies neuro-anatomiques de la photophobie en plus d'émettre l'hypothèse qu'il existe une pathophysiologie commune entre les CPT et la photophobie.

PREAMBLE

Concussion, or mild traumatic brain injury (mTBI), has gained significant importance in the literature over the past few years.

Although often used as synonyms, mTBI and concussion have slightly varying definitions.[1,2] For the purposes of this paper we will use both terms since they represent clinical practice, as well as

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keywords in the literature. Mild TBI is defined as a head injury associated with loss of consciousness of <30 minutes, Glasgow Coma Scale of 13 or higher, post-traumatic amnesia <24 hours, altered level of awareness of <24 hours and normal neuroimaging.[3] The most recent consensus statement on concussion in sport defines a concussion as a TBI induced by biomechanical forces and caused by either a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head, which typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously, but in some cases, the signs and symptoms evolve over a number of minutes to hours. The acute clinical signs and symptoms reflect a functional disturbance rather than a structural injury and may or may not include loss of consciousness. Resolution of the clinical and cognitive features typically follows a sequential course.[4]

Sports-related concussions occur between 1.4 and 3.8 million annually in the United States of America, with many going unreported by athletes.[1,5,6] This number does not include all the non-sports-related concussions or mTBIs. It is estimated that the annual costs related to mTBI in the United States are close to US $17 billion.[5] Thankfully, between 80% and 90% of these patients evolve favourably.[6,7] However, given the considerable number of these injuries, a significant minority, between 10% and 20% of these patients, develop chronic symptoms, often referred to as the post-concussive syndrome (PCS).[6,7] This syndrome is a constellation of symptoms that ultimately prevent the athlete or patient from successfully returning to play, workplace or school. The most common symptom in PCS is headache,[1,7–10] occurring in up to 88% of sports-related concussions,[1] followed closely and often concomitantly by photophobia. Individually disabling, but collectively worse, these symptoms prove to be a significant challenge to clinicians. The term post-traumatic headache (PTH) will be used in this review to describe headache attributed to traumatic injury to the head which does not include the disorder of headache attributed to whiplash. We reviewed PTH with photophobia together as our clinical experience indicates the combination of these two symptoms was frequent clinically without ever being specifically described in the literature. We hypothesized that there may be an underlying common pathophysiological explanation for this symptom combination.

OBJECTIVES

The purpose of this paper is to summarize the current level of knowledge and understanding of the pathophysiological basis behind PTH and photophobia in concussion/mTBI patients. The goal is to guide further fundamental research into the understanding of these mechanisms which will eventually help provide better and more targeted care for affected patients.

METHODS

A review of the literature was conducted using the databases CINAHL, EMBASE and PubMed. We have included our search terms and protocol in Annex. All types of articles, including review articles, randomized controlled trials, prospective and retrospective studies, series and case reports, and abstracts were initially included to ensure a global view of the subject. All papers were screened for topics or sections of pathophysiology of PTH or photophobia in patients with mTBI. We included papers published since 2000 in English and in French, and initially included

abstracts in order to encompass the largest scope and to minimize publication bias. Owing to the qualitative nature of this review, the goal was to obtain the broadest scope of knowledge about the subject despite some weaker quality papers. We included papers with adult and pediatric populations. We excluded papers specifically addressing moderate to severe TBI but included some papers where there was no distinction between the groups. Through a preliminary screen of titles and abstracts, papers with a potential to discuss the pathophysiology of PTH in mTBI were kept for a full-text screen. Any paper that discussed pathophysiological aspect of PTH was included. For photophobia, the same process was applied but with an even larger scope because of the paucity of literature.

Our original review included 3966 records. Using the database manager EndNote, duplicates were removed, with a resultant 3948 records. An initial screen of titles led to the exclusion of 3548 records. A more in-depth screen of abstracts and full texts, resulted in our final list of records totaling 51 titles which were analyzed and the narrative summary is provided in the following sections. To our knowledge this is the first paper solely focusing on the pathophysiology of PTH and photophobia in concussion/mTBI.

INTRODUCTION

Headache is the most common symptom in the acute and chronic phases of any severity of TBI (mild,[8,9,11–13] moderate or severe).[14–16] The majority of these headaches will resolve on their own within 6 months.[12] However, a significant minority of these patients will continue to experience headaches, commonly referred to as PTH. In the United States of America, 1.8 million develop acute PTH and 400,000 people develop chronic PTH annually.[12]

Post-traumatic headache are currently classified as a secondary type of headache.[17] Once the initial diagnosis of PTH is made, the clinical phenotype is then determined based on the more common primary headache types (most commonly tension or migraine). It is unclear whether these phenotypically similar patients have the same underlying pathophysiology or if the TBI "triggers" the same physiological mechanism.[8,16,18] Many hypotheses have been discussed, although not exclusively for the mTBI population. Current clinical practice bases its treatment approach for PTH on the clinical phenotype. Most PTH clinically resemble tension or migraine headaches or a mix of the two.[8,19] The exact distribution varies, but it is estimated that approximately 33%-50% of PTH have migraine features and 40%-97% have tension-type features.[1,9] Once this distinction is made, the clinician treats the patient with the standard therapeutic arsenal for typical tension or migraine headache.

Furthermore, all severities of TBI are often grouped together when discussing PTH and its pathophysiology, although clinical experience and several reports indicate that the mTBI population suffer from more PTH than their moderate-to-severe counterparts.[1,11,12,15,16,19–24]

In the PCS, photophobia is often the second most common symptom after headache and it often accompanies and complicates the headache disorder. This sensitivity to light and visual stimuli, including television or computer screens, is a significant burden for patients. In our clinical experience, it often has a compounding effect with the headache disorder. As with PTH,

very little is known about the pathophysiology of photophobia. We explore the literature in an attempt to determine our current level of understanding. We will attempt to link some fundamental science concepts from the review to clinical questions that may help bridge the gap between fundamental understanding and clinical practice.

Post-Traumatic Headaches in mTBI or Concussion

Tension and migraine headaches are discussed separately, although there are probably common mechanisms underlying both phenotypes and that several patients will present a mixed clinical picture in the setting of PTH.

Migraine is a neurovascular condition defined by attacks of moderate to severe throbbing headache. It is often accompanied by sensitivities, notably photophobia and phonophobia, but also sensitivity to odor and movement. Gastrointestinal symptoms are also common, as well as changes in brain states such as emotional, cognitive, autonomic or vestibular.[10] Chronic migraine occurs when headaches occur more than 14 days per month for 3 months, where only eight of these headache days need to have migraine characteristics.[25] Interestingly, head trauma may be a trigger for transformation from episodic to chronic migraine.[26]

Migraine is believed to be a primary neuronal dysfunction leading to changes, both intracranially and extracranially. The previously popular vascular theory of migraine is no longer considered accurate. The most up-to-date understanding of its pathophysiology relies on a combination of cortical spreading depression, activation of the trigeminovascular system and central and peripheral sensitization. The roles of serotonin and calcitonin gene-related peptide are also appreciated in the pathophysiology of migraines. Cortical spreading depression, a self-propagating wave of neuronal and glial depolarization, is thought to account for the aura of migraine and partially contribute to the pain of migraine through activation of the trigeminovascular system. The sensory neurons originating from the sensory trigeminal ganglion innervate large cerebral vessels, pial vessels, dura mater and large venous sinuses. Once the trigeminal ganglion stimulated, a release of vasoactive neuropeptides occurs and is associated with neurogenic inflammation, which also contributes to the pain component of migraine. Sensitization of these peripheral afferents as well as central sensitization of second order sensory neurons also plays a role in many symptoms associated with migraine.[25]

Tension-type headache (TTH) is the most prevalent headache disorder in the general population, whereas migraine is the most common headache diagnosis in the primary care setting[25,26] as it is generally more severe, and patients with migraine seek medical help. It is characterized by a mild to moderate bilateral headache. It is classically non-throbbing and has no associated symptoms or features. The pathophysiology of TTH is probably multifactorial. A common mechanism to TTH and migraine is the theory of sensitization. Sensitization of peripheral structures is believed to be important in episodic TTH, whereas central sensitization because of prolonged nociceptive input is believed to be the basis for conversion to chronic TTH. It is thought that TTH patients have deficient descending inhibition. There is also some evidence that neurogenic inflammation may also play a role in chronic TTH. Finally, unlike migraine, there seems to be only a minor role of hereditary and genetic factors in episodic TTH to the exception of chronic TTH.[27]

Headaches attributed to whiplash and medication overuse headaches are also commonly encountered in the PTH population.[3,18] Although clinically important, their pathophysiology will not be reviewed in depth. Whiplash headaches are postulated to be because of concomitant injury to cervical structures. The nociceptive inputs from these structures converge in the trigemino-cervical complex and explain the head pain caused by cervical spine injury.[3] Medication overuse headaches is believed to be due to dysregulation of serotonergic and opiate systems and chronic overuse of headache medication, and is mostly associated with opioids and caffeine.[3,28]

A general hypothesis to understanding the pathophysiology of PTH suggests that TBI activates an underlying TTH or migraine headache predisposition and pain then follows, or it accentuates headache patterns that were pre-existent to the trauma.

Acute Versus Persistent PTH

The distinction between acute and persistent PTH is based solely on time since the brain injury, and has a cut-off of 3 months.[29] The pathophysiology of acute and persistent PTH must be viewed as a continuum. Most acute PTH resolves on their own; however, 8%-35% of PTH will chronicize.[12,29] More emphasis in the literature is placed on persistent PTH, but appreciating the pathophysiology of the acute phase is an important step to understanding the chronic phase. Acute PTH is likely of multifactorial origin. Acutely, PTH patients may have impaired pain inhibition systems and a generalized sensitivity to pain.[30] The transition of an acute PTH to persistent PTH is an important clinical and research challenge. The reason for chronicity in some acute PTH remains unclear. Chronic neuroinflammation and concepts of sensitization are possible key mechanisms for persistent PTH.

Pathophysiology

Inflammation

With injury to the central nervous system (CNS), microglia, the main immune cells, become activated and can assume either pro or anti-inflammatory roles. Their anti-inflammatory role involves reparative and regenerative functions important for neuronal survival. The pro-inflammatory response, which includes the release of degradative, toxic and autocrine and paracrine compounds, is intended to clear the CNS of harmful substances, but can be harmful to normal cells. This activation has been histologically described, even in mTBI. Damage to the blood-brain barrier in all severities of TBI can alter its function and permeability, allowing entry of proteins, pathogens and leukocytes, which can all contribute to pro-inflammatory activities and ultimately cell damage. Cytokines which regulate this inflammatory process, normally in low amounts in the CNS, are activated mainly by glial cells and include interleukin-1 and tumor necrosis factor-α. This neuroinflammation, owing to direct injury to trigeminal nerve afferents or structures innervated by the trigeminal nerve, could be a plausible explanation for acute PTH.[16]

The role of inflammation in the pathophysiology of PTH is further supported by the findings of pain signaling molecules such as calcitonin gene-related peptide (CGRP) and nitric oxide synthase (NOs) which can activate the trigeminovascular system and

trigger migraine headaches.[19,21] A mTBI mouse model study was conducted and demonstrated increased levels of these molecules and this increase was associated with trigeminal allodynia as well as photophobia in the acute phase. Increases in CGRP levels were noted at several levels along the trigeminal pathway, even at distant sites from the injury. Notably, meningeal nociceptors were sensitized by this inflammation. Interestingly, treatment with sumatriptan and a CGRP antagonist decreased allodynia and photophobia in this mouse mTBI study. Further supporting the role of an inflammatory process are the findings of increased CGRP and substance P after injury to the somatosensory cortex in mice.[31] The CGRP levels in the brainstem correlated with periorbital allodynia as well.[31] Chronic sensitization in the context of a chronic inflammatory stimulus could be one explanation for the chronic PTH.[16,19,21,32] However, this theory alone would in difficult explain the higher incidence of PTH in mTBI as the more severe TBI would likely be more inflammatory.

The role of inflammation in the pain-sensitive dura has been implicated. The concept of sterile meningeal inflammation induced particularly by dural mast cells was demonstrated in an animal model of mTBI. Acute mast cell degranulation ipsilateral to the side of the mTBI was found up to 30 days and is thought to be due to the mechanical transmission of forces to the dura. Interestingly, mast cell degranulation was also noted on the contralateral side.[33] Could persistence of this dural inflammation lead to sensitization and ultimately contribute to persistent PTH?

An interesting study on systemic inflammation and mTBI using high-sensitivity C-reactive protein (HS-CRP) levels demonstrated correlation between elevated HS-CRP and unfavorable outcomes in this population during the first 3 months post-mTBI. Higher CRP levels were associated with persistent PCSs, psychological problems and cognitive impairment. It did not correlate with physiological symptoms such as headache, but it should be noted that headache is a symptom used in the diagnosis of PCS.[34]

Peripheral Origin

A model for mTBI on mice study showed that in the acute phase post-mTBI, there was selective enhancement of nociceptive responses to cranial structures (specifically the calvarial periosteum—considered a deep cranial structure by the authors) but not to extra-cranial structures (specifically the hindpaw). Moreover, there is evidence of inflammatory changes in deep cranial structures (mast cell degranulation) suggesting that in the acute phase post-mTBI, the PTH may originate from peripheral rather than from central or supraspinal pain pathways.[1] It is important to distinguish these findings which apply to acute PTH and may contrast with theories of central sensitization explaining how PTH can become chronic.[19,21] It can be therefore questioned if more aggressive treatment of PTH in the acute phase could prevent this central sensitization phenomenon[31] and thus prevent persistent PTH from developing.

A peripheral component to PTH can also be suspected based on findings that PTH patients also display cranial mechanical hyperalgesia, probably because of injury to peripheral structures, including blood vessels, nerve fibers and bone, as well as the initiation of an inflammatory cascade. This process may once again possibly contribute to sensitization.[14,15]

Central Origin

Structural brain matter damage has been described even in mTBI. It has been postulated that damage anywhere along the pain pathways can be a source of central pain.[14,21] Damage to spinothalamic or thalamocortical pathways would be most implicated and may occur even with mTBI.[15] Patients with PTH tend to have increased heat-pain thresholds which is in favor of a central origin.[14] Loss or a decrease of descending pain inhibition and loss of opioidergic systems could also contribute to PTH, a mechanism also reported in TTH and migraine.[14,15,21]

Further support for a central origin comes from imaging studies on mTBI patients with PTH migraines. Advanced magnetic resonance with diffusion-tensor imaging and proton spectroscopy is being increasingly studied as a means for the diagnosis of concussion or mTBI and PCS.[7,16] These imaging techniques were shown to differentiate mTBI patients from controls, as well as distinguish mTBI patients with migraines from mTBI patients without migraine based on white matter injuries.[5] The imaging techniques seem to be able to detect white matter injury patterns that correlate with PTH.[7] The role of these white matter changes in the pathogenesis of PTH is less clear, however.[7,35]

Functional rather than structural brain abnormalities are becoming increasingly recognized in the mTBI population as standard imaging modalities that often demonstrate no abnormalities. Blood flow abnormalities and damage to neurotransmitter systems (such as dopamine) post TBI are being evaluated with single-photon emission computed tomography. Mild TBI patients with PTH have been shown to have lower cerebral blood flow in the right frontal lobe and increased cerebral blood flow in the left parietal lobe when compared to controls.[32] These findings may be because of diffuse axonal injury and inflammation;[32] however, causality has yet to be determined.

Cortical Spreading Depolarization

Cortical spreading depolarization (CSD) is a pathological depolarizing phenomenon that has been described in several pathological states such as strokes, epilepsy, intracranial hemorrhages and migraines and TBI. It interrupts local cortical function for minutes to hours.[35] Glutamate-induced toxicity seems to be the common triggering mechanism for CSD, which ultimately leads to a depression in cortical activity. Concomitantly, there is also a pathological change in vascular response, where vasoconstriction, instead of vasodilation, occurs, which further contributes to brain injury.[36] Traumatic brain injury-induced hypermetabolism in conjunction with reduced blood flow leads to a metabolic mismatch.[37] Traumatic brain injury promotes an environment susceptible to CSD,[13] and patients exhibiting CSD tend to have worse outcome;[36] however, it is unclear how this applies to the mTBI population. The link between CSD and PTH is largely through the findings of CSD in the pathophysiology of migraines.[10] Injury-triggered CSD is more commonly seen with severe TBI, however.[10]

Glutamate

It is known that TBI results in glutamate release proportional to the extent of the TBI. Glutamate release from astrocytes and microglia occurs after a TBI. This effect of excess glutamate is

calcium influx and neuronal injury.[6,38] Furthermore, the excess glutamate overstimulates receptors, notably NMDA receptors, and creates ion imbalances.[38] The effect of this excitotoxicity on the pathogenesis of PTH is unclear but can be due to its ability to promote CSD and central sensitization.[24,38]

Autoimmune

One study found that auto-antibodies to glutamate receptors in pediatric persistent PTH were elevated even in the mild closed TBI. These auto-antibodies would be the result of hypoxic and neurometabolic changes in the brain.[39] There is a net result of glutamate receptor overstimulation.[39]

Electrolyte abnormalities

Magnesium is required to regulate transmembrane electrical activity and has a neuroprotective action by decreasing the excitotoxic effects of glutamate and N-methyl-D-aspartate (NMDA).[6] A pediatric study demonstrated that PTH patients had lower levels of ionized magnesium and higher ratios of ionized calcium to ionized magnesium. It is unclear if there is a causal relationship between these electrolytes findings and the pathophysiology of PTH.[21]

Genetic

A genetic predisposition to symptoms after mTBI has been postulated after reports of severe neurological symptoms in mTBI patients who are carriers of a CACNA1A gene mutation, an ion channelopathy associated with familial hemiplegic migraine.[13] This theory supports the idea by which some patients would present a genetically lower threshold to symptom development after a head trauma[13] and could help explain the discrepancy in symptom severity after a similar intensity trauma. This specific genetic mutation has not been directly linked to PTH; however, it does provide insight toward a genetic avenue in understanding the pathophysiology of PTH.

Hormonal Dysregulation

Hormonal dysregulation has been observed in TBI patients, including hypothalamic dysfunction, which could mediate headaches and be a potential contributor to PTH.[10] Hypothalamic injury in TBI may contribute to PTH through its effect on the sleep–wake cycle and circadian rhythms.[10] It is important to note that this finding is not specific nor associated with mTBI and is usually seen in more severe TBI. Therefore, its role in PTH in the mTBI population remains speculative.

Clinical Risk Factors

Different risk factors for the development of PTH have been identified with epidemiological studies. Women tend to develop more PTH. The mechanism of injury also seems to have an impact as motor vehicle accidents tend to predispose more to PTH. Pre-trauma history of headache, lower education and socioeconomic levels, short duration of post-traumatic amnesia and medication overuse are other risk factors for the development for PTH.[8,12] As with many pain conditions, comorbid psychiatric conditions such as anxiety or post-traumatic stress disorder (PTSD), and ongoing financial or legal proceedings regarding the injury can cloud the picture.[8,12,14,15,18,21]

Photophobia in mTBI or Concussion

Photophobia, or photosensitivity, is defined as an abnormal tolerance to light or visual discomfort in the presence of normal light levels.[40–42] Although occasionally reported in isolation, photophobia is commonly seen in patients with PTH and commonly associated with migraine-type headaches.[41] Tension-type headache sufferers also report more sensitivity to light compared with controls.[40]

Photophobia is an increased sensitivity to light and visual stimuli from all sources. Patients tend to be particularly sensitive to artificial indoor light, computer monitors including screens of all kind and glare.[41] Screen intolerance is particularly important given its omnipresence and patients will often dim the light intensity of the screen or modify the hue.[43] This may be due to the rate at which computer or cell phone screens refresh (60 Hz) with concussed individuals having a higher critical flicker frequency threshold.[44] Of particular interest, migraineurs report a high prevalence of photophobia during a headache attack, some report light as a trigger and some report light sensitivity even outside of their headaches.[40,41]

Photophobia is a common and debilitating symptom in mTBI patients and PCS,[40,41,45,46] and even more so when associated with PTH. A military study found a 22% prevalence of photophobia in troops with mTBI.[40] It may have a significant impact on the patient's quality of life.

It is not uncommon for patients with photophobia to be wearing sunglasses in a physician's waiting room.[41] In fact, colored glasses have been studied as a treatment method for patients suffering from light sensitivity. Blue, green, red and purple-colored glasses seemed to offer the most relief from light sensitivity. This therapeutic option can be helpful in alleviating symptoms of light sensitivity post-mTBI and may help with the recovery process.[47]

Clinical experience has shown that subtle photophobia in mTBI patients may be underappreciated clinically and can be discovered with proper patient questioning. Part of the cause for underrecognizing this symptom may be because of the lack of standardized tests for the diagnosis or quantification of this symptom.[42]

Photophobia is probably a response to light to protect the retina, but in some this threshold is lower than normal.[41,44] Retinal ganglion cells (RGC) are the cells which send axons to make up the optic nerve and collect information from photoreceptors.[47] Retinal ganglion cells send their axons to the lateral geniculate nucleus.[47] Intrinsically photosensitive RGC, also known as melanopsin cells, have been discovered and are postulated as the key cell in photophobia. These cells contain the photopigment melanopsin, which are activated via traditional visual pathways (photoreceptors such as rods and cones) or can be activated by light directly. These cells make up to <1% of ganglion cells.[41]

There are currently three postulated pathways involved in photophobia. The first pathway begins with "regular" ganglion cells which project via the optic nerve to the olivary pretectal nucleus, then to the superior salivatory nucleus. Through the pterygopalatine ganglion, this causes ocular vasodilation and activation of ocular trigeminal afferents through the trigemino-automic relfex.[40] These afferents then project to the trigeminal nucleus caudalis, the thalamus and to the cortex.[40,41] The trigeminal system is key in the pathophysiology of photophobia as it is very closely linked to pain sensation.[40] The ophthalmic division

of the trigeminal nerve (V1) is responsible for nociceptive afferents from the eye and orbit.[40]

The second pathway involves the previously described intrinsically photosensitive RGC. These cells, also through the optic nerve, project directly to the thalamus which is also receiving intracranial nociceptive input. The thalamus receives light and pain information, which is then projected to sensory and association cortices. The pathway involving the thalamus is particularly interesting because of the role of the thalamus for multiple sensory integration.[40,41] This pathway could explain the photophobia seen in patients with meningitis or sub-arachnoid hemorrhage.[40]

The third pathway also involves intrinsically photosensitive RGC, but through projections that do not involve the optic nerve.

These cells have been found in rodent iris and could activate trigeminal ocular afferents. This pathway could explain direct trigeminal stimulation in the absence of a functioning optic nerve,[40,41] and could help explain photophobia seen in some blind patients.[40]

These pathways are supported by findings on functional MRI which show increased activity in patients with photophobia in the trigeminal nucleus, superior colliculus, thalamus and cortex.[41]

An interesting report of three patients who had complete lack of photophobia because of bilateral ventral occipital lobe lesions from cerebral infarction points to another potentially crucial cortical area of the brain needed for photophobia,[44] which may compliment the above described pathways. This region of the brain, however, is not a classic site of injury in the context of TBI.
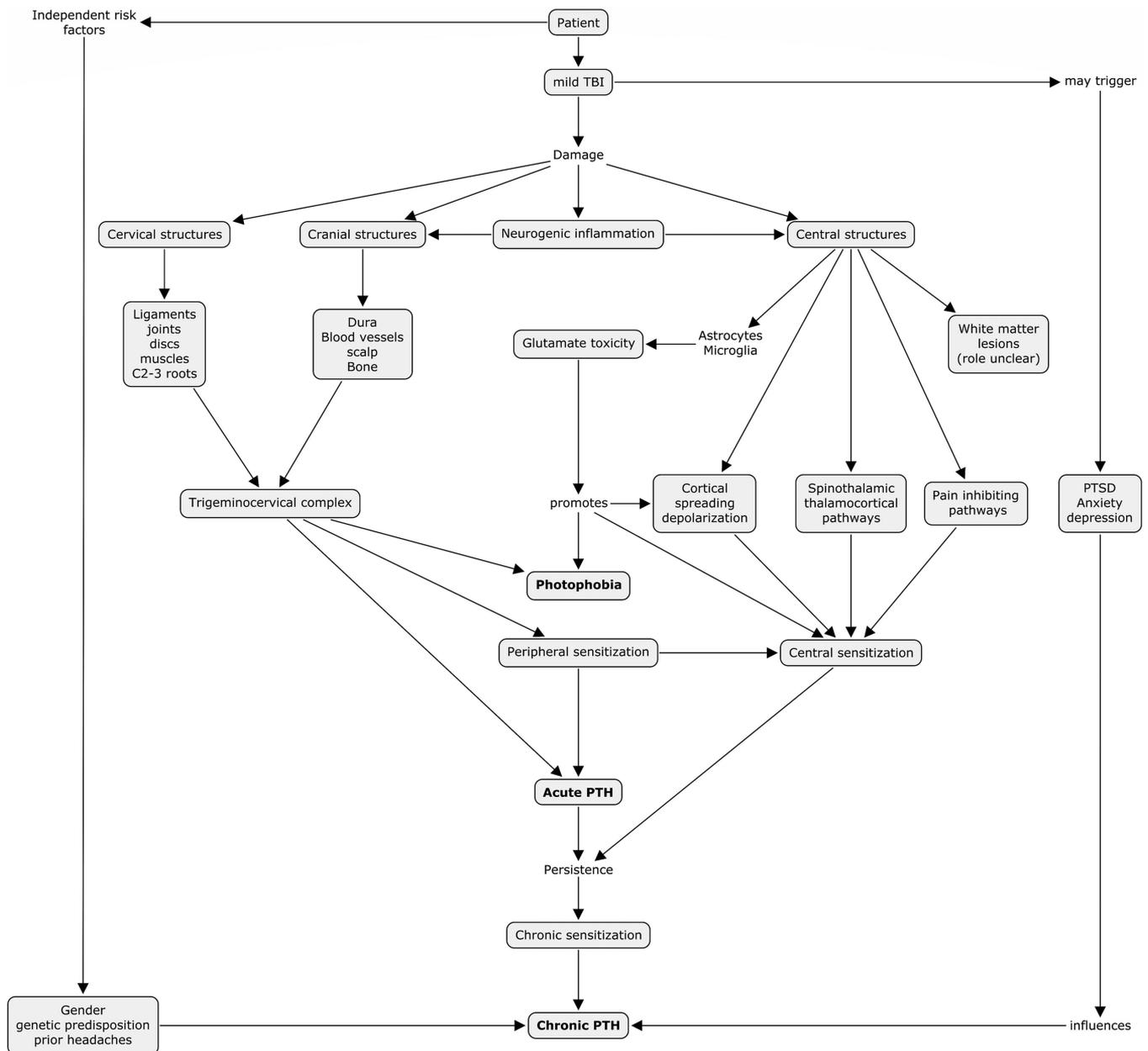
Figure 1: *Proposed pathophysiological mechanisms to PTH and photophobia in mTBI. PTH = post-traumatic headache, mTBI = mild traumatic brain injury, PTSD = post-traumatic stress disorder.*

CGRP and NO are important inflammatory pain signaling molecules that can activate the trigeminovascular system and are believed to be part of the pathophysiology of PTH as described earlier.[19] Blocking CGRP in a mouse TBI model was found to relieve photosensitivity.[19]

If photophobia persists in the chronic phase, it can often be attributed to concomitant migraine, as photophobia is a key diagnostic element,[40] and potentially even if the PTH phenotype is of the tension type.

Cortical damage has also been postulated to explain photophobia in TBI. Traumatic brain injury patients with photosensitivity presented with elevated dark adaptation thresholds, which are usually associated with retinal dysfunction. However, the subjects had no retinal dysfunction, which prompted the hypothesis of either post-retinal, cortical or subcortical processes to explain the abnormal dark adaptation with normal retinal function. Head trauma induces changes that result in a hyperexcitable state and increased neural gain which would lead to photosensitivity. A cortical adaptive mechanism attempts to attenuate light sensitivity at all levels that could translate into elevated dark adaptation thresholds.[48] The exact sites involved in the initial injury and postulated adaptive mechanisms require further research. The concept of cortical excitability has also been reported in conditions associated with photophobia, such as migraine and epilepsy.[49]

As with PTH, a biopsychosocial view of the subject is necessary. Viewing photophobia as a chronic "pain" condition may be necessary to understand the impact of comorbid anxiety, depression or PTSD. A study has showed more light sensitivity in TBI patients with PTSD than in TBI patients without PTSD.[50]

DISCUSSION

Post-traumatic headache and photophobia in the mTBI population are challenging symptoms for clinicians to treat. In order to provide better clinical care for these patients, more fundamental research is needed to help understand the underlying mechanisms behind the symptoms. Although it is often reported that little is known about the pathophysiology, this review highlights significant research advances.

It is likely that mechanisms of PTH overlap with primary TTH and migraine, but trauma does in fact cloud the clinical and pathophysiological picture. Post-traumatic headache is likely a multifactorial process that evolves over time from the acute to the chronic phase. The final pain-producing step is probably common to the traumatic and atrauamtic headache types, as evidenced by the same clinical phenotypes. However, the steps or mechanisms by which trauma ends up triggering these similar mechanisms are crucial to uncover.

We propose the following diagram (Figure 1), adapted from Defrin et al,[51] to describe our summarized understanding of the pathophysiological mechanisms to PTH and photophobia in mTBI as well as possible overlapping pathophysiological mechanisms between the two symptoms.

A multifactorial explanation to PTH and photophobia is evident and it is unlikely that a single eventual explanation exists. Anatomically, interactions between injured cervical, cranial and central neurological structures are evident and their respective contributions probably vary between individual patients. We highlight an interesting finding from our narrative review, which shows overlapping mechanisms between PTH and photophobia in the mTBI population through both peripheral and central mechanisms. This pathophysiological finding correlates with our clinical experience where patients with PTH often experience concomitant photophobia. Furthermore, it is not uncommon that photophobia is the more functionally limiting symptom as it limits going outdoors, interacting in visually stimulating environments and using computers or other electronic devices. Targeting these common mechanisms could lead to a breakthrough common treatment for both symptoms.

In order to precisely describe the mechanisms, we believe that focussing on mTBI and separating it from the moderate to severe counterparts is crucial. Further distinguishing the sub-population of sports-related concussions may also help as our experience shows that this population is quite different in the clinical setting. Furthermore, although overlap and mixed features probably exist, it could be beneficial to study mTBI PTH by dividing them into groups based on their clinical phenotypes (tension vs. migraine).

Our understanding of the pathophysiology of photophobia in general has also progressed. There is still more work to be done in order to determine how we can apply this knowledge clinically. Overlapping pathophysiological data is documented between PTH and photophobia, notably, the implication of the trigeminovascular system, dural irritation and inflammation, cortical hyperexcitability and migraines. A common pathway for both PTH and photophobia would be pleasing to the medical field, but more research is needed to prove this.

Some questions do remain. Why do patients with mTBI suffer from more PTH? Why do some patients develop a migraine PTH versus a tension type PTH? Can aggressive treatment of acute PTH prevent sensitization and the development of persistent PTH?

CONCLUSION

In conclusion, we believe that this narrative review highlights the current level of understanding of the pathophysiology of PTH and photophobia in patients with mTBI. These patients may be seen by a variety of specialists, including primary care, sports medicine, neurology, neurosurgery and physical medicine, and thus it is important that fundamental and clinical evidence be made available for all clinicians. We hope this review can be used as a guide for future fundamental and clinical research.

DISCLOSURES

CM, JHD, and MHD have nothing to disclose.

REFERENCES

1. Conidi FX. Sports-related concussion: the role of the headache specialist. Headache. 2012;52(Suppl 1):15-21.
2. Vargas BB, Dodick DW. Posttraumatic headache. Curr Opin Neurol. 2012;25(3):284-9.
3. Pinchefsky E, Dubrovsky AS, Friedman D, Shevell M. Part I—Evaluation of pediatric post-traumatic headaches. Pediatr Neurol. 2015;52(3):263-9.
4. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport—the 5th International Conference on Concussion in Sport held in Berlin, October 2016. Br J Sports Med. 2017;51:838-47.

5. Delic J, Alhilali LM, Hughes MA, Gumus S, Fakhran S. White matter injuries in mild traumatic brain injury and posttraumatic migraines: diffusion entropy analysis. Radiology. 2016;279 (3):859-66.

6. Maroon JC, LePere DB, Blaylock RL, Bost JW. Postconcussion syndrome: a review of pathophysiology and potential non-pharmacological approaches to treatment. Phys Sports Med. 2013;40(4):73-87.

7. Ghodadra A, Alhilali L, Fakhran S. Principal component analysis of diffusion tensor images to determine white matter injury patterns underlying postconcussive headache. Am J Neuroradiol. 2016;37 (2):274-8.

8. D'Onofrio F, Russo A, Conte F, Casucci G, Tessitore A, Tedeschi G. Post-traumatic headaches: an epidemiological overview. Neurol Sci. 2014;35(1):203-6.

9. Kjeldgaard D, Forchhammer H, Teasdale T, Jensen RH. Chronic post-traumatic headache after mild head injury: a descriptive study. Cephalalgia. 2014;34(3):191-200.

10. Monteith TS, Borsook D. Insights and advances in post-traumatic headache: research considerations. Curr Neurol Neurosci Rep. 2014;14(2):428.

11. Blume HK. Headaches after concussion in pediatrics: a review. Curr Pain Headache Rep. 2015;19(9):42.

12. Erickson JC, Neely ET, Theeler BJ. Posttraumatic headache. Continuum (Minneap Minn). 2010;16(6 Traumatic Brain Injury): 55-78.

13. Seifert T. Post-traumatic headache therapy in the athlete. Curr Pain Headache Rep. 2016;20(6):41.

14. 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(9):924-31.

15. Defrin R, Riabinin M, Feingold Y, Schreiber S, Pick CG. Deficient pain modulatory systems in patients with mild traumatic brain and chronic post-traumatic headache: implications for its mechanism. J Neurotrauma. 2015;32(1):28-37.

16. Mayer CL, Huber BR, Peskind E. Traumatic brain injury, neuroinflammation, and post-traumatic headaches. Headache. 2013;53 (9):1523-30.

17. Sarmento E, Moreira P, Brito C, Souza J, Jevoux C, Bigal M. Proton spectroscopy in patients with post-traumatic headache attributed to mild head injury. Headache. 2009;49(9):1345-52.

18. Heyer GL, Idris SA. Does analgesic overuse contribute to chronic post-traumatic headaches in adolescent concussion patients? Pediatr Neurol. 2014;50(5):464-8.

19. Daiutolo BV, Tyburski A, Clark SW, Elliott MB. Trigeminal pain molecules, allodynia, and photosensitivity are pharmacologically and genetically modulated in a model of traumatic brain injury. J Neurotrauma. 2016;33(8):748-60.

20. Benromano T, Defrin R, Ahn AH, Zhao J, Pick CG, Levy D. Mild closed head injury promotes a selective trigeminal hypernociception: implications for the acute emergence of post-traumatic headache. Eur J Pain. 2015;19(5):621-8.

21. Marcus JC, Altura BT, Altura BM. Serum ionized magnesium in post-traumatic headaches. J Pediatr. 2001;139(3):459-62.

22. Obermann M, Keidel M, Diener HC. Post-traumatic headache: is it for real? Crossfire debates on headache: pro. Headache. 2010;50 (4):710-5.

23. Solomon S. Chronic post-traumatic neck and head pain. Headache. 2005;45(1):53-67.

24. Riechers RG 2nd, Walker MF, Ruff RL. Post-traumatic headaches. Handb Clin Neurol. 2015;128:567-78.

25. Cutrer M. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. In: Dashe J, editor. UpToDate, 2017. Retrieved July 11, 2017 from: https://www.uptodate.com/contents/pathophysiology-clinical-manifestations-and-diagnosis-of-migraine-in-adults?source=search_result&search=migraine%20headache&selectedTitle=2~150

26. Garza I. Chronic migraine. In: Dashe J, editor. UpToDate, 2018. Retrieved July 7, 2018 from https://www.uptodate.com/contents/chronic-migraine

27. Taylor F. Tension-type headache in adults: Pathophysiology, clinical features, and diagnosis. In J. Dashe editor. Uptodate, 2016. Retrieved July 11, 2017 from https://www.uptodate.com/contents/tension-type-headache-in-adults-pathophysiology-clinical-features-and-diagnosis?source=search_result&search=tension%20headache&selectedTitle=2~94

28. Lane J, Arciniegas D. Post-traumatic headache. Curr Treat Options Neurol. 2002;4:89-104.

29. Bryan CJ, Hernandez AM. Predictors of post-traumatic headache severity among deployed military personnel. Headache. 2011;51 (6):945-53.

30. Lainez MJ, Piera A, Bono G. Headache attributed to head or neck trauma. Handb Clin Neurol. 2010;97:501-16.

31. 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(6):966-84.

32. Newberg AB, Serruya M, Gepty A, et al. Clinical comparison of 99mTc exametazime and 123I Ioflupane SPECT in patients with chronic mild traumatic brain injury. PLoS One. 2014;9(1): e87009.

33. Levy D, Edut S, Baraz-Goldstein R, et al. Responses of dural mast cells in concussive and blast models of mild traumatic brain injury in mice: potential implications for post-traumatic headache. Cephalalgia. 2016;36(10):915-23.

34. Su SH, Xu W, Li M, et al. Elevated C-reactive protein levels may be a predictor of persistent unfavourable symptoms in patients with mild traumatic brain injury: a preliminary study. Brain Behav Immun. 2014;38:111-7.

35. Torrente D, Cabezas R, Avila MF, Garcia-Segura LM, Barreto GE, Guedes RCA. Cortical spreading depression in traumatic brain injuries: is there a role for astrocytes? Neurosci Lett. 2014;565:2-6.

36. Kramer DR, Fujii T, Ohiorhenuan I, Liu CY. Cortical spreading depolarization: pathophysiology, implications, and future directions. J Clin Neurosci. 2016;24:22-7.

37. Seifert T, Shipman V. The pathophysiology of sports concussion. Curr Pain Headache Rep. 2015;19(8):36.

38. Packard RHL. Pathogenesis of posttraumatic headache and migraine: a common headache pathway? Headache. 1997;37:142-52.

39. Goryunova AV, Bazarnaya NA, Sorokina EG, et al. Glutamate receptor autoantibody concentrations in children with chronic post-traumatic headache. Neurosci Behav Physiol. 2007;37 (8):761-4; http://dx.doi.org/10.1007/s11055-007-0079-3

40. Digre KB, Brennan KC. Shedding light on photophobia. J Neuro-Ophthalmol. 2012;32(1):68-81.

41. Katz BJ, Digre KB. Diagnosis, pathophysiology, and treatment of photophobia. Surv Ophthalmol. 2016;61(4):466-77.

42. Truong JQ, Ciuffreda KJ, Han MHE, Suchoff IB. Photosensitivity in mild traumatic brain injury (mTBI): a retrospective analysis. Brain Inj. 2014;28(10):1283-7.

43. Clark J, Hasselfeld K, Bigsby K, Divine J. Colored glasses to mitigate photophobia symptoms posttraumatic brain injury. J Athl Train. 2017;52(8):725-9.

44. Mansur A, Hauer TM, Hussain MW, et al. A nonliquid crystal display screen computer for treatment of photosensitivity and computer screen intolerance in post-concussion syndrome. J Neurotrauma. 2018;35(16):1886-94.

45. Bulson R, Jun W, Hayes J. Visual symptomatology and referral patterns for operation Iraqi freedom and operation enduring freedom veterans with traumatic brain injury. J Rehab Res Dev. 2012;49(7):1075-82.

46. Goodrich GL, Flyg HM, Kirby JE, Chang CY, Martinsen GL. Mechanisms of TBI and visual consequences in military and veteran populations. Optom Vis Sci. 2013;90(2):105-12.

47. Blumenfeld H. Neuroanatomy through clinical cases. Sunderland Massachusetts: Sinauer Associates; 2010.

48. Du T, Ciuffreda KJ, Kapoor N. Elevated dark adaptation thresholds in traumatic brain injury. Brain Inj. 2005;19(13):1125-38.

49. Magone MT, Kwon E, Shin SY. Chronic visual dysfunction after blast-induced mild traumatic brain injury. J Rehab Res Dev. 2014;51(1):71-80.

50. Goodrich GL, Martinsen GL, Flyg HM, Kirby J, Garvert DW, Tyler CW. Visual function, traumatic brain injury, and posttraumatic stress disorder. J Rehab Res Dev. 2014;51(4):547-58.

51. Defrin R. Chronic post-traumatic headache: Clinical findings and possible mechanisms. J Man Manip Ther. 2014;22(1):36-43.

ANNEX

Search terms and protocol

photophobia[mh] **OR** headache[mh] **OR** migraine disorders [mh] **OR** headache disorders[mh] **OR** photophobia*[ot] **OR** headache*[ot] **OR** migraine*[ot] **OR** head pain*[ot] **OR** cranial pain*[ot] **OR** cephalalgia*[ot] **OR** cephalodynia* [ot] **OR** hemicrania*[ot] **OR** light sensitivit*[ot] **OR** photophobia* [tiab] **OR** headache*[tiab] **OR** migraine*[tiab] **OR** head pain*[tiab] **OR** cranial pain*[tiab] **OR** cephalalgia*[tiab] **OR** cephalodynia* [tiab] **OR** hemicrania*[tiab] **OR** light sensitivit*[tiab]

AND

rain concussion[mesh:noexp] **OR** post-concussion syndrome [mh] **OR** çraniocerebral trauma[mesh:noexp] **OR** "head Injuries, closed"[mesh:noexp] **OR** brain injuries[mesh:noexp] **OR** (athletic injuries[mh] AND (brain[tiab] OR head[tiab] OR skull [tiab])) **OR** brain concussion*[ot] **OR** commotiocerebri [ot] **OR** post concussion syndrome[ot] **OR** post concussive syndrome[ot] **OR** craniocerebral trauma*[ot] **OR** craniocerebral injur*[ot] **OR** "parietal trauma*"[ot] **OR** crushing skull injur* [ot] **OR** "occipital trauma*"[ot] **OR** "temporal trauma*"[ot] **OR** "frontal trauma*"[ot] **OR** "forehead trauma*"[ot] **OR** head injur*[ot] **OR** head trauma*[ot] **OR** brain injur*[ot] **OR** brain trauma*[ot] **OR** TBI[ot] **OR** TBIs[ot] **OR** brain damage*[ot] **OR** (athletic injuries[ot] AND (brain[ot] OR head[ot] OR skull [ot])) **OR** brain concussion*[tiab] **OR** commotiocerebri [tiab] **OR** post concussion syndrome[tiab] **OR** post concussive syndrome[tiab] **OR** craniocerebral trauma*[tiab] **OR** craniocerebral injur*[tiab] **OR** "parietal trauma*"[tiab] **OR** crushing skull injur*[tiab] **OR** "occipital trauma*"[tiab] **OR** "temporal trauma*"[tiab] **OR** "frontal trauma*"[tiab] **OR** "forehead trauma*"[tiab] **OR** head injur*[tiab] **OR** head trauma*[tiab] **OR** brain injur*[tiab] **OR** brain trauma*[tiab] **OR** TBI[tiab] **OR**TBIs [tiab] **OR** brain damage*[tiab] **OR** (athletic injuries[tiab] AND (brain[tiab] OR head[tiab] OR skull[tiab]))