

Examining the association between traumatic brain injury and headache

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Traumatic brain injury is a common and major cause of disability and death that might require emergency neurological and neurosurgical interventions. Traumatic brain injury can result in temporary or permanent physical, cognitive and psychological impairments. One of the most common complications associated with traumatic brain injury is post-traumatic headache, associated with significant disability and reduced quality of life. Post-traumatic headache is a public health concern that can affect the long-term outcome of traumatic brain injury patients. Clinical symptoms of post-traumatic headache significantly overlap with common primary headaches such as migraine and tension-type headaches. Beyond neurobiological factors, psychological factors can play crucial roles in the initiation and sustainment of post-traumatic headache. While neurological mechanisms underlying post-traumatic headache remains unknown, different studies suggest various mechanisms such as physical damages to the cranial nerves and neck structure, hyper-sensitization of the pain modulatory pathway, and inflammation as underlying causes for the neurobiology of headache. I explore the hypothesis that traumatic brain injury is associated with headaches. In particular, I provide an overview of the neurobiology of post-traumatic headache, its diagnosis, presenting recent findings on the etiology, explaining similarities and differences between with primary headaches such as migraine and tension-type headache, discuss pharmacological and non-pharmacological interventions for the treatments, as well as emphasising on the psychological importance of post-traumatic headache.

Keywords

Traumatic brain injury; Headache; Post-traumatic headache; Migraine; Tension-type headache; Neurology

1. Introduction

Traumatic brain injury (TBI) is a preventable injury caused by external biomechanical forces exerted on the head. The patient outcome can range from complete recovery to disability and death [1]. Referred to as a “silent epidemic”, TBI is estimated to affect sixty-nine million people globally every year [2]. TBI is a source of concern for public health practitioners, care providers, and health policymakers. 1.1% of the US population alone experience lifelong disabilities as a consequence of TBI [3]. The incidence of TBI can increase sporadically due to injuries sustained during military and combat operations [4], and the majority of TBI patients do not seek hospital treatment for their injuries [5].

TBI can cause direct damage to the brain dura and parenchyma, or it can be a closed-head injury with an intact skull and dura [6]. Multiple clinical factors such as the absence or decreased consciousness, the presence of transient or non-transient neurological symptoms, amnesia (i.e., loss of memory of events after the injury), changes in the mental state and radiological images, including computerized tomography (CT) and magnetic resonance imaging (MRI) are used to classify TBI into mild, moderate and severe [7]. TBI can be divided into subconcussive head trauma, repetitive mild head TBI, post-concussive syndrome, and chronic traumatic encephalopathy [8] (Fig. 1).

Approximately 80–90% of TBI cases are mild TBI, also known as concussion, which is caused by blunt, non-penetrating forces, mostly by falls, motor vehicle accidents, sports and violence, with a high incidence rate among males, adolescents and young adults [6, 9–11]. While a single test cannot establish the clinical diagnosis, 10–15% of patients with mild TBI can be diagnosed with post-concussive syndrome [12] if their symptoms persist for more than three months [13]. Although subconcussive head trauma does not result in any obvious clinical symptoms, repetitive mild head TBI is the underlying reason for chronic traumatic encephalopathy [7]. This is a progressive neurodegenerative disorder characterized by the deposition of hyperphosphorylated tau at a depth of sulci among contact sports participants and military veterans [14].

Clinical manifestations associated with TBI can be categorized into three groups of physical, cognitive and psychological symptoms [15–17]. Highly variable physical symptoms associated with mild TBI include nausea, dizziness, vomiting, headache, emotional irritability and, in some cases, loss of consciousness [11, 18, 19]. Cognitive impairments in multiple neuroscientific domains such as learning, memory, attention, processing speed, problem-solving, reasoning, and language are associated with TBI [20, 21]. Psychological symptoms of TBI include depression, anxiety, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder, panic attack, psychosis and personality changes such as apathy and aggression [22, 23]. Most symptoms in patients experiencing concussions are resolved within 12 weeks of the incidence [7]; however, having underlying psychological and physical

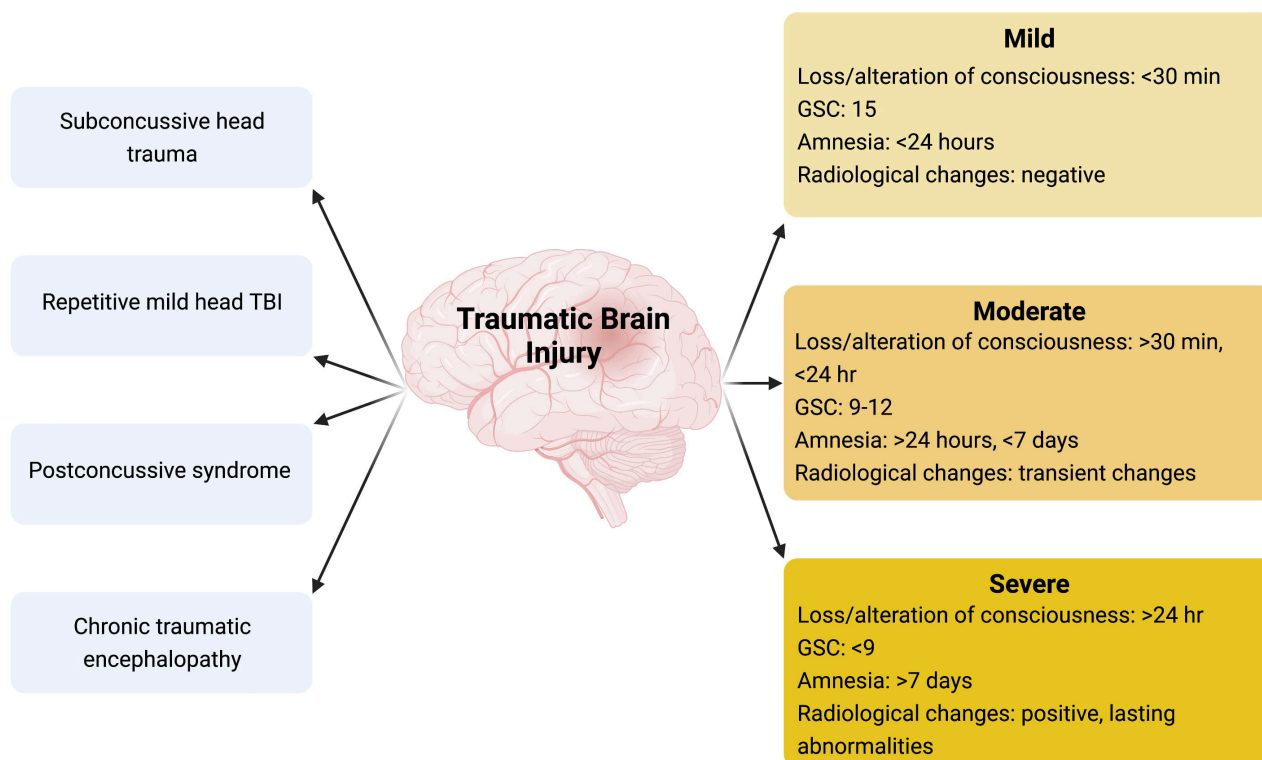


Fig. 1. Traumatic brain injury (TBI) can be classified as mild, moderate and severe based on symptoms manifestation. TBI can also be classified into subconcussive head trauma, repetitive mild head TBI, postconcussive syndrome, and chronic traumatic encephalopathy.

conditions and other factors, such as substance abuse, can prolong the patient's recovery [24, 25].

Headache has been identified as the most common, persistent and debilitating symptom associated with TBI [19, 26]. TBI patients with post-traumatic headache (PTH) can have poorer outcomes and a longer recovery time than those who do not experience headaches [27, 28]; however, a causal relationship has not been established. PTH patients complain about pain in different head and neck regions, such as temples, forehead, neck, posterior region of the head, eyes, and vertex [29]. Some studies showed that 15% of TBI patients had headaches three months after the incident [30], while others showed that 90% of TBI patients suffered from headaches even up to five years after their injury [28, 31]. Variations in the prevalence of PTH can be due to the severity of TBI and type of pain [32, 33].

Comparing TBI to general traumatic injuries, a study reported 18%–22% of PTH patients experienced new or worsened headache symptoms one year after the injury [34], indicating that PTH is not necessarily related to the inciting TBI. Similar studies estimated that between 14%–58% of patients with mild TBI developed headaches 12 months after the trauma [35, 36]. In contrast, others did not find PTH symptoms after three months in TBI patients compared to controls [37]. Multiple reasons such as the sampling bias, assessment methods, study types, and the country where the study was conducted can potentially explain discrepancies ob-

served in PTH prevalence in different studies [26, 38]. For example, one caveat can be the inclusion of TBI patients who had pre-existing headaches in some studies, causing a higher reporting of PTH [39]. A study suggested that variations in reporting the frequency of the post-concussion syndrome could be related to cultural differences [40]. Others corroborated these findings by showing that culture and language background could affect how patients report their symptoms. Therefore, they should be considered in investigating symptoms of post-concussion syndrome [41]. Nevertheless, headaches, especially migraines-like headaches, have negative consequences on the quality of life of individuals experiencing mild TBI [42, 43].

PTH may be accompanied by other symptoms and disabilities such as cognitive, behavioral, emotional and somatic impairments [18, 44]. Similarly, chronic primary headaches can be associated with anxiety, depression, suicidal behaviors [45–47], as well as comorbidities such as back pain, ischemic heart disease and stroke [48]. Recent studies demonstrate that the association of psychiatric comorbidities with migraine is complex, and a bidirectional relationship exists between migraine, major depression and panic disorder [49]. Beyond depression, PTH can be associated with other psychiatric disorders such as post-traumatic disorder [50].

Table 1. A summary of different studies investigating risk factors associated with PTH. The table provides an overview of the most significant risk factors associated with PTH and is not exhaustive.

Risk factor	Study type	Participants	Association strength	Reference
Pre-existing psychological history, history of migraine, new co-morbidities associated with PTH, medication overuse	Retrospective study with inclusion criteria of adults over 18 years old diagnosed with PTH.	300 PTH patients (150 acute, 150 persistent). Median age: 47 years. Female: male ratio of 2.7:1.	$p < 0.0001$	[60]
Female sex, prior mild TBI, injury under the influence of alcohol	Population-based longitudinal study with 12 months follow-up	378 mild TBI patients, 83 community controls and 82 trauma controls, 16–59 years old.	$p < 0.05$	[58]
Prior history of mild TBI, history of anxiety, poor memory, and light sensitivity	Matched, case-control study	85 cases and 340 controls. Average age (mean \pm SD) = 25.4 ± 14.3 . 56.5% male.	$p < 0.05$	[61]
Previous history of mild TBI	Population-based historical cohort study	940 patients and 38,751 controls. Average age at injury (mean \pm SD) = 39.9 ± 19.6 . Average age at participation (mean \pm SD) = 50.6 ± 17.9 . 45% females.	$p < 0.05$	[62]
Previous mental health problems (depression), extra-cranial bodily injuries, depression	Prospective study with one-year follow-up	126 mild TBI patients. Average age (mean \pm SD) = 37.8 ± 13.5 . 56.3% females. Controls = 66 age- and sex-matched individuals.	$p < 0.001$	[63]
Minimal traumatic intracranial hemorrhage, post-traumatic seizure	Retrospective matched case-control study	57 mild TBI patients. Average age (mean \pm SD) = 34.7 ± 11.2 . 25 females. 57 matched controls. Average age (mean \pm SD) = 34.4 ± 11.9 . 26 females.	$p < 0.05$	[64]
Pre-injury headache, particularly migraine-type	Prospective, longitudinal cohort study with 12 months follow-up	450 participants. Average age (mean \pm SD) = 43.0 ± 10.2 . 71% males.	$p < 0.05$	[65]
Pre-injury headache, female sex	Prospective, longitudinal cohort study with 12 months follow-up	452 TBI patients. Average age (mean \pm SD) = 43.7 ± 19.7 . 71% males.	$p < 0.01$	[66]
Use of analgesics, pre-injury headache, female sex	Prospective, longitudinal cohort study with 12 months follow-up	168 individuals aged 18–60 years.	$p < 0.02$	[67]
Female sex, experiencing headache 3 months after the injury	Prospective, longitudinal cohort study with 22 years follow-up	249 patients. Average age (mean \pm SD) = 45 ± 15 . 78% females.	$p < 0.02$	[68]
Age ≤ 60	Prospective, longitudinal cohort study with 12 months follow-up	212 subjects. Average age (mean \pm SD) = 44.4 ± 19.3 . 76% males.	$p < 0.001$	[35]
Depression	Cross-sectional cohort study	58 mild TBI outpatients. Average age (mean \pm SD) = 36.0 ± 13.1 . 60% males. 72 healthy community controls. Average age (mean \pm SD) = 49.9 ± 11.7 . 59.5% females.	$p < 0.02$	[69]
Affective disorders such as PTSD and depression	Prospective observational descriptive study with 6 months follow-up	30 military personnel. Average age (mean \pm SD) = 27.36 ± 4.82 . 100% males.	$p < 0.05$	[70]
Chronic pain other than headache, pre-existing headache, affective disorders	Prospective observational study with 90–100 days follow-up	100 patients with acute mild injury. Average age (mean \pm SD) = 34.4 ± 13.1 . 59 males.	$p < 0.0001$	[16]

TBI is a major public health concern. It has been estimated that over half of the world's population experience at least one type of TBI over their lifetime [5]. The underlying mechanism of PTH remains unknown, and there is no clear-cut treatment method available. Headache is a common symptom associated with TBI, particularly mild TBI. Individuals can experience different types of headaches as a result of TBI. The reported prevalence of PTH has been variable, ranging from 15% to 90% [35].

The presence of headaches is an important factor in the treatment of TBI. Assessment, diagnosis, and management of headache in TBI require robust clinical recommendations and guidelines. A universally accepted protocol is required to be established for the treatment of headaches following TBI. This requires a robust and non-subjective system for the classification of PTH. Identification of biomarkers for PTH can provide an efficient diagnosis to improve prognosis. However, migraine and PTH are differentiated clinically by the presence or absence of biomechanical injury to the head. The majority of patients with PTH present clinical symptoms which are not indistinguishable from migraine.

The exact neuroscientific mechanism contributing to PTH is not comprehensively understood [49, 51]. While some studies have attempted to identify genes associated with psychiatric disorders and mental health [47], future studies using next-generation sequencing techniques [52] are required to investigate the association between genes and environment to identify genetic risk factors associated with mental health headaches. Beyond neurobiological and cognitive symptoms, the effect of TBI and PTH in other organ systems, such as the gastrointestinal system [53], can be explored to investigate the possibility of behavioral changes, including diet modification to alleviate pain.

2. Is post-traumatic headache different than other types of headaches?

The International Classification of Headache Disorders (ICHD) divides headaches into two major categories. Primary headaches such as migraine, tension-type headache, and trigeminal autonomic cephalalgias are considered not to have underlying causes, whereas secondary headaches such as PTH and headaches attributed to vascular and non-vascular cranial disorders, infections and substance withdrawal, etc. are considered to have associated underlying causes [54]. In its latest version, ICHD-III classifies PTH as a secondary headache caused by injury or trauma to the brain, which forms within seven days following the injury, after regaining consciousness and/or after regaining pain sensation and reporting [54]. PTH can be subdivided into acute and persistent headaches. While acute PTH is resolved within three months of experiencing TBI, persistent PTH lasts longer than three months from the incident [39]. PTH can be caused by mild, moderate or severe TBI (Fig. 2) [54]. While PTH is present in all types of TBI, it is most commonly seen in mild TBI [55].

2.1 Risk factors associated with post-traumatic headache

Experiencing PTH after mild TBI is quite common, corresponding to 4% of all secondary headache disorders [44, 56]. Particularly, patients with mild TBI have a higher prevalence (72.7%–77.9%) of forming PTH compared to patients with moderate and severe TBI (29.3%–34.9%) [55]. Multiple risk factors such as being a female, older age, pre-existing headache, pre-existing psychiatric disorders, experiencing a headache at the medical emergency room, the severity of TBI, medication overuse, and being injured under the influence of alcohol are associated with the development of PTH [29, 34, 57–59]. In contrast, factors such as race, recovery time, the severity of headache, education level, marital status, and Glasgow Coma Scale score are not considered risk factors for PTH [29, 39, 59, 60]. A summary of risk factors and predictors associated with PTH is demonstrated in Table 1 (Ref. [16, 35, 58, 60–70]).

2.2 Neuropathophysiology of post-traumatic headache: similarities and differences between post-traumatic headache and primary headaches

Resembling different phenotypes associated with primary headaches, PTH is associated with nausea, vomiting, experiencing and/or exacerbating headache after stress, physical activity, light, sound, as well as impaired cognition and psychosocial behaviors [71]. Migraine-like and tension-type-like headaches are the most common headaches associated with PTH [36, 39], and other rarer types of headaches such as mixed and cluster-like can be observed as well [71]. Contradicting reports exist on whether PTH is more similar to migraine-like or tension-type-like headaches, indicating the enigmatic nature of PTH. While some studies reported PTH patients have a higher prevalence of migraine-like headaches [31, 35], others contradict studies that demonstrated a higher prevalence of tension-type-like headaches [26, 72]. For example, Kjeldgaard *et al.* [26] showed that 97% of patients with *de novo* headaches after experiencing mild TBI had a tension-type-like headache.

In contrast, Lucas *et al.* [35] demonstrated that 49% of patients had a migraine-like headache after experiencing mild TBI. A summary of different types of headaches associated with TBI is shown in Table 2 (Ref. [29]). Multiple factors such as sampling bias, methods used to assess headache, time of evaluation, and classification of PTH can potentially explain some of the variations observed in the data regarding headache types in TBI.

According to the International Headache Society [72], a migraine is an episodic, unilateral, pulsatile headache with nausea, vomiting, photophobia, phonophobia, and worsening symptoms with physical activity. Multiple studies have reported that patients with PTH present clinical symptoms of migraine such as unilateral headache location, throbbing headache, pain exacerbation following physical activities, photophobia and/or phonophobia, nausea and vomiting [27, 31, 73–75].

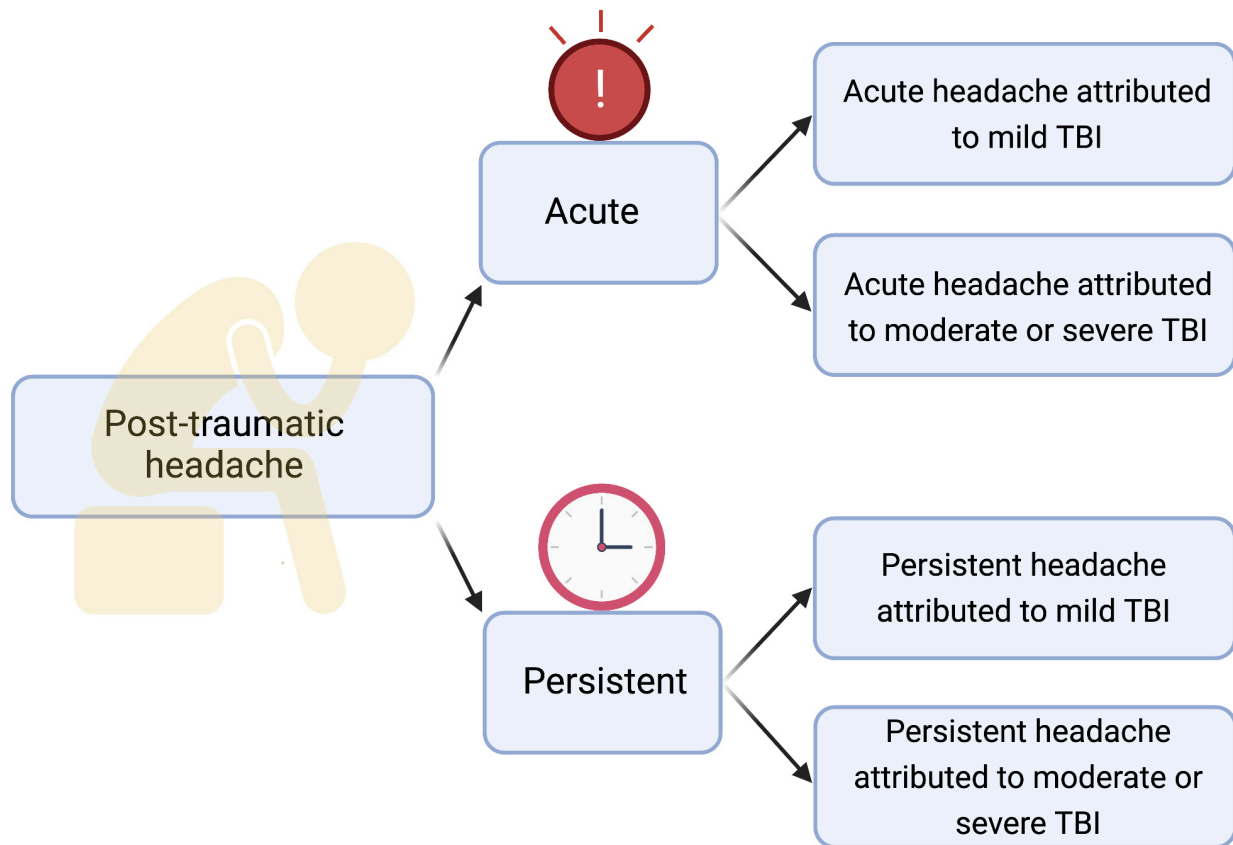


Fig. 2. Classification of acute and persistent headache according to the International Classification of Headache Disorders, 3rd version [54]. Post-traumatic headaches can be divided into acute and persistent. Each category can be subdivided into mild and moderate/severe.

Tension-type headache is the most common neurological disorder in the world [76]. The hallmark of tension-type headache is its recurrent nature with mild to moderate pain intensity, which tends to be bilateral with pain in the forehead, posterior head regions and neck [77]. Tension-type headache can be distinguished from migraine due to a lack of photophobia, phonophobia and nausea [78]. Based on the frequency of headaches, tension-type headaches can be subdivided into infrequent episodic (<12 days with headache/year), frequent episodic (≥ 12 and <180 days/year) and chronic (≥ 180 days/year) [78]. While infrequent tension-type headaches do not require treatments from physicians, chronic tension-type headaches are challenging to treat and can cause disability [79].

Alternatively, headache alone or associated with cognitive and psychological symptoms can be the only phenotype associated with PTH [80]. Furthermore, persistent PTH can be associated with anxiety, depression, and PTSD [16, 29, 44, 59], sleep disturbance [81], as well as autonomic dysfunction symptoms such as orthostatic intolerance and bladder incontinence [82]. The intensity of PTH can be associated with PTSD [29]. Neurosurgical procedures, such as craniotomy, can mimic PTH, post-craniotomy headaches

[83]. Future research is required to establish the pathogenesis of such headaches and understand whether post-craniotomy headaches can be prevented for successful patient outcomes in neurosurgical procedures.

While its exact etiology remains unknown [56], various changes to the neurophysiology of the brain have been proposed as a potential underlying mechanism of PTH. PTH can be due to direct injury to the tissue during TBI, such as cervical injuries, bone and/or soft tissue trauma, and peripheral nerve damage [29]. Alternatively, indirect consequences of TBI such as pressure palsies, spasticity, deep vein thrombosis, periarticular new bone formation, and abnormal posturing [29, 84]. Chronic sensitization of nociceptors can also cause PTH [51, 85, 86].

Inflammation plays a role in the neuroscience of headaches (Fig. 3). Damage to cranial and neck structures can cause neurogenic inflammation resulting in hyperexcitability and hyperactivity of nociceptors [29, 87]. Studies of humans and animal models revealed that TBI could cause the release of cytokines and chemokines to activate and recruit monocytes and facilitate activation of glial cells and release of nociceptive peptides [88–91]. This chain of events, combined with vascular disruption, can cause activation

Table 2. A summary of clinical characteristics and manifestations of PTH. Some of the information was used from [29].

	Migraine-like PTH	Tension-type-like PTH	Cluster-like	Cervicogenic-like
Location	Various (unilateral)	Various (bilateral)	Retro/perito- orbital, with a possibility of spreading (unilateral)	Originates in the neck and spreads anteriorly (mainly unilateral)
Intensity	Moderate to severe	Mild to moderate	Severe	Mild to severe
Quality	Pounding, throbbing, sharp	Pressing, dull	Throbbing	Dull
Exacerbation	Physical activity, light, sound	Psychological stress, tension	Alcohol consumption	Posture

and sensitization of nociceptors to stimuli, resulting in spontaneous pain [91–95]. Mechanical hypersensitivity can also occur in the trigeminal nerve due to myelin sheath deterioration as the result of compression of the nerve by a vein or an artery [96–98]. In parallel, damage to the spinothalamic/thalamocortical pathway can cause dysfunction of the pain-inhibition pathway, resulting in hyperexcitability and hyperactivity of central neurons [29, 99]. Various damages to the brain, such as diffuse axonal injury, increased release of glutamate, cerebral flow alterations, and widespread neuronal depolarization, are seen in TBI [100–102].

The majority of TBI patients suffer from PTH symptoms that are not distinguishable from migraine symptoms. Such similarities in clinical symptoms of PTH with migraine raises speculations on whether PTH has a specific neuropathophysiology or whether TBI triggers migraine manifested as PTH. Common neuropathological changes exist between migraine and mild TBI, such as an increase in the level of extracellular potassium and intracellular sodium, calcium and chloride [28, 71, 101, 103–105]. The frequency and/or intensity of PTH is increased two-fold in patients with migraines who develop PTH [60, 66]. In contrast, a slight increase in PTH frequency in patients with tension-type headaches [35, 106].

Multiple neuroimaging studies have investigated structural [107–110] and functional [5, 98, 111, 112] changes associated with PTH. For example, by studying 54 patients with mild TBI without pre-existing headaches and comparing them to 46 healthy controls, Niu *et al.* [5] showed that most patients developed PTH up to 12 weeks after their injury. Patients with PTH had a weaker connection between the periaqueductal grey matter in their brainstem, an area responsible for opioid antinociception and the right inferior parietal lobe, which is responsible for self-reference interoception [5]. The strength of the periaqueductal grey connectivity could predict patients' complaints about the impact of PTH on their lives [5]. However, a causal relationship remains to be established. They also suggested that disruption to the functional connectivity of periaqueductal grey matter can be used as a biomarker to identify TBI patients susceptible to developing PTH [5]. Periaqueductal grey is a vulnerable region in mild TBI, especially during acceleration-deceleration forces [113, 114].

Previous studies showed that patients with mild TBI were more susceptible to perceiving pain and had a lower threshold for pain. However, the development and maintenance of such pain thresholds could be affected by psychological

factors [95]. These findings were corroborated with other studies where patients with PTH had a lower grey matter in the anterior cingulate and dorsolateral prefrontal cortex three months after their injury, and morphological changes were resolved after one year upon cessation of the headache [110]. Additionally, TBI patients with PTH had injuries to their corpus callosum and fornix/septohippocampal circuit [107]. Similar changes in the white matter were observed in patients with migraines [107]. White matter hyperintensity lesions were also associated with less depression in patients with chronic headaches [108]. Indeed, diffuse axonal injury due to shearing forces is a hallmark of TBI and a predictor of the patient outcome [115, 116]. Previous studies investigated the neuroscience of axon injury and demonstrated injuries to axons and focal lesions due to TBI [116].

Conversely, a history of TBI can accelerate aging and increase the risk of neurodegenerative diseases such as Alzheimer's disease [117]. Axonal injuries can disrupt multiple neuronal functionals, including cargo transportation. Future studies can investigate the role of disruption to motor-mediated mRNA localization and local translation in neurons of TBI patients [118–120]. Recent studies have proposed the “autonomous clock” idea to control different aspects of organelle biogenesis, such as mitochondria, in cells, autonomous of the cell cycle [121]. Expansion of this idea to neurons can investigate whether regulation of organelle biogenesis in neurons can have any role in therapeutics.

In contrast, a study showed significant differences in the brain of migraine patients and PTH patients without a history of pre-existing headache by comparing regional brain volumes, the thickness of the cortex, brain curvature and surface area [122]. Morphological and structural changes were present in the right supramarginal gyrus, right lateral orbitofrontal lobe, left precuneus, left causal middle frontal lobe and left superior frontal lobe [122]. Similarly, by comparing 33 TBI patients with PTH with healthy controls, Chong *et al.* [109] demonstrated that PTH patients had a less cortical thickness in the right hemisphere parietal and bilateral frontal regions, indicating morphological changes in the brain associated with PTH.

Major differences in static and dynamic functional connectivity exist between migraine and PTH [112]. Furthermore, distinct structural differences are present in the brain of patients with migraines compared to PTH patients, indicating unique morphological changes that can occur in TBI. By comparing regional volume, cortical thickness, and sur-

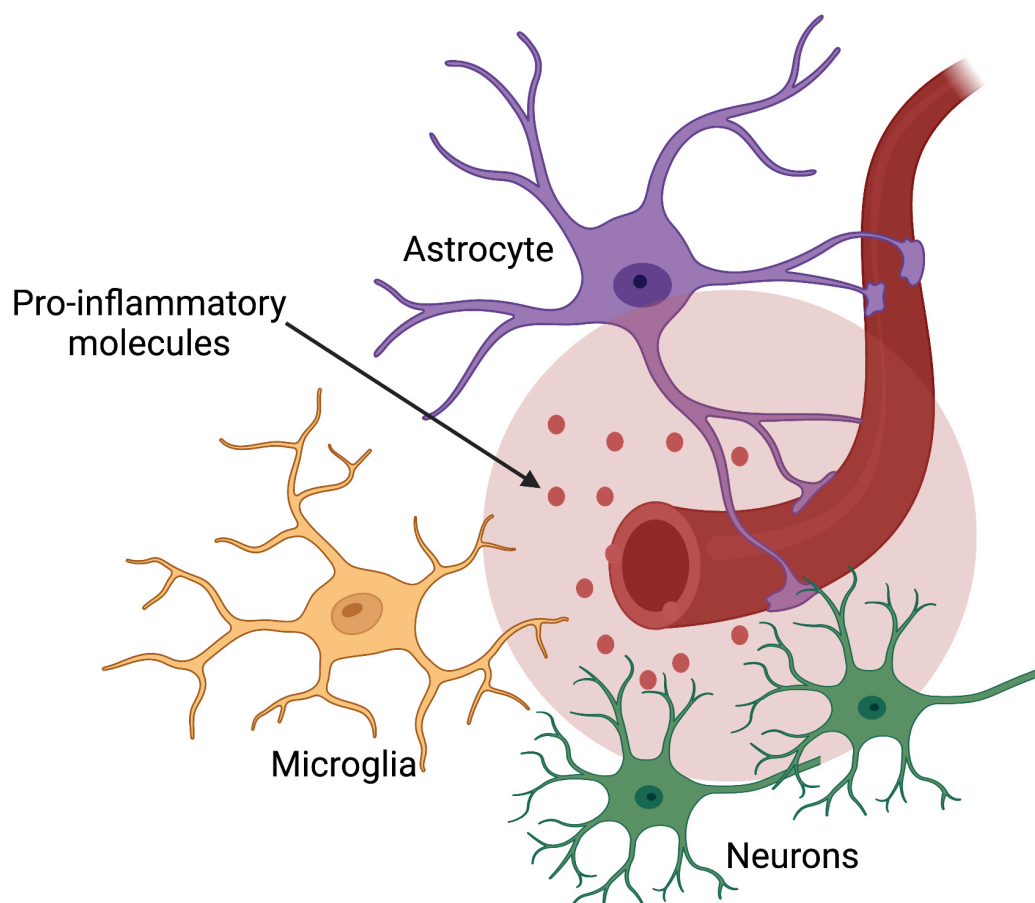


Fig. 3. A summary of key cells involved in the neurobiology of inflammation associated with PTH. The involvement of glial and immune cells, such as astrocytes and microglia, and secretion of pro-inflammatory molecules in post-traumatic headache after cervical damage can contribute to PTH formation by hyper-excitability and hyper-activity nociceptors.

face area from MRI scans of persistent PTH patients with migraine patients and controls, a study showed that structural differences exist in the brain if PTH patients and migraine, indicating potential unique neuropathophysiology [122]. Particularly, structural differences were observed in the right lateral orbitofrontal lobe, left caudal middle frontal lobe, left superior frontal lobe, left precuneus, and right supramarginal gyrus [122]. Brain measurements from these regions did not differ significantly between migraine and healthy controls [122]. Other studies supported these results by finding that TBI patients had a reduction in the cortical thickness in the frontotemporal region, which is particularly susceptible to TBI [123, 124], abnormal enlargement of lateral ventricles [125], and a decline in episodic memory and verbal fluency [125]. However, such differences were not found in mild TBI patients' cerebellum or subcortical regions compared to controls [124].

Changes in the frontal region of the brain have been found in patients with migraine, cluster headache and medication overdose headache [126–129], and frontal regions play a significant role in encoding, evaluation, and affective response

in the pain and reward pathway [130, 131], suggesting a potential link between structural and functional changes to pain perception areas and PTH. For example, the precuneus, which was previously shown to be involved in migraine, cluster headache and medication overdose headache [126, 132–134], is associated with the default mode network and plays a pivotal role in determining the pain sensitivity and pain threshold [134–137]. In addition, the supramarginal gyrus is involved in migraines and medication overdose headaches [138, 139] and can play a role in the evaluation of pain [140, 141]. While the exact etiology remains to be discovered, one can speculate that these regions are more susceptible to injury during TBI and can trigger PTH [122].

The plasticity of the brain can change in TBI patients with PTH. Imaging studies revealed significant correlations between years lived with headache with functional connectivity of different brain regions such as right primary somatosensory and left supramarginal gyrus [112], indicating a potential causal correlation. Similar functional connectivity, but in different brain regions, namely left middle cingulate with right pulvinar and right posterior insula with left hypothalamus,

correlated with the frequency of PTH [112]. Therefore, it is plausible that despite overlaps in clinical symptoms, migraine and PTH can have unique neuropathophysologies. Future large data sets with the help of artificial intelligence analysis [142] are required to establish the neurobiological changes associated with TBI.

Although there is less abundance of electroencephalography (EEG) data on PTH than neuroimaging, some studies dating back a few decades ago reported early abnormalities such as focal swelling, amplitude asymmetry, and absence of fast activity [143–145].

Discriminative pain pathways can also be affected in PTH (Fig. 4). Recent data on impaired descending modulation has been suggested as one of the underlying reasons for PTH [73]. Descending pain modulation system is responsible for connecting various cerebral sites and neuronal pathways to control pain [146]. A lack of balance between descending inhibitory and descending facilitatory systems can play a crucial role in chronic pain [146], and such imbalance can contribute to PTH [73]. While data on the role of descending pain modulation system in PTH is scarce, restoring the balance by pharmacological interventions can potentially offer a therapeutic option to PTH patients. Future advanced imaging studies are required to have a better understanding of descending pain modulation system and PTH.

To assess the sensory profile of PTH patients by using systematic quantitative somatosensory testing, Defrin *et al.* [95] showed that generalized impairment of the spinothalamic system following TBI could result in a higher threshold for thermal sensation. This effect was specific as the threshold of light touch, and graphesthesia was not different in PTH patients, indicating an intact dorsal column system transmitting tactile sensations [147]. Furthermore, PTH patients reported pain from normally innocuous stimuli (allodynia) on the head [95].

Abnormalities in functional connectivity following TBI can result in cognitive deficits and post-concussive symptoms such as PTH [148]. A reduced regional cerebral blood flow was observed in patients with PTH [102]. Single-photon emission computed tomography (SPECT) studies corroborated these findings by demonstrating that cerebral blood flow can differ in TBI patients within days to years after the injury [149–151]. In comparison, arterial spine labeling (ASL) studies have produced contradicting results on cerebral perfusion following head trauma. A study reported an increased cerebral blood flow in the left dorsal anterior cingulate cortex and left insula of 15 teenage athletes after sports-related concussion compared to 15 matched controls [152]. In contrast, cerebral blood flow was decreased in bilateral frontotemporal regions of 14 chronic sports-related and recreational pediatric patients with mild TBI compared to 15 controls [153].

Similarly, another study on twelve children aged 11–15 years with sports-related concussions found decreased cerebral blood flow in mild TBI patients. However, 64% of par-

ticipants showed improvements towards controls' cerebral blood flow value at >30 days after the injury [154]. Cerebral blood flow was also increased in pediatric TBI patients with post-traumatic symptoms, but no increase was observed in asymptomatic patients [152, 155]. Contradictory to these findings, while pediatric patients showed normal neurophysiological scores seven months post-concussion, a bilateral decrease in cerebral blood flow was observed in frontotemporal regions [153]. It is plausible to conclude that TBI can cause changes in cerebral blood flow, which are more significant in symptomatic patients [77]. Future studies are required to assess the association between cerebral blood flow and PTH and the recovery time.

2.3 Treatment of post-traumatic headache

Headache interrupts and demands attention. Despite the high prevalence of PTH, there is no global consensus on PTH treatment, and a variety of approaches exist regarding the appropriate treatment. To provide a better framework for the treatment of PTH, many physicians rely on the management of primary headache to address PTH, which, as mentioned previously, is a secondary headache [36, 106, 156]; this can result in undesired and poor response to treatments [157].

There is a lack of evidence-based studies on pharmacological interventions of persistent PTH [158]. To the best of my knowledge, no Food and Drug Administration (FDA)-approved drug exists for PTH, and no randomized controlled clinical trial has assessed the effectiveness of treatments for PTH. PTH patients, therefore, experience unnecessary and irrelevant treatments [158]. Effective pharmacological intervention for PTH should address both the intensity and frequency of headache attacks [39]. Comorbidities, side effects and efficacy for treating primary headache, which resembles PTH, can affect the choice of drug used [159].

Pharmacological intervention of the acute phase of PTH consists of analgesic and non-analgesic treatments. Analgesic drugs such as acetaminophen [27], ketorolac [160], non-steroid anti-inflammatory drugs [27], and a mixture of drugs (Midrin, Cafegot, Excedrin) [27] can be used for the acute treatment of PTH. A study showed that more than 70% of individuals with headaches used acetaminophen or non-steroid anti-inflammatory medications to manage their symptoms [42]. Other specific analgesic drugs for PTH include lidocaine [161], opioids and triptans [27]. Antiemetic drugs prescribed to treat nausea and vomiting associated with PTH are prochlorperazine [160], ondansetron [160], and metoclopramide [160, 162]. Other drugs used for the acute treatment of PTH include diphenhydramine [162], triamcinolone and methylprednisolone acetate [163].

Mild TBI patients with PTH might rely on self-treatments by using over-the-counter medications to relieve their pains and symptoms, even though such medications are not effective for all patients [42]. Over-the-counter prescriptions such as paracetamol (acetaminophen), ibuprofen, aspirin, and naproxen are used to treat tension-type headaches [39]. Self-medication can result in medication overdose, and pa-

Discriminative Pain Pathways

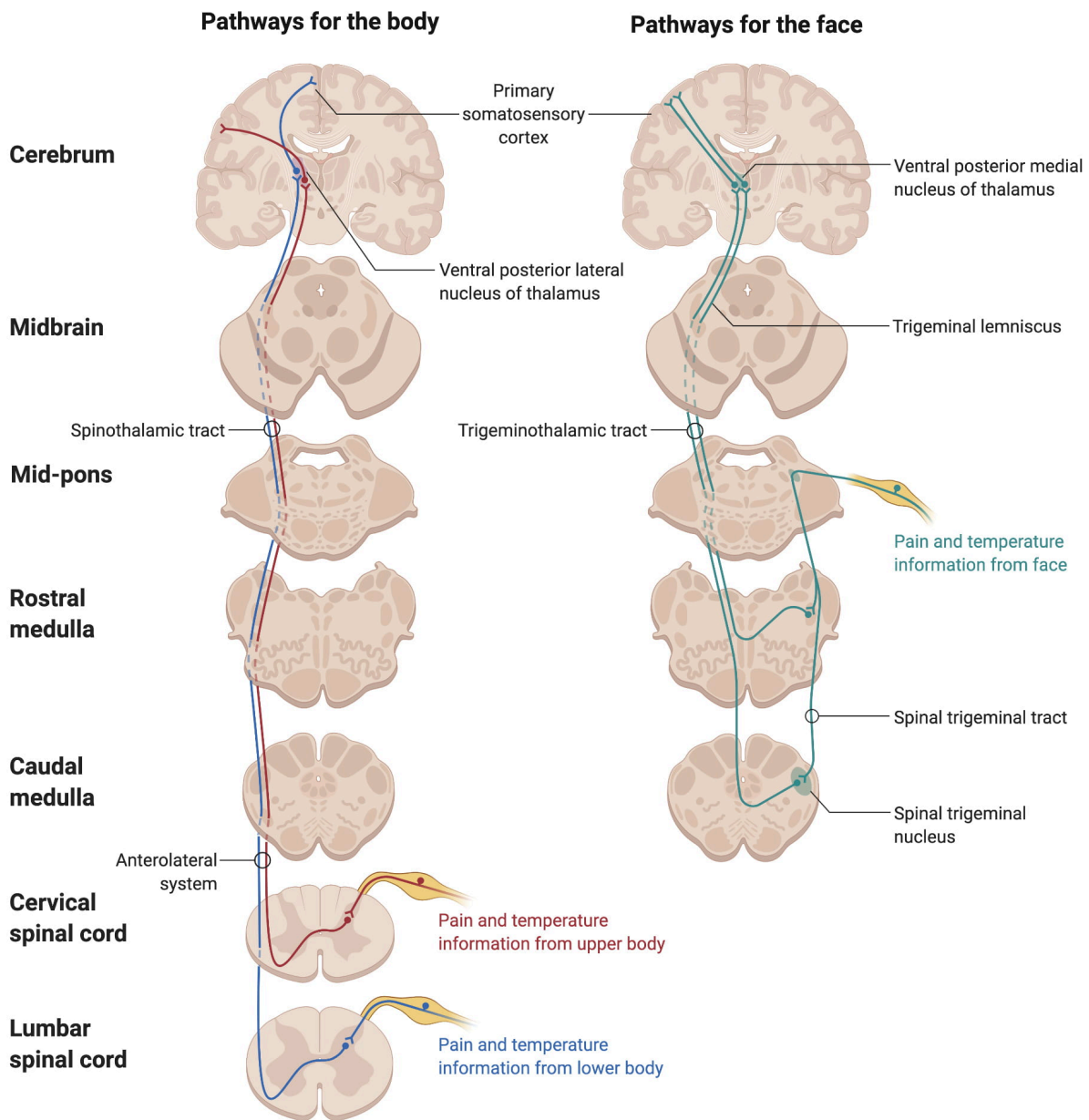


Fig. 4. An overview of the discriminative pain pathways in the body and face. The pain pathways can be affected in PTH. Nociceptors, as free nerve endings, act as afferent nerve fibers with their cell bodies located in terminal ganglion or dorsal root ganglia, terminating in the dorsal horn of the spinal cord. While all pain fibers terminate in the dorsal horn, they adopt different routes to this location, with most entering the dorsal horn via the ventrolateral bundle of the dorsal root. Second-order neurons ascend to higher brain centers in the anterolateral section of the spinal cord via spinothalamic and spinoreticular tracts. The thalamus processes somatosensory information. Descending pathways of pain play roles in modulating pain.

tients with persistent headaches after trauma can develop headaches associated with medication overdose [168], which can negatively impact the quality of their lives [164]. Excessive usage of analgesic medications after a concussion can also contribute to PTH development [165]. Medication overdose headache can resemble migraine, tension-type headache, or the underlying headache [165, 166]. 19%–42% of PTH pa-

tients can face excessive analgesic use, and the majority of them experience improvements in their symptoms after medication withdrawal [167, 168].

Effective treatment of PTH requires appropriate classification. Most PTHs can be classified using primary headache criteria, and the majority of PTH cases are classified as migraine and probable migraine using such criteria [106].

Intravenous migraine therapy using prochlorperazine, ondansetron, and metoclopramide reduced the PTH scores reported by children 8 to 21 years old 14 days after mild TBI [160]. Treatment of acute PTH in children can be relatively successful as 38%–55% of children with PTH have symptoms resembling acute migraine headaches [106], effectively treated by ketorolac, metoclopramide and prochlorperazine [169–172]. A small study of 21 patients with PTH showed that intravenous metoclopramide and diphenhydramine were effective treatments for acute PTH [162].

Some reports of successful PTH have been made using various drugs such as amitriptyline [173], botulinum toxin [174], intravenous chlorpromazine [175], intravenous dihydroergotamine with metoclopramide [176], divalproex sodium [177], intraoral topical ketoprofen [178], and subcutaneous sumatriptan [179]. Like chronic tension-type headaches, PTH patients can be treated with prophylactic medications such as amitriptyline [168] or its metabolite, nortriptyline, which has lower anticholinergic side effects [180]. Medications such as triptan class drugs as selective serotonin receptor inhibitors can treat PTH [27].

Nerve blockage is another approach for the treatment of acute PTH. Dubrovsky *et al.* [181] showed that peripheral nerve blockade of the scalp immediately relieved symptoms of young PTH patients below 18. Occipital nerve blockage using lidocaine and methylprednisolone acetate, which is used to treat occipital neuralgia, can also alleviate acute PTH symptoms [163]. Cognitive-behavioral therapy can supplement pharmacological interventions for PTH to achieve a better patient outcome [182].

Recent structural and functional neuroimaging data have revealed that different networks other than migraine exist in persistent PTH [183]. Furthermore, calcitonin gene-related peptide gene expression level is not elevated in persistent PTH, but monoclonal antibodies against calcitonin gene-related peptide gene can be effective [183]. Future results from trials assessing the efficacy of such medications can provide novel treatments for PTH.

2.4 Psychological aspect of headache after traumatic brain injury

Although Lishman originally proposed that neurobiological factors contribute to the formation of the post-concussive syndrome and psychological factors account for the maintenance of symptoms in the chronic phase [12], we now understand that both neurobiological and psychological factors play pivotal roles in post-concussive syndrome from its onset [13]. Patients suffering from PTH can have psychological symptoms such as anxiety, depression, insomnia [80]. Anxiety and depression are major causes of disability [184] and can significantly hinder individuals from reaching their full potential [185]. Experiencing mTBI can be related to behavioral changes such as attention-deficit/hyperactivity disorder, substance abuse, and mood disorder [186]. A study showed that patients with persistent PTH had higher levels of depression and anxiety compared to patients with migraine and healthy controls [122].

Other psychological conditions such as post-traumatic stress disorder can be associated with PTH or exacerbate its symptoms [186–189]. Another complication associated with TBI is that some of the clinical symptoms, such as a cognitive decline in late adulthood, manifest many decades after the apparent recovery from the injury, making it challenging to establish a connection between TBI and symptoms [125]. Furthermore, patients with mild TBI tend to be hypervigilant, meaning they are excessively concerned about injuries to their brains and associated physical symptoms such as headaches [92, 111, 190]. Hypervigilance can potentially change brain networks responsible for the perception and modulation of pain [5]. Therefore, excessive attention to pain can explain the lower threshold and higher perception of headaches and pain in TBI patients [191, 192].

Therefore, considering their psychological well-being, a holistic approach to PTH patient treatment is essential to achieve better outcomes. Psychological treatments for TBI patients with headaches should be an integral part of their treatment regimen.

2.5 Challenges associated with studying post-traumatic headache

There are multiple challenges associated with studying PTH in TBI patients. One major limitation is that many TBI patients can have comorbidities which can act as confounding factors to affect the phenotypes observed from radiological and neurophysiological data [122]. As previously mentioned, some PTH patients can suffer from stress, anxiety, depression and PTSD and use medications for psychological problems [193, 194]. Therefore, it remains challenging to disentangle whether some functional and structural changes seen in PTH patients' brains are consequences of medications or not. Future robust studies are required to address this issue.

As previously mentioned, some TBI patients with PTH can have pre-existing headaches, which can be exacerbated by the injury [16, 60]. Therefore, another caveat of some PTH studies is the inclusion of participants with pre-existing headaches or not evaluating whether participants had pre-existing headaches. Patients with pre-existing headaches might be more susceptible to developing a headache after TBI [16]. Furthermore, TBI patients can use medications before the initiation of studies that can affect the data.

Another major limitation is the lack of sufficient evidence to disentangle the effect of trauma during TBI from PTH on the brain. It is not clear whether some of the structural and functional changes found in studies were due to trauma on the brain or simply because of the headache. Future studies where TBI patients without headaches are compared to TBI patients with PTH can answer these gaps in our knowledge.

Combining these limitations and caveats means that future studies are required to better address questions regarding PTH.

3. Conclusions

In conclusion, as PTH is a multi-faceted condition, its treatment should be multi-faceted and multi-disciplinary too.

A holistic and personalized approach to integrating pharmacological and non-pharmacological interventions such as lifestyle modifications and stress management can effectively treat persistent PTH [130]. In addition to their headache, TBI patients can suffer from other symptoms, including anxiety, depression, PTSD, which requires medications [193, 194]. Future involvement of artificial intelligence in clinical studies can reduce the subjectivity of clinical decision-making and patient care [142]. One of the main implications is that psychiatric conditions should be considered in PTH management to tailor the treatment to patients [49]. Psychiatric disorders can be neglected in managing headaches in TBI patients; however, long-term management of PTH patients needs to consider a biopsychosocial model for patient treatment [195]. Further research is required to understand the neurobiological and neuropathological mechanisms contributing to secondary headaches following TBI and pave the way for more effective, patient-centered treatments.

Abbreviations

CT, computerized tomography; ICHD, international classification of headache disorders; MRI, magnetic resonance imaging; PTH, post-traumatic headache; PTSD, post-traumatic stress disorder; TBI, traumatic brain injury.

Author contributions

MM conceptualized, prepared, drafted, and edited the paper.

Ethics approval and consent to participate

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