Post-traumatic headache: epidemiology and pathophysiological insights

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Abstract | Post-traumatic headache (PTH) is a highly disabling secondary headache disorder and one of the most common sequelae of mild traumatic brain injury, also known as concussion. Considerable overlap exists between PTH and common primary headache disorders. The most common PTH phenotypes are migraine-like headache and tension-type-like headache. A better understanding of the pathophysiological similarities and differences between primary headache disorders and PTH could uncover unique treatment targets for PTH. Although possible underlying mechanisms of PTH have been elucidated, a substantial void remains in our understanding, and further research is needed. In this Review, we describe the evidence from animal and human studies that indicates involvement of several potential mechanisms in the development and persistence of PTH. These mechanisms include impaired descending modulation, neurometabolic changes, neuroinflammation and activation of the trigeminal sensory system. Furthermore, we outline future research directions to establish biomarkers involved in progression from acute to persistent PTH, and we identify potential drug targets to prevent and treat persistent PTH.

Post-traumatic headache (PTH) accounts for ~4% of all symptomatic headache disorders[1] and is one of the most common sequelae of mild traumatic brain injury (mTBI)[2,3], also known as concussion. Estimates suggest that 69 million people per year experience a traumatic brain injury (TBI) worldwide[4]. In addition, patients with PTH commonly suffer from comorbidities such as anxiety and depression[5], both of which are among the leading causes of disability worldwide[6]. Yet much remains unknown about the underlying pathophysiological mechanisms of PTH, and no evidence-based, PTH-specific treatment currently exists[7]. For these reasons, novel, mechanism-based treatment options are needed from human and socioeconomic perspectives.

In this Review, we present the current knowledge about the epidemiology of PTH and the underlying pathophysiological mechanisms. We outline future research opportunities to advance our understanding of the disease mechanisms, and treatment options for PTH.

Classification and terminology

In the International Classification of Headache Disorders (ICHD)[8], PTH is considered a secondary headache defined by the onset of headache 'within seven days following trauma or injury, or within seven days after recovering consciousness and/or within seven days after recovering the ability to sense and report pain'[8]. PTH is further subdivided into 'acute headache attributed to traumatic injury to the head' and 'persistent headache attributed to traumatic injury to the head'[8]. If the headache resolves within 3 months of onset, it is characterized as acute PTH, whereas headache that persists beyond 3 months is defined as persistent PTH (FIG. 1). In addition, the head trauma that leads to PTH can be classified as either mild (often referred to as mTBI or concussion) or moderate to severe (FIG. 1).

The requirement for reporting headache within 7 days is somewhat arbitrary and based on expert opinion rather than scientific evidence. Indeed, the current ICHD-3 guidelines encourage further testing of the diagnostic criteria for PTH[8]. In some studies, extension of the time interval beyond 7 days has been proposed[9,10]. Notably, the original ICHD-1 criteria for PTH required that patients report the onset of headache within 14 days of a TBI[11].

The diagnostic criteria for PTH attributed to mild traumatic injury to the head include the criteria for mTBI[12], and those for PTH attributed to moderate to severe traumatic injury to the head include the criteria for moderate and severe TBI[12]. In addition, headache is a cardinal symptom of post-concussion syndrome[3]. Given this tight relationship between TBI and PTH, current knowledge of concussion and TBI is highly relevant to the pathophysiology of PTH (BOX 1).

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Key points

- Post-traumatic headache (PTH) is one of the most common sequelae of traumatic brain injury; the most common headache phenotypes in PTH are migraine-like headache and tension-type-like headache.
- PTH is associated with somatic symptoms, including nausea, vomiting, photophobia and phonophobia, and cognitive and psychological symptoms.
- Possible disease mechanisms of PTH include impaired descending modulation, neurometabolic changes and activation of the trigeminal sensory system.
- The emphasis of future studies of PTH should be on establishing biomarkers of progression from acute PTH to persistent PTH.
- Identification of potential treatment targets, such as calcitonin gene-related peptide, should enable randomized controlled trials to be conducted in patients with PTH.

The term PTH also includes headache attributed to whiplash or craniotomy[8]. However, knowledge of the disease mechanisms of whiplash and craniotomy is sparse, so in this Review, we focus on data from patients who experienced a head trauma event unless otherwise stated.

Epidemiology and characteristics

In a population-based study conducted in Norway[13], the reported 1-year prevalence of persistent PTH was 0.21%. In another study conducted in Denmark, the lifetime prevalence of PTH was 4.7% in men and 2.4% in women[14]. In addition, 10% of patients who were newly referred to the Danish Headache Center (a tertiary headache unit) had persistent PTH[15]. Some evidence has suggested that female gender and younger age are risk factors for PTH, but several studies have produced conflicting evidence[16–19]. The negative impact of PTH on work life and social activities[18,20] is considerable. Among patients with PTH, 35% have not returned to work by 3 months after the injury[18]. Given that >3.8 million people are diagnosed with concussion in the USA annually[21], the persistence of PTH should be considered a substantial public health concern.

Two studies with rigorous methodology have shown that the most common causes of TBI that results in PTH include traffic accidents (24–58%) and falls (24–45%) followed by sports (3–18%) and violence (5–7%)[16,22]. PTH seems to be more common after mTBI than after moderate to severe TBI[2,11]. In this context, it is worth highlighting that in one population-based study, mTBI accounted for 95% of all TBIs[23], and in one prospective study[16] in patients with mTBI, the cumulative incidence of new or worse headache compared with before the injury was 91%. In addition, 40% of patients with TBI who reported acute PTH in one study later developed persistent PTH[18].

The most common headache phenotypes in PTH are migraine-like and tension-type-like;[24] rarer phenotypes include cluster-like headache and cervicogenic-like headache. However, whether migraine-like headaches or tension-type-like headaches are the most common remains unclear. Some studies have found that most people with PTH have tension-type-like headaches[9,22], whereas others have found a higher prevalence of migraine-like headache[16,25]. For example, in one study, 97% of patients with de novo headache after mTBI and persistent PTH had a tension-type-like headache phenotype[22]. However, 36% of the patients with persistent PTH reported more than one headache phenotype, and migraine was the most prevalent overall. By contrast, another study showed that 49% of people with persistent PTH at 1 year after mTBI had either a migraine-like headache or a probable migraine-like headache[16], whereas only 32% had a tension-type-like headache. In two other studies[17,26], migraine-like or probable migraine-like headache was also reported by 53% of patients with de novo headache after moderate to severe TBI at 1 year after trauma. The discrepancies in the data on headache phenotypes in PTH might be partially explained by methodological differences, such as the time point of evaluation, selection criteria and classification of PTH. Also worth noting is that primary headache phenotypes are essentially restricted to three types: migraine, tension-type headache and trigeminal autonomic cephalalgias. Most recurrent headaches with a secondary cause, including PTH, will present with one of these three headache phenotypes.

PTH is also associated with somatic symptoms, including nausea, vomiting, photophobia and phonophobia[17], and cognitive and psychological symptoms[5]. Two studies[22,27] have shown that ~30% of patients with persistent PTH have post-traumatic stress disorder (PTSD). In addition, patients with PTH and TBI often report symptoms of anxiety and depression[18,28]. Indeed, in one study[29], the frequency of anxiety and depression was higher among patients with persistent PTH than among patients with migraine and healthy controls.

In the diagnosis of PTH, the possibility of co-occurring medication-overuse headache (MOH) is an important consideration. A study conducted at the Danish Headache Center showed that 42% of patients who fulfilled the criteria for PTH at the time of referral also fulfilled the criteria for MOH[9]. A subsequent study at the same centre found that 13% of patients fulfilled the criteria for PTH and MOH simultaneously[22]. These data have led to suggestions that sustained, refractory headache in persistent PTH is partly caused by MOH[9]. In support of this idea, one study identified analgesic overuse in 44% of patients with PTH[9]; however, in half of these patients, the headache did not improve after detoxification therapy.

Genetics and pre-existing headache

The heterogeneity of the headache phenotype in PTH might partially be explained by genetic predisposition and a history of headache. In fact, one study found that patients with concussion who had a family history of migraine were more likely to exhibit a migraine-like headache phenotype than those without a family history of migraine[30]. Interestingly, genes associated with familial hemiplegic migraine types 1 and 2 have been associated with increased neurological responses after minor head trauma[31–33]. In a study of US collegiate athletes, a history of concussion was associated with an increased risk of a post-traumatic migraine-like headache phenotype[34]. In another study, an increased risk of post-traumatic migraine-like headache was seen in patients with a history of migraine[17].

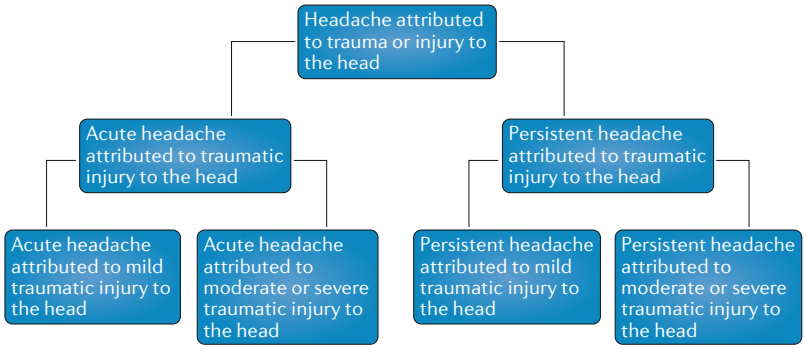

Fig. 1 | **Classification of headache attributed to trauma or injury to the head.** This classification is based on the International Classification of Headache Disorders, 3rd edition[8].

Pathophysiology

The pathophysiological mechanisms that underlie PTH remain largely unknown, but several possible disease mechanisms have been proposed, for which we present the supporting data below. These mechanisms include impaired descending modulation, neurometabolic changes and activation of the trigeminal sensory system (FIG. 2).

Impaired descending modulation

Descending pain modulatory systems have been extensively characterized in animal and human studies[35,36]. These systems link multiple cerebral sites and neuronal pathways, and are key to descending control of pain[37]. Disruption of descending pain modulatory systems can facilitate chronification of pain[38], and this effect has led to the hypothesis that impaired modulation of neuronal excitability, rather than general hyperexcitability, could be an underlying cause of migraine[39]. Given the clinical similarities between migraine and PTH, impaired descending modulation could be implicated in PTH pathophysiology.

Advanced MRI techniques can detect pathological cerebral changes that cannot be found with routine MRI[40,41], enabling descending modulation function to be assessed. In recent years, MRI processing techniques, such as voxel-based morphometry (VBM), voxel-based cortical thickness measurements, diffusion tensor imaging (DTI) and functional MRI (fMRI), have proven to be powerful tools in the assessment of PTH and TBI pathology[41,42].

Structural cortical remodelling. Diffuse axonal injury (DAI) that results from TBI can be detected with high sensitivity with DTI[43]. Fractional anisotropy (a measure of white matter integrity) is a useful DTI measure in this context, as it enables assessment of structural alignment and myelination within white matter fibre tracts. Studies in which DTI has been used to study patients who have a concussion have revealed fibre tract disruption that is indicative of DAI[44,45]. Although no consensus has been reached, fractional anisotropy is thought to increase during the acute post-concussion phase, in contrast to a decrease in fractional anisotropy during the chronic post-concussion phase[41]. On the basis of these observations, one possibility is that top-down structural remodelling of fibre tracts from cortical brain sites (such as the somatosensory and insular cortices) within the pain matrix impairs descending neuromodulation of pain-modulating systems, such as the periaqueductal grey, nucleus raphe magnus and rostral ventromedial medulla.

On the basis of this reasoning, studies have been conducted to assess the correlation between DAI severity and the severity of post-concussion symptoms, and these studies have shown that white matter abnormalities are associated with chronic post-concussive sequelae[46–48]. However, structural MRI data, including DTI-detected abnormalities, must be interpreted with caution in relation to causal factors and diagnosis of post-concussion symptoms. In fact, one MRI study[49] of US military personnel demonstrated the uncertainty in the causal relationship. Of 63 individuals who had received a diagnosis of mTBI after blast exposure, 18 (29%) had multifocal DTI abnormalities, 20 (32%) had one DTI-detected abnormality and 25 (40%) had no abnormalities.

Fractional anisotropy can also provide information about headache phenotypes. In one retrospective MRI study of patients with PTH[50], DTI was used to compare 58 patients with mTBI and a migraine-like headache phenotype with 16 controls who had mTBI but either no PTH or PTH without a migraine-like headache phenotype. Fractional anisotropy in the corpus callosum and the fornix–septohippocampal circuit was lower in patients with a migraine-like headache phenotype than in controls[50]. Interestingly, abnormalities of the corpus callosum have also been detected with DTI in patients with atraumatic migraine[51]. However, methodological issues limit the conclusions that can be drawn from these measurements of DTI changes[50]. First, the control group consisted of a mix of patients without headache and with non-migraine-like PTH. Second, pre-existing headache conditions were not assessed in any of the participants. Third, the time from sustaining the mTBI to MRI was highly variable: the range was 2–506 days in patients with a migraine-like headache phenotype and 1–261 days in controls. Finally, whether participants had onset of headache <7 days after mTBI was not reported. The combination of these limitations means that spontaneous development of a primary headache disorder could have occurred between the mTBI event and MRI assessment.

Studies of structural remodelling in headache phenotypes have also been used to investigate whether PTH and primary headaches share pathophysiological substrates. In one MRI study[29], regional brain volumes and cortical thickness, surface area and curvature in 28 patients with persistent PTH (75% of whom had a migraine-like phenotype) were compared with those in 28 patients with migraine and 28 healthy controls. Comparison of patients with persistent PTH and patients with migraine revealed differences in measurements (area, curvature, volume and/or thickness) in seven cortical locations in the precuneus, supramarginal gyrus, lateral orbitofrontal region and the superior and middle frontal regions. No differences were seen in these areas between patients with migraine and

Box 1 | **The relationship between TBI and PTH**

Traumatic brain injury

- Each year, 69 million people worldwide experience a traumatic brain injury (TBI).
- Mild TBI (mTBI) accounts for 95% of all TBIs, according to one population study[23].
- Annually, 2 million people are diagnosed with a mTBI in the USA[21].
- The annual European economic burden of TBIs is estimated to be €33 billion[148].
- The care burden of 25,000 US soldiers who have been diagnosed with TBI is projected to be $14 billion over the next 20 years[149].

Post-traumatic headache

- The 1-year cumulative incidence of new or worsened headache in patients with mTBI is 91%[16].
- Of patients with TBI who report acute post-traumatic headache (PTH), 40% later develop persistent PTH[18].
- Of all patients with PTH, 35% have not returned to work by 3 months after sustaining the TBI[18].
- Migraine-like and tension-type-like headache are the two most common headache phenotypes after TBI[24].

healthy controls. Of these seven cortical areas, three (right supramarginal gyrus, right lateral orbitofrontal region, left superior frontal region) also showed differences between patients with persistent PTH and healthy controls; cortical thickness was lower in patients with persistent PTH. All three of these cortical areas have previously been implicated in headache pain, pain sensitivity and cognitive evaluation of pain[52–56]. The same researchers[57] have also reported that cortical thicknesses in bilateral frontal regions (superior frontal, caudal middle frontal and precentral cortex) and right hemisphere parietal regions (right supramarginal, right superior and inferior parietal, and right precuneus region) were lower in 33 patients with persistent PTH than in 33 healthy controls, indicating structural cerebral remodelling. This study also showed that lower cortical thickness in bilateral superior frontal regions correlates with a higher frequency of headache in patients with persistent PTH. No association was seen between the number of years lived with persistent PTH and cortical thickness.

In another MRI study, structural remodelling was assessed with VBM in 32 patients with PTH who were compared with 30 healthy controls[58]. MRI was performed within 14 days of the whiplash injury and again after 3 months. Of the 32 patients with PTH, 12 developed persistent PTH and were scanned a third time after 1 year. In these 12 patients, cortical thickness in the anterior cingulate and dorsolateral prefrontal cortex had decreased after 3 months and subsequently normalized in parallel with headache cessation after 1 year. However, the patients who developed persistent PTH still had increased cortical thickness in anti-nociceptive cerebral structures, such as brainstem centres, the thalamus and the cerebellum. The investigators speculated that the increase in cortical thickness could have been due to an adaptive anti-nociceptive mechanism. Importantly, no longitudinal grey matter changes were found at 14 days or 3 months after whiplash injury in the 20 patients without persistent PTH, but cerebral changes in frontal regions have been observed in patients with atraumatic migraine[59].

Taken together, MRI findings in patients with PTH have revealed structural cerebral remodelling in grey matter and white matter regions, and this remodelling could impair descending neuromodulation. The extent to which this remodelling affects the persistence of PTH remains unclear.

Functional remodelling. Changes in cerebral blood flow (CBF) after head trauma have been investigated with single-photon emission computed tomography (SPECT) and arterial spin labelling (ASL). SPECT studies have revealed alterations in CBF within days to years after head trauma[60–62] and an association between CBF changes in certain brain regions and post-concussion symptoms. By contrast, ASL studies have produced diverse results with respect to CBF changes after head trauma: some paediatric studies have demonstrated decreases in CBF[63,64], whereas others have identified increases in regional CBF in teenage athletes with concussion[65]. In two studies of paediatric patients with acute concussion, CBF was increased in patients who developed post-traumatic symptoms but was not increased in patients without these symptoms[65,66]. By contrast, another paediatric study showed that CBF in fronto-temporal regions was bilaterally decreased at a mean of 7 months after concussion, despite normal neurophysiological scores, relative to healthy controls[64]. The conflicting results from SPECT and ASL studies mean that we can draw only two broad conclusions: first, TBI induces CBF changes that result in either hyperperfusion or hypoperfusion, and second, regional[65] and global[66] CBF changes are most pronounced in patients with post-concussion syndrome.

Functional cerebral remodelling that involves alterations in brain activation after TBI has been proposed as a mechanism that underlies sequelae of trauma, such as headache and nausea[67]. Resting-state fMRI has demonstrated that functional connectivity in the default mode network is decreased in the semi-acute phase of TBI, and these changes correlate with the prevalence of symptoms and cognitive dysfunction[68]. In one resting-state fMRI study, functional brain connectivity in 32 patients with mTBI (within 4 weeks) was abnormal compared with that in healthy controls[67]. Specifically, connectivity in the striatal motor system network was impaired and connectivity in the right frontoparietal network was increased in patients with mTBI. Interestingly, one fMRI study has shown that patients with chronic symptoms after TBI have increased default mode network functional connectivity[69]. In the same study, fluctuation of resting-state blood oxygen level-dependent (BOLD) signals were increased in patients with mTBI, particularly in the default mode network, and patients with the lowest functional connectivity had the worst cognitive outcomes. These patients also had more structural white matter abnormalities detected with DTI. However, the correlations between cognitive outcomes after TBI and findings from resting-state fMRI and DTI remain unclear[68,70]. For example, with respect to default mode network functional connectivity, some studies have suggested that patients with concussion present with a pattern of hyper-connectivity in frontal regions

and hypo-connectivity in posterior regions[71,72], but contradictory findings have also been reported[73]. On the basis of these observations, one could speculate that functional remodelling of cerebral circuits is implicated in impaired descending neuromodulation.

Neurometabolic changes

Preclinical data suggest that the acute phase after TBI involves extensive cellular and axonal metabolic changes, which depend on the intensity of the trauma. Mechanical trauma results in cellular injury, which in

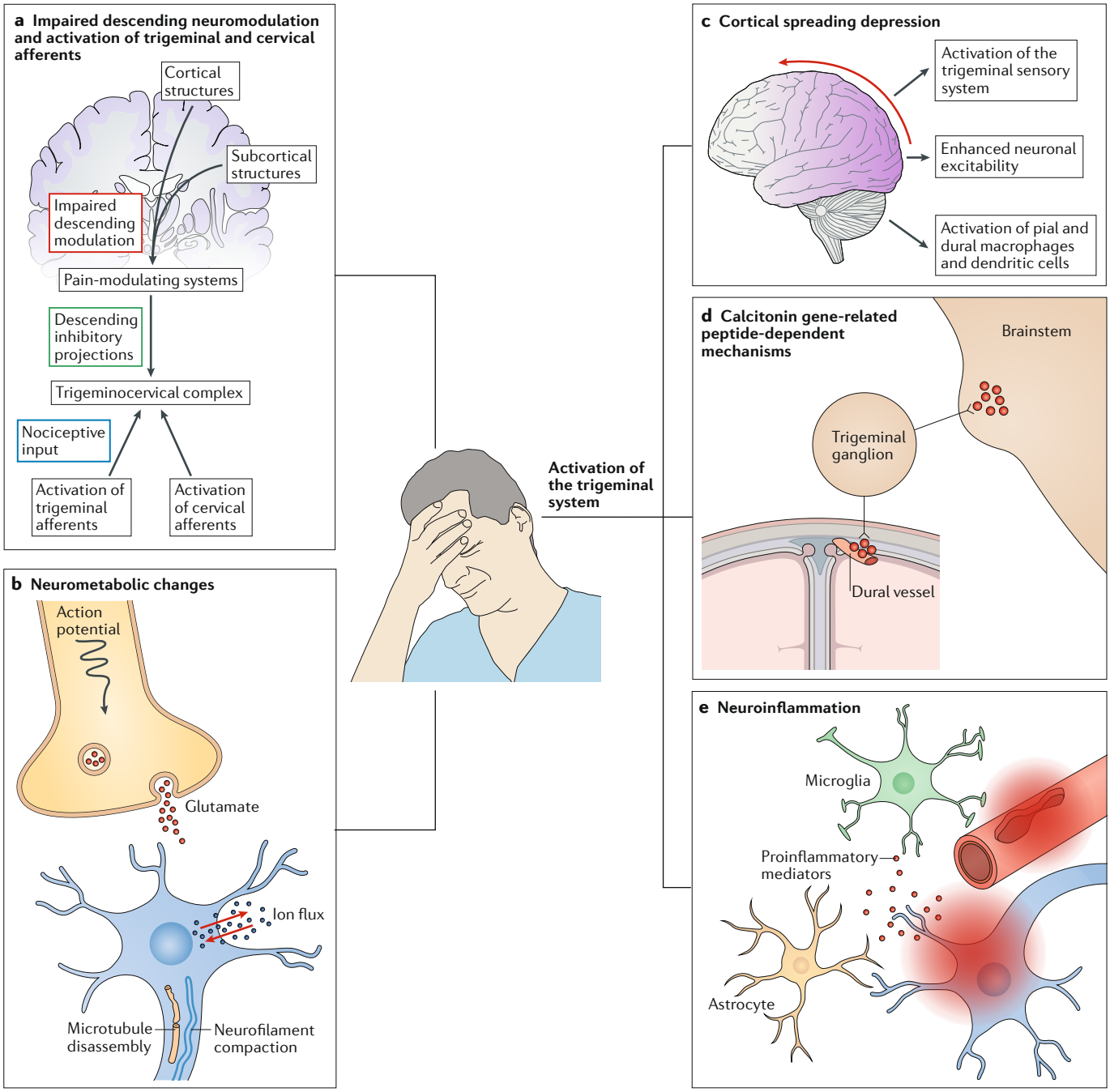

Fig. 2 | **Possible mechanisms underlying the pathophysiology of PTH.** **a** | Impaired descending modulation and afferent activation. Structural and functional remodelling in cortical and subcortical regions after traumatic brain injury (TBI) could impair descending neuromodulation of pain-modulating systems, which normally send inhibitory projections to the trigeminocervical complex. Nociceptive input from trigeminal and upper cervical afferents might also converge on the trigeminocervical complex. **b** | Neurometabolic changes. Neuronal injury from mechanical trauma leads to unregulated flux of ions, and restoration of ion homeostasis causes energy depletion and oxidative stress. Mechanical disruption also triggers a cascade of neurofilament collapse and microtubule disassembly, causing axonal damage. **c** | Cortical spreading depression (CSD). CSD events might occur after TBI, leading to activation of the trigeminal sensory system, enhanced neuronal excitability and activation of pial and dural macrophages and dendritic cells. **d** | Calcitonin gene-related peptide (CGRP)-dependent mechanisms. CGRP is involved in migraine, and animal data suggest that CGRP-dependent pain mechanisms are involved in headache generation after TBI. **e** | Neuroinflammation. Activation of glial cells following traumatic brain injury results in the production and release of pro-inflammatory mediators, which then cause neuronal damage, vascular damage and leakage from the blood–brain barrier. PTH, post-traumatic headache.

turn induces excessive glutamate release and unregulated flux of ions (potassium efflux, sodium influx and calcium influx)[74,75]. ATP-driven ionic pumping is then increased to restore ionic homeostasis. This process rapidly depletes cellular energy sources[76], and the mismatch in supply and demand eventually causes lactate accumulation and oxidative stress[77]. Moreover, increases in intracellular calcium can induce mechanical disruption of axons[78], triggering a cascade of neurofilament collapse and microtubule disassembly that results in structural axonal damage known as secondary axotomy[79,80].

In humans, magnetic resonance spectroscopy (MRS) can detect subtle cerebral metabolic changes[81]. To date, N-acetyl aspartate (NAA; a marker of neuronal and axonal integrity), choline (a marker of cell membrane turnover) and creatine and phosphocreatine (markers of cell energy metabolism) are the most studied metabolites in patients with TBI[82]. MRS studies in patients with mTBI have tended to demonstrate reductions in NAA, increases in choline and stable creatine and phosphocreatine[83]. However, the use of MRS to detect pathognomonic changes in PTH remains highly speculative and the existing data are conflicting[82].

Nevertheless, combining advanced neuroimaging modalities such as DTI and MRS in the acute phase after mTBI could provide interesting insights. One MRI study has indicated that structural and metabolic cerebral alterations persist beyond resolution of clinical symptoms[84]. However, no studies have been conducted to investigate neurometabolic changes in patients with PTH specifically, so it is challenging to tie together preclinical and clinical data in TBI and transfer these data to help understand the pathogenesis of PTH. We hypothesize that unregulated efflux of potassium after TBI[74] could be particularly important for the development of PTH. In line with this hypothesis, some evidence suggests that ATP-sensitive potassium channel opening has an important role in headache and migraine pathogenesis[85]. Moreover, many migraine triggers generate oxidative stress in the brain[86], suggesting that increased oxidative stress after TBI[77] could have a role in triggering PTH. In support of this hypothesis, one MRI study has shown that antioxidant status is decreased in patients with migraine and cerebral white matter hyperintensities[87].

Trigeminal sensory system activation

Cortical spreading depression. The aura phase of migraine is thought to be caused by a transient, self-propagating wave of cellular depolarization in glial cells and neurons called cortical spreading depression (CSD)[88]. This extreme depolarization in the cerebral cortex results in disruption of ionic gradients, increases in extracellular potassium and excessive glutamate neurotransmission[89], which increases neuronal excitability and activates the trigeminal sensory system[90]. Some evidence indicates that CSD could have a role in PTH: TBI increases release of ATP similar to that seen with CSD[91], and electrocorticographic recordings taken during neurosurgery in 14 patients with acute TBI demonstrated CSD events occurring in foci near the damaged cortical tissue[92]. However, the importance of CSD in PTH pathophysiology remains largely unknown.

The relationship between PTH and CSD has mostly been investigated in experimental TBI models, such as lateral fluid percussion (LFP) and controlled cortical impact (CCI)[93,94]. In one LFP rat study[95], elevated intracranial pressure was associated with higher numbers of repetitive CSD cycles across different TBI severities. The same study showed that the greatest TBI severity was associated with mortality of 44% and a higher number of repetitive CSD cycles. However, LFP and CCI models involve penetrative brain injuries, so data from these animal models should be interpreted with caution because most head traumas in humans are classified as mTBI[24]. A more appropriate model might be the use of a weight-drop device[96,97], which causes mTBI in unrestrained animals, thereby avoiding craniotomy and better recapitulating the biomechanical forces to the head and neck that are thought to have a role in the pathophysiology of PTH[98].

Neuroinflammation. Neuroinflammation could link TBI with the generation and persistence of headache[99], possibly mediated through CSD, which in turn activates the trigeminovascular system[90]. For instance, activation of glial cells after TBI is well-described[99] and has also been implicated in the pathophysiology of migraine[100]. In particular, microglial activation is considered to be important in the initiation and prolongation of neuroinflammatory processes by stimulating production of inflammatory mediators[101]. Post-mortem examination has also demonstrated that the mRNA of inflammatory mediators is elevated in the brain within minutes of TBI[102]. Observation of these inflammatory processes has led to the suggestion that neuroinflammation after TBI increases CNS excitability[103,104], which could facilitate the genesis of CSD (see Cortical spreading depression above). Consistent with this hypothesis, CSD upregulates matrix metalloproteinases (MMPs)[105], which are elevated immediately after TBI[106] and in patients with migraine[107,108]. However, in one study of patients with migraine, MMP plasma levels during migraine attacks without aura did not differ from levels between attacks[109].

This link between neuroinflammation after TBI and CSD is intriguing because much evidence implicates CSD in activation of the trigeminovascular system[110]. In fact, some evidence suggests that CSD triggers opening of neuronal pannexin 1 mega-channels as a result of excessive potassium and glutamate release[111], and pannexin 1 channels initiate an inflammatory response through pial and dural macrophages. This inflammatory response activates trigeminal nociceptive fibres that are involved in headache[105]. Further evidence that supports this link comes from one in vivo animal study[112], in which CSD was found to activate pial and dural macrophages and dendritic cells. Furthermore, animal studies have shown that head injury activates dural mast cells[113] and is associated with trigeminal hypernociception[114]. In humans, one study[115] found more pronounced generalized cephalic cutaneous allodynia in patients with persistent PTH compared with patients

with traumatic head injury without persistent PTH, indicating damage to central nociceptive and thermal systems. Similar findings in patients with migraine have also been reported[116]. The cause of generalized cephalic cutaneous allodynia is probably related to peripheral nerve damage that causes central sensitization[117] that is itself thought to be associated with neuroinflammatory processes that cause specific sensitization of trigeminal dorsal horn neurons[116,118]. However, the hypothesis that neuroinflammation after head trauma causes central sensitization is still speculative, and causality cannot be inferred.

One animal study[119] has provided evidence of neuroinflammatory processes, generation of reactive oxygen species, vascular damage and meningeal cell death in the acute phase of mTBI. In this study, a closed-skull brain injury model was used to mimic the trauma mechanisms of mTBI. The neuroinflammatory processes breached the glia limitans, which, in coordination with the blood–brain barrier, regulates molecular movement into the cerebral parenchyma. Release of inflammatory mediators from the glia limitans has been implicated in activation of the trigeminovascular system[111].

The hypothesis that neuroinflammation contributes to PTH pathophysiology is further supported by experimental studies that have shown that N-acetyl cysteine (NAC) has anti-inflammatory and neuro-protective effects in preclinical models of TBI[120–122]. In one study in humans[123], the efficacy of NAC versus placebo was tested in US service members with symptoms (headache, dizziness and cognitive dysfunction) after blast-related mTBI. The study was a randomized, double-blinded, placebo-controlled study that included 81 US service members. Secondary analysis showed that individuals with mTBI who received NAC within 24 h of sustaining their injury had an 86% likelihood of no clinical symptoms at 7 days post-trauma, versus a 42% likelihood in those who received placebo.

Calcitonin gene-related peptide-dependent mechanisms. The clinical similarities between PTH and primary headache disorders raise the question of whether the molecular signalling mechanisms that trigger PTH are similar to those that trigger primary headache disorders, such as migraine. Human migraine provocation studies have established that upregulation of cAMP is a key mechanism in migraine pathogenesis[124]. Given that cAMP levels in vascular smooth muscle cells are increased by CGRP[124] and that CGRP is a well-documented trigger of migraine-like attacks in patients with migraine[125], CGRP-mediated mechanisms could play a pivotal role in PTH pathogenesis. Results of one animal study suggest that mitigation of prolonged increases in CGRP by the use of CGRP antagonists could be a therapeutic approach for treatment of PTH[126]. In addition, anti-CGRP antibodies are effective in migraine prevention[127], so could be a promising therapeutic approach to PTH.

CGRP receptors are expressed at multiple levels in the trigeminal sensory system: in the peripheral trigeminal nerve fibres, the trigeminal ganglion and the spinal trigeminal nucleus[128]. CGRP is released upon activation of the trigeminal ganglion, and is a potent dilator of human cerebral arteries[129,130]. In a rat model, animals with concussion developed cephalic pain hypersensitivity (a measure of headache-like behaviour), and after this symptom had resolved, administration of glyceryl trinitrate (GTN; a known migraine trigger) renewed and increased the hypersensitivity[131]. The GTN-induced cephalic pain hypersensitivity was inhibited by anti-CGRP monoclonal antibody treatment. The potential importance of this study is twofold. First, the results suggest that anti-CGRP monoclonal antibodies could be a much-needed treatment option for PTH. Second, the findings indicate that development of PTH could involve a CGRP-dependent mechanism. Moreover, in the same study, anti-CGRP monoclonal antibodies were administered immediately after induced mild closed-head injury and again every 6 days after trauma. The antibodies did not inhibit cephalic pain hypersensitivity at 72 h, but did so on day 7 and day 14. The reasons for this effect are unknown, but the investigators speculated that cephalic pain hypersensitivity might be mediated by something other than CGRP at 72 h after head injury, or that the anti-CGRP monoclonal antibodies had not reached maximal efficacy at 72 h but had by day 7.

In conclusion, the exact role of CGRP in PTH pathophysiology has not yet been sufficiently elucidated. However, anti-CGRP antibodies do hold promise for prevention of PTH, and one randomized clinical trial is currently ongoing[132]. Further work is needed to explore CGRP-mediated mechanisms in PTH and to establish whether the response to intravenous CGRP infusion differs between patients with PTH and patients with migraine.

Other mechanisms

Hyperadrenergic state. Nociceptive drive from adrenergic activation should be considered as a possible mechanism of PTH. Some evidence in humans has indicated that autonomic dysfunction is involved in the persistence of post-concussive symptoms[133]. Moreover, one animal study[134] has shown that noradrenaline induces headache-like behaviour in rats, probably through sensitization of trigeminal sensory afferents and the release of pro-nociceptive IL-6. However, in healthy human volunteers, intravenous infusion of noradrenaline did not induce headache or cranial arterial changes (middle cerebral artery and temporal artery)[135]. Therefore, further evidence is needed to determine the role of adrenergic activation in PTH pathogenesis.

Activation of extracranial dural afferents. In 1940, a landmark study by Ray and Wolff[136] demonstrated that intraoperative noxious stimulation to dural and extracranial structures could induce headache. These findings led to the hypothesis that neuronal hyperexcitability that causes headache partly depends on activation of peripheral nociceptors[137]. This hypothesis was further strengthened by the discovery that intracranial and extracranial tissues share functional connections through collaterals of dural sensory afferents that probably originate from the trigeminal nerve[138,139].

On this basis, one could speculate that a concussion could trigger sensory activation of extracranial nerves and meningeal sensory fibres, which in turn convey information through the trigeminal nerve to deep-brain structures. In fact, one animal study in which a weight-drop model was used showed that mild closed-head injury increased nociceptive responses emanating from calvarial periosteal afferents, which originate from the ophthalmic division of the trigeminal nerve[114]. Thus, this study points to sensitization of the trigeminal nociceptive system rather than neuronal hyperexcitability of deep-brain CNS structures as the underlying mechanism of headache perception.

Nociceptive drive from cervical afferents

The relationship between headache and neck injury is well-established[98], as is the association between neck pain and primary headache disorders, such as migraine and tension-type headache[140]. The mechanisms of PTH could also involve a nociceptive drive from upper cervical afferents, as most concussions involve a rotational injury[141]. Evidence that supports this hypothesis comes from a study in which stimulation of the first cervical nerve (C1) evoked frontal and periorbital pain in six of six patients with migraine, whereas C1 stimulation in four patients with chronic occipital pain caused only occipital and cervical pain[142]. Convergence of trigeminal and cervical nociceptive input in the trigeminal nucleus caudalis has been proposed[143,144], and the possible nociceptive drive from upper cervical afferents might be particularly relevant when onset of PTH follows whiplash injury to the neck[98].

Future directions

Although research into PTH has rapidly increased over the past 5 years, the underlying disease mechanisms largely remain an enigma. Above, we describe the plethora of mechanisms thought to be involved in PTH pathophysiology (FIG. 2). However, further animal and human studies are warranted. Below, we discuss future directions and suggestions for targeted studies of PTH pathophysiology.

Animal studies

Animal models of TBI have already helped improve our knowledge of the basic mechanisms that are implicated in PTH pathophysiology[145]. However, future animal studies should be conducted to investigate PTH-specific symptomatology. In this context, lessons learned from animal models of migraine could provide valuable inspiration[146]. For example, it would be interesting to examine the association of photophobia and phonophobia with experimentally induced mTBI, given that both symptoms are reported by a considerable number of patients with PTH[147]. Furthermore, CSD is involved in activation of the trigeminovascular system; thus, assessment of the association between experimentally induced mTBI, CSD and subsequent trigeminovascular activation could provide valuable pathophysiological insights into PTH. However, interpretation of the findings from such studies should be done while keeping in mind that inference of disease mechanisms of PTH from animal models of TBI is challenging, mainly because PTH is a disorder of unknown aetiology, making disease-specific modelling complicated.

Future animal studies could also aid with development of novel PTH-specific treatments. Currently, one randomized controlled trial is being conducted to investigate the efficacy of anti-CGRP monoclonal antibodies for the prevention of persistent PTH[132]. This investigation underscores the importance of investigating the effects of anti-CGRP monoclonal antibodies on mTBI-induced physiological phenomena such as allodynia in animals.

Future efforts should also seek to elucidate the role of headache-inducing molecules and their respective inhibitors besides CGRP and anti-CGRP monoclonal antibodies. For this purpose, pituitary adenylate cyclase-activating polypeptide and ATP-sensitive potassium channel openers could be used to study PTH-specific mechanisms after experimentally induced mTBI. Both molecules have been implicated in migraine pathogenesis and their inhibitors have been suggested as novel therapeutic targets in migraine[85,124]. The integration of headache-inducing molecules and their respective inhibitors into animal models of PTH would greatly increase our understanding of the signalling pathways involved in PTH pathogenesis.

Human studies

To guide future efforts in PTH research, more human studies are needed to identify PTH-specific biomarkers, which can then be used to develop precision medicine strategies. First, deep phenotyping of clinical characteristics and associated symptoms in patients with PTH are imperative. Importantly, headache is not the only complication after a concussion; depression, anxiety, PTSD and other post-concussive comorbidities can occur, and their prevalence should be investigated in a large population of patients with PTH. The findings could aid translation of phenotype-guided assessments into better clinical management and prevention of PTH. Second, genetic and biochemical studies of patients with PTH who have undergone deep clinical phenotyping have the potential to delineate biomarkers of PTH, which could be used to predict outcome and the risk of developing persistent PTH. Third, MRI studies are needed to identify structural, functional and metabolic changes that occur in the acute and persistent phases of PTH. Correlation beween cerebral changes and clinical and biochemical characteristics could identify PTH-specific biomarkers.

Beyond comparisons of patients with PTH and healthy controls, comparisons with patients who have primary headache disorders would be useful to determine whether cerebral changes in PTH are comparable to those in primary headache disorders. Similarly, these comparisons could be used to investigate pathophysiological differences and differences in biochemical and imaging biomarkers between migraine-like and tension-type-like headache phenotypes in PTH. In addition, no biochemical or MRI studies to date have systematically investigated the pathophysiological mechanisms

involved in chronification of PTH, so studies in this area are needed.

Finally, human provocation models could also prove valuable in the study of PTH. These models would demonstrate whether intravenous infusion of nociceptive signalling molecules, such as CGRP, induces headache attacks in patients with persistent PTH. If so, a novel model for the provocation of headache attacks in PTH could be established, and this model could be used to examine whether the efficacy of anti-CGRP antibody treatment in patients with persistent PTH can be predicted on the basis of their hypersensitivity to CGRP.

Conclusions

PTH is a highly disabling disorder with intolerably high socioeconomic costs and no adequate treatment options. Some progress has been made in understanding the underlying mechanisms, but more targeted animal and human studies are needed. The emphasis of future studies should be the establishment of biomarkers that are involved in progression to persistent PTH and the identification of potential treatment targets to enable randomized controlled trials to be conducted in this patient population.

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All authors researched data for the article, discussed the content, wrote the text, and reviewed and edited the manuscript before submission.

Competing interests
F.M.A. is a lecturer or scientific adviser for Novartis and Teva. M.A. is a consultant, speaker or scientific adviser for Alder, Allergan, Amgen, Eli Lilly, Novartis and Teva. H.W.S. is a lecturer for Novartis. D.W.D. reports the following competing interests: personal fees from Alder, Allergan, Amgen, Association of Translational Medicine, Autonomic Technologies, Aural Analytics, Biohaven, Charleston Laboratories, Daniel Edelman, Axsome, Dr Reddy's Laboratories/Promius, Electrocore, Eli Lilly, eNeura, Foresite Capital, Impel, Ipsen, Neurolief, Nocira, Novartis, Oppenheimer, PSL Group Services, Satsuma, Sun Pharma (India), Supernus, Teva, Theranica, University of British Columbia, University Health Network, Vedanta, WL Gore, XoC, Zosano and ZP Opco; CME fees or royalty payments from Academy for Continued Healthcare Learning, Cambridge University Press, Chameleon, Global Access Meetings, Global Life Sciences, Global Scientific Communications, Haymarket, Healthlogix, Medicom Worldwide, Medlogix Communications, Mednet, Miller Medical, Oxford University Press, PeerView, Universal Meeting Management, UpToDate (Elsevier), WebMD Health/Medscape and Wolters Kluwer Health; stock options with Aural Analytics, Epien, GBS/Nocira, Healint, King-Devick Technologies, Matterhorn/Ontologics, Second Opinon/Mobile Health and Theranica; consulting without fee for Aural Analytics, Epien, Healint and Second Opinion/Mobile Health; position on the board of directors for Epien, King-Devick Technologies and Matterhorn/Ontologics; patent 17189376.1-1466: vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis without fee; research funding from American Migraine Foundation, Henry Jackson Foundation, Patient-Centered Outcomes Research Institute and US Department of Defence; professional society fees or reimbursement for travel from American Academy of Neurology, American Brain Foundation, American Headache Society, American Migraine Foundation, Canadian Headache Society and International Headache Society; and use agreement through employer for Myndshft. The other authors declare no competing interests.

Review criteria
Articles discussed in this Review were identified by PubMed searches performed between 1 May 2018 and 1 September 2018 with no restrictions on the date of publication. The search terms used were 'post-traumatic headache', 'PTH', 'concussion', 'traumatic brain injury', 'pathophysiology' and 'imaging'. The reference lists of identified papers were searched for further relevant articles, and related citations for identified papers as listed on the PubMed site were evaluated. The final references included were chosen based on the relevance to the scope of this Review.