Headache management in Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is estimated to rank as the third most important disease burden worldwide. About 60% of the survivors develop chronic headaches and visual symptoms. The long-term management of headaches in these patients is controversial. Importantly, the care pathway of most patients is fragmented, complicating conclusive headache management. Here we review the epidemiology and aetiology of post traumatic headaches (PTH), discuss the diagnostic work up and summarise the acute and long-term management.

Keywords: headache, traumatic brain injury, acute pain, chronic pain.

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Table 1: *Typical clinical features of different forms of headache following TBI. A patient may suffer from one or several headache types. Autonomic features include nausea, vomiting, photo-/phono-/osmophobia, unilaterally blocked nose, unilateral tearing red eye. The aura includes visual symptoms such as scintillating scotomata, blurred vision, sensory or motor symptoms.*

Headache	Pain characteristic	Duration	Frequency	Other
Episodic tension-type	pressing	hours	variable	± migraine
Chronic tension-type	mainly pressing	constant	daily	± migraine
Migraine	pressing/pulsating	hours	variable	± Aura, autonomic symptoms
Cluster headache	pressing	minutes	in clusters	autonomic features
SUNCT	lancinating	seconds	variable	autonomic features
Low pressure	dull	constant	daily	CSF leak
High pressure	pressing	variable	daily	hydrocephalus
Neuralgia	lancating	seconds	variable	trigger zone

1 Introduction

Traumatic brain injury (TBI) is a significant societal burden and ranks as the most prevalent neurological disorder[1]. In the US alone, an estimated 1.4 to 1.6 million individuals are affected by TBI annually[2], and globally, over 55 million cases were reported from 1990 to 2016. The worldwide incidence rate stands at 369 per 100,000, with a prevalence of 759 per 100,000, and these numbers are on the rise[1]. The economic impact is substantial, with TBI-related costs in the US reaching approximately $60 billion[3]. Many survivors experience chronic headaches[4], often associated with visual symptoms like blurred vision, light sensitivity, visual snow, and convergence insufficiency[5,6]. This review aims to define post-traumatic headache (PTH) and examine its incidence, including risk factors. We will also explore the underlying mechanisms of PTH, followed by an overview of the diagnostic approach. Lastly, we discuss management strategies for PTH in both its acute and chronic stages.

2 Classification

Typically, any headache following a traumatic brain injury (TBI) is considered posttraumatic. However, it is often possible to diagnose a primary headache disorder, such as migraine or tension-type headache, in these cases. Additionally, TBI can trigger or worsen pre-existing headache disorders[7–12]. This is highlighted in a summary of the clinical characteristics of headaches post-TBI (Table 1). Consequently, the International Headache Society (IHS) has established criteria (IHCD) for classifying acute and persistent headaches resulting from head injuries[13] (Table 2). Acute and chronic post-traumatic headaches (PTH) are terms that correspond to the previous, widely used nomenclature. The key distinction is made between *acute* and *chronic* PTH, based on the arbitrary duration threshold of three months. Although recognized, visual symptoms are not included in this classification.

The first unifying IHS criterion of the previous classification was that the

headache described by the patient does not fulfil any known typical characteristics and it is still a criterion in the last version. This is important, because as summarised in Table 1 headaches other than PTH are present after TBI. In fact, a prospective study using the IHS criteria found that in 91% of patients the headaches following TBI were of the following categories: episodic tension-type (11%), chronic tension-type (51%), migraine without aura (2%), chronic tension-type and migraine without aura (8%), chronic tension-type and probable migraine (19%)[11]. Only 9% had headaches that could not be classified because of alternating pain characteristics and/or accompaniments[11]. In a recent study, up to 49% of headaches met criteria for migraine and probable migraine, 40% for tension-type headache[14]. Furthermore, pre-existing headaches are an independent risk factor for the development of PTH, with attacks becoming more frequent and more severe, triggering a higher consumption of analgesics[15]. The other risk factors for chronic PTH are female gender[15–18], increased age[19–21], longer duration of post-traumatic amnesia[22], lower severity of TBI, psychiatric co-morbidity[16,23]. Any form of financial or secondary gain (sickness benefit, early retirement, reduced working time, litigation) are other possible[18,24,25], but not uniformly accepted[26–28] independent risk factors for chronic PTH. Others doubt the existence of PTH as a separate entity outside the context of financial compensation[29,30].

The next unifying criterion is that the onset of the headaches is no longer than seven days after TBI or regaining consciousness. In one prospective study, the onset of headaches ranged from few hours to 3 days[11]. In another study, 54% of subjects reported new or worse headaches compared to pre-injury immediately after injury[14]. Similarly, in sport injuries, the onset of headaches was within hours after mild TBI[10].

Appropriate recognition of the different types of headache occurring after TBI is crucial for patient management to be rewarding. In this review the term PTH is used as an umbrella term, but other types of headache will be mentioned specifically where relevant for patient management.

3 Incidence and prevalence

The one-year prevalence for migraine ranges from 6% in men to 18% in women[31,32]. The one-year prevalence for tension-type headache (TTH) is about 28–63% in man and 34–86% in woman[33,34]. Reports on the PTH incidence need to be considered when looking at the high prevalence of primary headache in the general population.

In reported incidence of PTH following TBI varies from 8% to 90%[35–40].

This wide range reflects both methodological difficulties and discrepancies between studies. The IHS Classification of Headache Disorders excludes primary headaches, even if they start after TBI for which reason the prevalence of "pure" PTH is lower than by earlier estimates.

It is generally accepted that the prevalence declines with time from injury. The literature on epidemiological data is confusing and cannot be lumped

Table 2: *Definition of PTH, adapted from the International Headache Society (IHS) criteria for post-traumatic headache[13]. The full table is presented as supplementary material. PTA = post-traumatic amnesia, — = not required/ not applicable.*

TBI	Acute PTH		Chronic PTH	
	moderate or severe	mild	moderate or severe	mild
Duration of loss of conciousness	>30min	<30min	>30min	<30min
Glasgow Coma Scale Score:	<13	≥13	<13	≥13
	PTA>48h	Concussion	PTA>48h	Concussion
Imaging demonstration of a traumatic brain lesion	required	—	required	—
headache develops within 7 days after head trauma or after regaining conciousness	required	—	required	—

without being open to criticism because they consist of retrospective, prospective, selected and unselected populations. As a rule of thumb the prevalence of PTH ranged from 31–90% one month after TBI[35–37], from 32–78% after 2–3 months[38,41], about 27% after six months[19] and approximately 8–35% after one year[19,39]. About 24% of patients continued to suffer from PTH two to four years after TBI[19].

Because of the tendency of PTH to improve with time and the overlap with other headache disorders it is difficult to estimate the overall prevalence of chronic headaches after TBI. A recent meta-analysis on 12 studies (1670 patients) estimated the prevalence to be about 57.8% (95% CI: 55.5%–60.2%)[4].

4 Pathophysiology of pain perception

Acute PTH is likely to be nociceptive and chronic PTH is likely to be neuropathic in nature[42]. Nociceptive pain in TBI can result from damage to the cerebral and dural arteries, the dura mater and the trigeminal, glossopharyngeal and vagus nerves. The trigeminal system is the principal mediator for perception of facial pain as well as pain caused by damage to the large cerebral vessels, pial vessels, large venous sinuses and the dura mater[43]. The central pain pathways of the trigeminal system are illustrated in Figure 1. This is complemented by the pain fibre pathways of the upper cervical dorsal roots which innervate the posterior fossa[43]. Pain perception is processed within the trigeminal or dorsal root ganglia (first order), the trigeminal nucleus and spinothalamic tract (second order), thalamus (third order) and finally the cortex. Given the detailed anatomical data, there is surprisingly little evidence-based medicine on the pathophysiological changes associated with PTH.

Damage of these pathways/centres was thought to be linked to severity of TBI and development of PTH. However, the prevalence of PTH with mild TBI

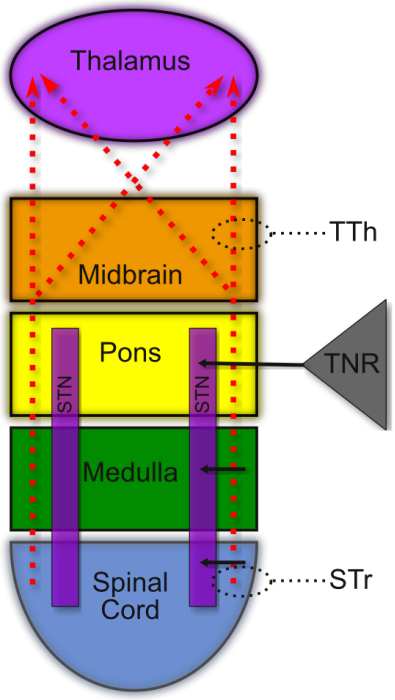

Figure 1: *Pain pathways of the trigeminal system. The trigeminal nerve root (TNR) reaches the rostral and caudal nuclei of the spinal trigeminal nucleus (STN) through the pons. Pain fibres innervate the STN in the spinal cord (pars caudalis), the medulla (pars interpolaris) and the pons (pars oralis). The afferent central pain pathways of the STN project in the spinal trigeminal tract (STr) and dorsal trigeminal thalamic tract (TTh). The STr and TTh (dashed red arrows) traverse the brainstem from the spinal cord to the ipsi- and contralateral thalamus. (Figure modified from reference [44])*

has been consistently higher (75.3%, 95%CI, 72.7–77.9%)[15,23,24,38,45–50] compared to severe TBI (32.1%, 95%CI, 29.3–34.9%, p<0.001)[4,46,47,49–55]. The reason for this paradoxical observation remains unknown. Numerous methodological problems have been highlighted[56–58], including impaired cognitive functioning in patients with severe TBI[59]. Importantly, pain perception is also modulated by psychological and cognitive factors[60] and their involvement in PTH has been reviewed in depth by Solomon[61]. In this review, addressing mainly physicians in intensive care and rehabilitation services, we thought it most didactic to dissect anatomically extra- from intracranial mechanisms.

4.1 Extracranial mechanisms

Musculoskeletal injuries are common in TBI[62]. Injury to the neck, jaw, scalp and periosteum can aggravate intermittent migraine, cause tension type headache and develop into a chronic daily headache. Injury to the temporomandibular joint may cause jaw pain on speech or mastication as well as triggering headaches. Traumatic or iatrogenic damage to the extracranial portion of the cranial nerves may result in neuralgia[63]. The trigeminal nerve is usually affected, rather than the glossopharyngeal or the other cranial nerves, which are rarely affected. Neuralgia due to peripheral nerve damage may be caused by the local accumulation of $Na_v1.6$ channels[64]. The local increase of channels may then facilitate generation of axon potentials and thus contribute to chronic activation of pain pathways[65]. Injury to the carotid sheath can cause severe ipsilateral dysautonomic cephalgia[66].

Other clinically significant pain generators involved in PTH are referred cervicogenic pain from the C2 and C3 facet or upper cervical musculature. Temporomandibular joint disorders (TMJD) and associated articular and myofascial dysfunction; neuritic and neuralgic headaches associated with craniotomies, focal impact injuries, facial trauma/fractures as well as occipital neuralgia.

4.2 Intracranial mechanisms

Structural changes of the brain have been associated with headache in clusterheadache[67], migraine[68–72] and tension-type headache[73]. Consistently they showed loss of grey matter in structures involved in pain perception such as the anterior cingulate, brainstem, cerebellum, insula, prefrontal, primary and secondary somatosensory cortex and thalamus[74]. Structural changes are a possible cause for post-traumatic headache because diffuse axonal injury (DAI) due to shear forces, contusions, haemorrhages and ischaemic damage is the major pathological feature of the central nervous system (CNS) following TBI[75,76]. The brainstem, dorsolateral midbrain, corpus callosum, internal capsules and fornices are particularly vulnerable to DAI[77,78]. DAI of an eloquent area such as the probable migraine centre in the brainstem[79], the spinothalamic tracts and its cortical projections, the periaqueductal grey or thalamus causes central pain and headaches[80–86].

Volumetric brain imaging using a 3T magnet did demonstrate a transient decrease of grey matter volume in the anterior cingulate, dorsolateral prefrontal cortex in patients with *chronic* post-traumatic headache who made a full recovery within one year[87]. It is interesting but more difficult to explain why all of these patients also showed an increase of grey matter in the brainstem, thalamus and cerebellum. In contrast, patients with *acute* post-traumatic headache did not have any evidence for changes in grey matter volume[87].

Alteration of the neurochemistry in TBI mirrors changes seen during a migraine attack[88]. This suggests that the same molecular derangement may cause headaches in TBI and migraine. These shared biochemical alterations are: increased of extracellular K^+, of excitatory amino acids, serotonin (5-HT), norepinephrine, endogenous opioid and nitric oxide; decrease of intracellular Na^+, Ca^+, Cl^{2-}, Na^+. Depolarisation due to Leão's spreading depression[89] observed both in TBI[90] and migraine[91] further enhance the electrolytic imbalance and cause a wave of hyperaemia followed by oligemia.

There are anecdotal reports that any of the three trigeminal autonomic cephalgias (TAC) may develop after TBI; (1) short-lasting Unilateral Neuralgiform pain with Conjunctival injection and Tearing (SUNCT)[92], (2) cluster headache (CH)[93] and (3) chronic paroxysmal hemicrania (PH)[94]. The site of the lesion remains unknown, as the development of autonomic symptoms requires increased cranial parasympathetic activation via the trigemino-autonomic reflex[95,96]. Whilst both extra- and intracranial involvement may be possible, hypothalamic activation of hypothalamic-trigeminal connections may be the unifying mechanism in SUNCT and cluster headache[96].

Other, well established mechanisms include tension pneumocephalus, syndrome of the trephined, carotid-cavernous fistulas, epilepsy, cavernous sinus thrombosis, carotid dissection, post-trauma sinus problems, late extra-axial collections such as sub (SDH) and extradural haematoma (EHD).

5 Diagnostic workup

5.1 History

Given the prevalence of primary headache disorders, a thorough history is essential to identify their typical clinical features (Table 3). Patients may experience multiple headache types, where one could obscure the other. Key questions should cover accompanying symptoms, temporal patterns, and laterality, including specific inquiries about light sensitivity and visual snow. Additionally, past medical and family histories of primary headache disorders should be explored.

Table 3: *Clinical features of primary headache disorders in the differential diagnosis of PTH (Table modified and extended from [97]).*
Tension type headache = TTH, medication overuse headache + MOH, trigeminal autonomic cephalgias = TAC, cluster headache = CH, paroxysmal hemicrania = PH, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing = SUNCT, female=F, male=M. Rating: — = not proven effect, (+) = possibly small effect (≤10%), + = some effect (≤35%), ++ = good effect (35–70%), +++ = excellent effect (>70%).

				TAC			Cranial nerve
	TTH	Migraine	MOH	CH	PH	SUNCT	neuralgia
Gender ratio (F:M)	1.8:1	3:1	3.5:1	1:3	1:1	1:1.5	2:1
Location							
holocephalic	+++	—	+++	—	—	—	—
unilateral	—	+++	—	+++	+++	+++	+++
can change side	—	+	—	(+)	—[1]	(+)	—
Attacks							
Frequency (per day)	—		—	1–8	20	100	
Length (min)	—		—	30–180	2–30	1–5	
Episodic	—	++	—	+++	+	(+)	(+)
Chronic	+++	+	+++	(+)	++	+++	+++
Triggers							
Alcohol	—	+	—	+++	+	—	—
Nitroglycerin	—		—	+++	+	—	—
Cutaneous	—	—	—	—	—	+++	+++
Restlessness	—	—	—	+++	+++	++	++
Periodicity[2]	—	+	—	++	—	—	—
Treatment effects							
Oxygen	—	—	—	+++	—	—	—
Sumatriptan, 6 mg	(+)	+++	(+)	+++	+	(+)	—
Indomethacin	(+)	—	—	—	+++	—	—
Medication overuse	++[3]	+	+++	—	(+)	—	—
Migraine features							
Nausea	(+)	+++	+[4]	++	++	+	(+)
Phobia[5]	—	+++	—	++	++	+	+
Aura	—	++	—	—	(+)	—	—

5.2 Clinical examination

The importance of a meticulous physical examination cannot be overstated. In our view, all paraclinical tests merely supplement the clinical insights gained from history-taking and physical assessment. This examination should encompass tests for visual function and eye movement evaluation.

5.3 Skull and cervical spine X-ray

In the acute and intensive care setting, a routine X-ray is the quickest and least resource demanding examination to exclude a fracture of the skull/cervical spine as possible extracranial sources for pain.

5.4 Brain imaging

Brain imaging is mandatory in any patient with focal neurological signs or reduced GCS. If the GCS is normal, symptoms such as a severe headache, nausea and vomiting should also prompt imaging. A meta-analysis (3375 patients) found the odds ratio for an abnormal CT brain scan to be significantly elevated for severe headache (OR 3.2, 95% CI 2.2–4.6), nausea (OR 2.1, 95% CI 1.5–3.1) and vomiting (OR 4.4, 95%CI 2.8–6.9)[102].

In the acute phase, CT brain imaging will help with the majority of the differential diagnoses in PTH, such as subdural and epidural haematoma, cerebral haemorrhage or hydrocephalus. MRI brain imaging is superior to CT for detection of non-haemorrhagic contusions, small lesions and diffuse damage and will be the preferred test for most neurologists in a routine headache clinic[103–105]. MRI/MRV/MRA brain imaging may be necessary to rule out a cerebral vein thrombosis, cavernous sinus thrombosis and arterial vessel dissection. Imaging may be suggestive of CSF hypotension, but this will require confirmation by lumbar puncture (see below). Finally, imaging of the posterior fossa is mandatory in any new onset TAC after TBI[92–94].

5.5 Neck & spinal cord imaging

Most patients with loss of consciousness in the context of TBI will have had their cervical spinal cord imaged for direct trauma and vertebral fractures. After

[1] Cases with bilateral pain have been reported[98–100] and there is one patient with unilateral side alternating attacks[101].

[2] Periodicity needs to be kept in mind when adjusting the drug dose in order to prevent development of MOH because the dose may continue to increase with each new period of high frequency attacks.

[3] in chronic TTH.

[4] Frequently caused by gastric irritation due to high analgesia intake.

[5] Phobia to sensory stimuli such as light (photophobia), noise (phonophobia), odour (osmophobia) and movement (eg car/ship journey) can be easily identified in the history. One way to explain the nature of this phenomenon to the patient is to think about migraine as a "magnifying glass" which enhances all these sensory stimuli until they become intolerable. Consequently many patients prefer to take a rest in a dark, silent room during an attack.

regaining consciousness careful examination for ligamentous injury is mandatory prior to removal of a neck collar. Persistent neck pain/headaches together with a new onset focal neurological deficit may require re-imaging to exclude an evolving syrinx. A suspected cervical or carotid artery dissection can be screened for by doppler, but should be confirmed using MRI/MRA.

5.6 Doppler

In suspected dissection of the carotid or vertebral arteries, the doppler examination of extra- & intracranial vessels provides a quick non-invasive bed-side assessment.

5.7 Angiography

Rarely (about 0.1–1.1% of TBI cases), angiography of the extra- & intracranial vessels may be required in the diagnostic workup of a suspected dissection or other blunt vessel injury[106]. This invasive examination is associated with an about 0.5–1% risk of stroke.

5.8 Optical Coherence Tomography

Because of the frequently reported visual symptoms revision of the retinal structure using optical coherence tomography (OCT) is recommended[107].

5.9 Electroencephalography

The routine use of electroencephalography (EEG) is not recommended for the diagnostic workup of PTH[108,109].

5.10 Cerebrospinal fluid

Examination of the cerebrospinal fluid is mandatory if a meningo-encephalitis is suspected[110]. It is also helpful in the diagnostic workup of a CT negative SAH[111,112]. Finally the CSF opening pressure is the only way to be certain about a diagnosis of low pressure headache.

5.11 Nasal fluid

The presence of a CSF leak into the nasal sinuses can cause low pressure headaches. Analyses of nasal secretions for the presence of tau protein (asialotransferrin) establishes the diagnosis[113]. The relationship between onset of headache and adopting an upright posture is a strong clinical indicator.

5.12 Neuropsychology

Frontal lobar injury is frequent in severe TBI and the neuropsychological work-up will allow estimating the level of functioning of those cognitive domains relevant for appropriate patient management[114]. Even after mild TBI cognition may remain impaired, particularly sustained attention and vision[20,115]. The interested reader is referred to the extensive body of literature on this subject which is beyond the scope of this review.

5.13 Headache diaries

Headache diaries are extremely useful for the diagnostic work up and to guide patient management. A headache diary can be filled in by the patient himself if cognition permits. Alternatively the patient's carer can help to provide the information.

6 Management

The approaches to managing acute and chronic post-traumatic headache (PTH) are interlinked, yet the perspectives and priorities of intensivists treating acute cases differ from those of physicians managing the later stages of patient care. Moreover, there are no FDA-approved medications specifically for PTH, necessitating reliance on guidelines often centred on primary headache disorders. Additionally, the intensive pharmacological treatment of acute PTH carries a risk of leading to medication overuse and chronic PTH in approximately 25–44% of patients[11,116]. This risk may increase if patient care is fragmented, if patients are lost to follow-up, or if they resort to self-medication. There is moderate evidence suggesting that visual symptoms associated with PTH can be effectively managed with corrective measures such as refraction, prisms, and tinted glasses[115].

6.1 Management of acute PTH

Pharmacological management of acute pain on the ITU is generally prompt (Table 4). However, there is considerable and justified fear within the general medical community that aggressive pain management clouds the level of consciousness and therefore masks any neurological deterioration[117]. Needless to say, patients with acute PTH are at risk to suffer for a prolonged period from severe pain because of inappropriate pain management in the acute phase.

In TBI patients with severe acute pain opiates are effective. The most frequently used compounds are MORPHINE, HYDROMORPHONE and FENTANYL[118,119]. The pharmacodynamic properties are summarised in Table 4. A systematic Cochrane review did not reveal any relevant difference between HYDROMORPHONE and MORPHINE compounds for the treatment of acute pain[120]. FENTANYL or HYDROMORPHONE are the preferred opioids in haemodynamic unstable patients or those with kidney failure[118]. Based on the rapid onset of analgesia

Table 4: *Pharmacological treatment of pain in the intensive care unit. Adapted from reference*[118].

Drug	Application	Adverse effects	Route	Dose	Half-life	Evidence
Fentanyl	continuous	rigidity with high doses	i.v.	0.7–10 μg/kg/hr	1.5–6 hrs	class IV
Remifentanil	intermittent	nausea, shivering, hypertension	i.v.	0.6–15 μg/kg/hr	3–10 min	class IV
Hydromorphine	continuous	respiratory depression, itching, nausea, constipation, sweating	i.v.	7–15 μg/kg/hr	2–3 hrs	class IV
Morphine	continuous	histamine release	i.v.	0.07–0.5 mg/kg/hr	3–7 hrs	class IV
Ketorolac	intermittent	bleeding, GI and renal	i.v.	15–30 mg q 6h	2.4–8.6 hrs	class IV
Ibuprofen	intermittent	bleeding, GI and renal	p.o.	400 mg q 4–6 hr	1.8–2.5 hrs	class IV
Acetaminophen	intermittent	hepatotoxicity, GI bleed	p.o.	325–600 mg q 4–6 hr[6]	2 hrs	class IV

with FENTANYL, scheduled administration is preferred in the acutely distressed patient[118].

REMIFENTANIL has not yet been widely studied, but because of its very short half life (3–10 minutes) it may become an important drug for the management of the neurocritical care patient. Scheduled administration of remifentanil should allow regular neurological assessment[121]. Side-effects affecting more than 10% of patients include nausea (37%), vomiting (13%), shivering (12%) and fever (10%)[122]. For intermittent therapy, MORPHINE and HYDROMORPHONE are better suited because of their longer half-life (Table 4).

For less severe PTH first line non-specific oral agents are ASPIRIN (1000 mg), ACETAMINOPHEN (1000 mg), PARACETAMOL (500–1000 mg), NAPROXEN (500–1000 mg) or IBUPROFEN (400–800 mg).

All NSIADs inhibit an enzyme in the inflammatory cascade known as cyclooxygenase (COX). NSAIDs have potentially severe adverse effects such as gastrointestinal bleeding, bleeding secondary to platelet inhibition, development of renal insufficiency, allergic reactions and cardiac and cerebral vascular events. Despite efforts to circumvent these problems by developing specific COX-2 inhibitors, recent experience shows that this issue is far from being solved[123–125]. There is class III evidence that acetaminophen may reduce opioid requirements[126]. There is class I evidence that oral indomethacin or naproxen are effective in treating postoperative pain in adults[127,128]. Most NSAIDs can only be administered orally, and a liquid formulation exists for ibuprofen and naproxen. The only NSAID available for i.v. administration is KETOROLAC which should not be used for more than 5 days[126].

In order to minimise the risk of medication overuse headache, treatment should be restricted to not more than two to three days per week for a period of about one month. The routine use of codeine-containing drugs in headache management is not recommended. This is because codeine-containing drugs are known to be a major cause of medication overuse headache[129]. Furthermore, they contribute to constipation. In patients suffering from central pain constipation can be an aggravating factor[130]. It is recommended to keep a headache diary.

Acute PTH resembling any other primary headache disorder is treated as

[6]avoid $>$ 4 g/d.

such.

Migraine Specific drugs for the treatment of a TBI triggered acute migraine attack[131] include ERGOTAMINE, DIHYDROERGOTAMINE, and the TRIPTANS (sumatriptan, eletriptan, naratriptan, rizatriptan, zolmitriptan, almotriptan, frovatriptan)[131]. In patients with severe nausea oral absorption may be impaired. Therefore additionally pharmacological treatment of nausea with anti-emetics (DOMPERIDON, METOCLOPRAMID, 10–20 mg oral) may be required. Alternative routes of administration are nasal sprays, inhalators, suppositories and injections[131]. In severe cases analgesia through the iv or sc route may be required. The use of opiates is discouraged[131]. Wrap-around tinted glasses are of help in very light sensitive individuals.

Tension-type headache In the acute phase IBUPROFEN (200–400 mg) is the first choice drug because of superior effectivity compared to aspirin or placebo[132]. The initiation of more specific treatments is recommended in chronic PTH, because most agents may take 4–8 weeks to become effective.

Cluster headache Treatment of attacks include inhalation of oxygen (7 l/min over 15 minutes)[133,134], nasal sumatriptan or zolmitriptan spray[135,136], nasal lidocaine (4%) spray, injections of SUMATRIPTAN (6 mg s.c., max two doses over 24 hours or 4 mg s.c. for more frequent application) or DIHYDROERGOTAMINE (1–2 mg)[134]. Exposure prophylaxis from extremely bright light is recommended in susceptible individuals.

Paroxysmal hemicrania The response to INDOMETHACIN (75–225 mg daily) is such that this is considered a diagnostic test by many[134,137]. Gastrointestinal problems are an important side-effect which may require change-over to CYCLO-OXYGENASE II (COX-II) inhibitors or TOPIRAMATE[133,138]. Alternatives are local anaesthesia (lidocaine) or methylprednisolone injections of the greater occipital nerve[139,140]. An emerging strategy is neurostimulation[141].

SUNCT A treatment trial with LAMOTRIGINE, TOPIRAMATE (50 mg twice daily) or GABAPENTINE may be considered as well as the combination of LAMOTRIGINE with CARBAMAZEPINE[134,142–147].

6.2 Management of PTH due to complications

The two main complications one may encounter in the interface between acute and long-term management of PTH are headaches due to high or low intracranial pressure.

Headaches associated with high intracranial pressure Posttraumatic hydrocephalus is a rare cause of PTH. In cases with suspected normal pressure hydrocephalus (NPH) overnight recording of the ICP may be required.

Posttraumatic headache should also be considered if the patient fails to improve or new symptoms develop such as incontinence, obtundation, psychomotor retardation, impaired memory and gait. The headache in hydrocephalus is a direct consequence of increased intracranial pressure[148]. There are also anecdotal reports of facial pain[149,150], trigeminal neuralgia[151] and localised limb pain in the context of hydrocephalus[152]. A persistent high opening pressure on lumbar puncture (LP) map indicates need for neurosurgical placement of a shunt[153]. The short-term pharmacological management includes treatment with the carbo-anhydrase inhibitor acetazolamide alone or combined with a loop-diuretic agent such as furosemide[154]. Osmotic agents such as mannitol or hypertonic saline should be reserved for those rare cases with rapid clinical deterioration in whom high ICP is a complication of failed systemic treatment (e.g. hyponatraemia with secondary brain oedema), infection (eg encephalitis, meningitis, ventriculitis) or a new space occupying process (e.g. subdural haematoma, clot expansion, ischaemia). Some individuals are very light sensitive and wrap-around, tinted glasses may be found helpful.

Headaches associated with low pressure headache Low pressure headache is usually seen in patients following the loss of a large volume of CSF. It can occur in any patient with an EVD, following trans-sphenoidal hypophysectomy/foramen magnum decompression or microvascular decompression of the trigeminal nerve. The headache is made worse by sitting up and is associated with nausea/vomiting and sometimes dizziness. A rare pitfall is the presence of low-pressure headache in the context of posttraumatic hydrocephalus due to over-drainage via an extra-ventricular drain (EVD) or following valve dysfunction after insertion of an ventriculo-peritoneal shunt[155]. Further worsening of the headache following increased CSF drainage, probably made with the best of intentions, usually leads to the diagnosis. Another pitfall is the development of low-pressure headaches following LP[156].

In either case the management consists of bed rest and if required a regular antiemetic (e.g. cyclizine). Most patients will improve spontaneously. Those who don't may require i.v. fluids (to supplement oral intake, aiming for 3 litres total daily input), caffeine (e.g. in the form of Coca-Cola or strong tea/coffee), regular laxatives. Patients who fail to respond to conservative treatment may need an epidural blood patch to seal the leak, epidural saline or dextran. A minority of cases may require surgical closure of a dural gap[156].

6.3 Management of chronic PTH

If the PTH persisted for longer than 3 months, it fulfils the IHS criteria for persistent headache attributed to traumatic injury to the head, previously termed chronic PTH. Chronic PTH typically manifests most commonly as migraines followed by tension type headaches[157]. Common symptoms include. Visual symptoms associated with chronic PTH may include a blind spot in the visual field, bright lights or photophobia[158]. The contribution of light sensitivity is frequently overlooked, but can be easily treated conservatively with tinted glasses,

tinted contact lenses or wrap around glasses.

The lack of published recommendations or guidelines around when to acquire imaging studies in patients with PTH has meant there is a lack of conclusive evidence surrounding its underlying pathophysiological mechanisms[159]. There is also a lack of evidence surrounding treatment of chronic PTH, with no evidence to suggest that the pharmacological management of acute headache on the intensive care unit for example with opiates is efficacious.

Adequate neurobiological markers of chronic PTH do not exist[160], therefore several different schools of thought surround its cause. One theorie is that the headache may be a consequence of medication overuse. To determine if this is the case, reviewing the patient's headache diary would be appropriate, and a detailed history should be repeated in order to identify any primary headache disorders which may benefit from targeted treatment. One has to bear in mind that patients at this stage may suffer from more than one type of headache, and each may have different causes.

There is a wide range of adjuvant management options available for chronic PTH and a multidisciplinary approach to patient management was found to be effective by some[161], whilst others found this to be only of modest benefit[11].

Medication overuse headache (MOH) The regular ($\geq$ 3 months) overuse of one or more drugs that can be taken for acute and symptomatic treatment of headaches puts patients at risk to develop MOH[162]. The magnitude of the problem has become clearer with the introduction of clear diagnostic criteria. MOH is now a recognised world-wide phenomenon. Medication overuse can affect up to 42% with PTH[11,163]. Treatment consists of detoxification, which may require hospital admission[162] with adjunctive pharmacological treatment[162]. These data were largely based on select headache clinics and one may not readily extrapolate to the general population.

Tension-type headache Specific treatment includes the tricyclic antidepressants. A first line choice is amitriptyline (10–100 mg/d), but due to the wide range in the biological half-life of 10–50 (average 15) hours, some patients feel tired in the morning and have difficulties concentrating at work. An alternative in these patients is trimipramine (10–150 mg) which has a slightly shorter half-life (11–23 hours). Next choice is amitriptylinoxid (30–90 mg/d) or maprotilin (25–75 mg/d)[37]. Other alternatives are doxepin (50–100 mg/d, max 150 mg/d), impramin (75–100 mg/d, max 150 mg/d), nortiptylin (25–100 mg/d) and the MAO-inhibitor tranylcypromin (20–40 mg/d)[37].

Migraine Patients need to be advised on identification and avoidance of migraine triggers, maintaining a stable life style and be actively engaged in the initiation of preventive pharmacological treatment[131]. Exposure prophylaxis in very light sensitive visual migraine is advised. Specific pharmacological treatment strategies for the long-term management of these PTH patients[164] are similar to the general prophylactic treatment in migraine[131]. A good first

choice in patients who are not asthmatic are β-adrenergic receptor antagonists such as PROPANOL (40–120 mg twice daily) or METOPROLOL (100–200 mg daily). AMITRIPTYLINE (25–75 mg at bedtime) or TOPIRAMATE (25–200 mg daily) are good alternatives. Next in line are VALPROATE (400–600 mg daily), GABAPENTINE (900–2400 mg daily), FLUNARIZINE (5–15 mg daily) and PIZOTYLINE (PIZOTIFEN) (0.5–3 mg daily). As a rule of thumb the individual patient's tolerability of side-effects will determine which drug will achieve satisfactory treatment. Teratogenicity is an important side-effect in VALPROATE and fibrotic complications are rare but serious complications following treatment with METHYSERGIDE (1–6 mg daily)[131].

Cluster headache VERAPAMIL remains the drug of choice for preventive treatment of chronic cluster headache[134,165–167]. A reasonable starting dose is 40 mg twice daily[168]. Dose escalation up to 960 mg daily may be required[168]. A baseline electrocardiogram (ECG) and repeat ECGs during increase of dosage are recommended[169]. In patients who fail to respond to pharmacological treatment occipital nerve stimulation (ONS) represents an emerging treatment strategy[141,170]. Last resort options are destructive procedures such as radiofrequency trigeminal ganglion ablation[171] and trigeminal rhizotomy which are associated with a fair amount of morbidity[172,173].

Central pain For central pain it has been shown that AMITRIPTYLINE at a dose of 25 or 50 mg OD may be of benefit in some patients[174,175]. There is reliable evidence that LAMOTRIGINE (200 mg/day) reduces central pain syndrome (CPSP)[176]. LIDOCAINE (i.v.) and MEXILETINE (oral) provided some short term pain relief in CPSP, but the role of these drugs is still uncertain[177].

Adjunct therapy To the best of our knowledge there is no double blind randomised controlled trial evidence to support adjunct therapy, but in our personal experience non-invasive measures which can readily be applied by the nursing care can have substantial impact on patient comfort in individual cases. Admittedly, some of these measures overlap with treatment of cervical pain (e.g. cervicogenic pain originating from the C2/C3 facet or upper cervical musculature). These relatively simple adjuvant measures are:

- neck roll to support the back of the neck, and arm supports to reduce the weight of the arms following complex cervical spine surgery.
- warm pack, cold pack, airline eye covers (for severe headache and photophobia, diplopia), physiotherapy, moral support etc.
- loosening of tight head bandages if there is no neurosurgical contraindication.
- massage is often effective in the relief of troublesome muscle spasm.
- cervical orthoses.

- dim/indirect light.

In addition, there is published evidence on the efficacy of electrotherapy (TENS)[178], manual therapy[179] and greater occipital nerve injections (GON)[140,180].

Emerging treatment options The release of calcitonin gene-related peptide (CGRP) in the cranial venous outflow plays a key role in acute PTH, as CGRP causes release of proinflammatory mediators, causing inflammation in the meninges[181–183]. Therefore, blocking the CGRP pathway using monoclonal antibodies (mAbs) helps reduce the frequency of migraines. There are two ways to block this pathway, the antibody can either target the CGRP (action of eptinezumab and glacanezumab), or block its receptor (action of erenumab)[184]. Erenumab and galcanezumab are administered monthly via subcutaneous injections, with the recommended dosage being 70 mg and 120 mg respectively, although some patients may benefit from double this amount[185]. Alternatively, eptinezumab is given via intravenous administration, and it was found that less frequent dosing every 12 weeks (100–300 mg) is optimal[186]. The most common adverse effect was injection site reactions, therefore alternatives such as lasmiditan (5-HT agonist which inhibits the release of CGRP) are advantageous, as they are administered orally[187–189].

7 Conclusion

Headache management post-traumatic brain injury (TBI) presents a global challenge for neurologists, especially when acute pain treatment might obscure signs of neurological decline. In severe cases, short-half-life opioids are advised for intermittent use. Once stability is achieved, longer-acting pharmacological treatments become preferable. Milder cases can often be managed with oral paracetamol or NSAIDs. However, caution is advised with codeine-containing drugs due to the high risk of medication overuse headaches (MOH). The exacerbation of visual symptoms by headaches is an important, yet frequently overlooked, aspect.

Another major concern is the fragmented care pathway for these patients, potentially leading to diagnostic dilemmas and overlooked secondary headache issues like MOH, resulting in suboptimal patient management. For patients with frequent MOH, withdrawing pain medication should be considered, which might necessitate hospitalisation and adjunct treatments. Misdiagnosis of post-traumatic headache (PTH) due to complications like abnormal intracranial pressure (ICP) must be vigilantly avoided. Additionally, TBI often triggers primary headache disorders, necessitating thorough history-taking for targeted treatment. A small subset of patients may develop chronic PTH with central pain, where a trial of pharmacological treatment, supplemented by adjunctive measures, should precede any invasive approaches.

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Supplementary Material

The International Headache Society (IHS) criteria for post-traumatic headache [13].

5.1 Acute post-traumatic headache

5.1.1. Acute post-traumatic headache attributed to moderate or severe head injury

Diagnostic criteria:

B. Head trauma with at least one of the following:

1. Loss of consciousness for < 30 minutes
2. Glasgow Coma Scale < 13
3. Post-traumatic amnesia for > 48 hours
4. Imaging demonstration of a traumatic brain lesion (cerebral hematoma, intracranial and/or subarachnoid hemorrhage, brain contusion, and/or skull fracture)

C. Headache develops within 7 days after head trauma or after regaining consciousness following head trauma

D. One of the following:

1. Headache resolves within 3 months after head trauma
2. Headache persists, but 3 months have not yet passed since head trauma

5.1.2. Diagnostic criteria for acute post-traumatic headache attributed to mild head injury

A. Headache, no typical characteristics known, fulfilling criteria C and D

B. Head trauma with at least one of the following:

1. Loss of consciousness for < 30 minutes
2. Glasgow Coma Scale ≥ 13
3. Symptoms and/or signs diagnostic of concussion

C. Headache develops within 7 days after head trauma

D. One of the following:

1. Headache resolves within 3 months after head trauma
2. Headache persists, but 3 months have not yet passed since head trauma

5.2.1. Chronic post-traumatic headache attributed to moderate or severe head injury

Diagnostic criteria:

A. Headache, no typical characteristics known, fulfilling criteria C and D

B. Head trauma with at least one of the following:

1. Loss of consciousness for > 30 minutes
2. Glasgow Coma Scale < 13
3. Post-traumatic amnesia for > 48 hours
4. Imaging demonstration of a traumatic brain lesion (cerebral hematoma, intracranial and/or subarachnoid hemorrhage, brain contusion, and/or skull fracture)
5. Symptoms and/or signs diagnostic of concussion

C. Headache develops within 7 days after head trauma or after regaining consciousness following head trauma

D. Headache persists for 3 months after head trauma

5.2.2. Diagnostic criteria for chronic post-traumatic headache attributed to mild head injury

C. Headache, no typical characteristics known, fulfilling criteria C and D

D. Head trauma with all of the following:

1. No loss of consciousness or loss of consciousness < 30 minutes
2. Glasgow Coma Scale < 13
3. Symptoms and/or signs diagnostic of concussion

C. Headache develops within 7 days after head trauma

D. Headache persists > 3 months after head trauma

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