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Advances in the understanding of headache in idiopathic intracranial hypertension

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Purpose of review
To review the most relevant developments in the understanding of headache in idiopathic intracranial hypertension (IIH).

Recent findings
The phenotype of the typical IIH headache is diverging from the historical thinking of a raised intracranial pressure headache, with the majority being classified as having migraine. A larger proportion of those with IIH have a past medical history of migraine, compared with the general population, highlighting the importance of re-examining those who have a change or escalation in their headache. The mechanisms underlying headache in IIH are not understood. Additionally, factors which confer a poor headache prognosis are not established. It is clear, however, that headache has a detrimental effect on all aspects of the patient's quality of life and is currently ranked highly as a research priority by IIH patients to better understand the pathophysiology of headache in IIH and identification of potential headache specific therapeutic agents.

Summary
Headache remains the predominate morbidity in the majority of those with IIH. Headache management is an unmet need in IIH and future studies are required to investigate the probable complex mechanisms, as well as effective management.

Keywords
headache, idiopathic intracranial hypertension, medication overuse headache, migraine, raised intracranial pressure

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is characterised by an elevation of intracranial pressure (ICP) with no identifiable cause [1▪▪]. There is a rising incidence in this disease [2], and it appears that the incidence is related to country specific prevalence of obesity [3]. It typically affects women of working age [4] and headache is the predominant morbidity in over 90% [4–7]. Headache is also the key factor driving reduced quality of life in IIH [8,9].

Previous characterisation of the typical phenotype of a raised ICP headache was of a nonspecific headache that is worse on waking. The features of IIH-related headache vary substantially and in the context of the recent clinical studies that have characterised them (Table 1), migraine is now the predominant phenotype. Our understanding has changed and, indeed, the international criteria have been modified in which ICP reduction is no longer a requirement as a diagnostic criterion of headache attributable to IIH [10]. Caution does need to be applied before rapid conclusions are drawn as to the relationship between ICP and headache in the context of this rare disease where less than 200 patients have been reported on, in randomised controlled trials [11,12].

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KEY POINTS

- Headache in IIH is heterogenesis; it occurs in any location and the majority have headaches that have characteristics of episodic and chronic migraine.
- Headache causes major morbidity in almost all patients with IIH.
- There is likely to be a complicated relationship between intracranial pressure, headache presence and disability in both adults and children.
- There are no trials currently investigating the management of headache in IIH.

HEADACHE AND THE PERSON WITH INTRACRANIAL HYPERTENSION

Headache in IIH is known to have a detrimental effect on quality of life [8,9] and chronic headaches have a profound effect on people's lives, showing similarities with other pain conditions [13]. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a key trial, was a North American multicentre, double-blind, randomised, placebo-controlled study of 165 participants with investigating utility of acetazolamide in mild visual loss [11]. In this cohort, headache, particular when associated with photophobia, was the major factor in detrimental general and visual quality of life [9,14▪▪].

In an observational study, headache frequency and severity of depression symptoms were independent predictors of disability in IIH with mean score of 22.8 (±15.2), compared with an average Italian

Table 1. Summary of current studies that report headache characteristics in idiopathic intracranial hypertension

Reference	Study characteristics	Number of participants with IIH	Total number with/without headache	Phenotype (as per ICHD-3B)	Headache frequency	Location of pain
Friedman *et al.* [14▪▪]	Randomised controlled trial multicentre included adults only at 38 sites in North American	165 (161 female; 4 males)	144 reported headache and 21 had no headache at baseline 5 had no headache throughout the study	52% migraine 22% tension-type headache 16% probable migraine 4% probable tension-type headache 7% unclassifiable	Mean frequency 12 days/month at baseline 23% constant daily pain and 38% reported to use daily analgesic use	68% frontal 47% ocular 47% nuchal 39% posterior 36% global 30% unilateral
Hamedani *et al.* [28▪]	Retrospective cohort, single centre included children only in Philadelphia, North America	127 (64.6% were female 61 definite PTCS 10 probable PTCS 31 elevated opening pressure no papilloedema 25 normal opening pressure and no papilloedema	116 had headache 11 had no headache	–	Of those with definite and probable PTCS and headache Constant/daily 21/60 Episodic 26/60	Focal 19/60 Global 5/60 Head; neck; shoulders 21/60
Raggi *et al.* [15]	Observational, cross-sectional single centre included adults only in Milan, Italy	51 (45 females; 6 males)	40 (78.4%) had headache diagnosis	–	Mean frequency 35.7 (SD 35.2) per 3 months 20 (39.2%) chronic headache diagnosis (migraine or tension type on >15 days a month for 3 months)	–
Sina *et al.* [20]	Retrospective, single centre included both children and adults in Tehran, Iran	68 (84% female; 16% male)	–	63% migraine (of which 11% had migraine with aura)	51% Chronic daily headache	33% frontal 16% occipital 51% generalised
Yiangou *et al.* [49]	Prospective, single centre included adults only in Birmingham, United Kingdom	52	52 (100%)	80% migraine 35% attributed to raised ICP 14% tension type 19% other/not classifiable	–	–
Yri *et al.* [6]	Prospective, single centre included adults only at the Danish Headache Centre, Denmark	44 (98% female; 2% male)	100% had headache	68% migraine 82% migraine attacks <4 h included 25% tension type 9% mixed migraine and tension 5% unclassifiable	64% constant 86% daily 6% 2–4 days/week 2% <1 day/week	16% holocranial 52 frontal 34% temporal 23 parietal 34% occipital 50% frontal or fronto-temporal predominantly 34% neck 64% retrobular 66% bilateral 30% strictly unilateral 5% varying

ICP, Intracranial pressure; IIH, intracranial hypertension.

general population of 12.9. This indicated that consideration should be given to reducing headache and treating depression in IIH [15]. In the United Kingdom, the James Lind Alliance priority setting partnership investigated over 500 IIH patients and clinician preferences, understanding of headache mechanisms and treatment was ranked in two domains of the top 10 research priorities for IIH. This reflects the unmet need of the disability of headache in everyday life of our patients [16▪].

PHENOTYPING INTRACRANIAL HYPERTENSION-RELATED HEADACHE

Historically, a raised ICP headache is positional, with nocturnal awakening, worse on waking and aggravated by Valsalva manoeuvre. Studies now have classified those with headache and IIH would meet the International Headache Society criteria [10] as having either episodic migraine, chronic migraine or tension-type headache (Table 1). According to the IIHTT, the quality of the pain was pressure-like in 47% and throbbing in 42% [14▪▪], which is similar to migraine [17]. Photophobia, phonophobia, nausea, vomiting and worsening on physical activity were reported and none of these migraine features separated IIH headache from migraine [14▪▪]. Other symptoms included constant visual loss; transient visual obscurations, diplopia and dizziness; these could help distinguish primary migraine from migraine in IIH; however, the authors cautioned that 14% with headache and papilloedema had none of these associated symptoms [14▪▪] (Table 2).

In children with pseudotumour cerebri (PSTC), Lee *et al.* [18▪] studied the difference in children's drawings of their headaches. A total of 21 children with PSTC and 518 children with migraine showed that drawings had similar features except one-third (28.6%) with PSTC depicted diplopia which was highly significant ($P = 0.00001$). Diplopic images

Table 2. Table comparing and contrasting clinical features between headaches in IIH and typical migraine

	Headache in IIH			Migraine
		Yri *et al.* [6]		
Clinical features	**IIHTT [9,14▪▪]**	**IIH**	**Controls**	**Kelman [17] *n* = 1283 (84.3% female; mean age 37.7 (SD 12 years)**
Body mass index	40.0 (8.5) AZA arm 39.9 (8.1) placebo	34.6	30.8	–
ICP—lumbar puncture opening pressure (cm CSF)	34.0 (SD 9.1) AZA arm 34.2 (SD 7.1) placebo	39.6	18.2	–
Photophobia	70%	66%	–	84–95%
Phonophobia	52%	73%	–	77–93%
Nausea	47%	75%	–	90%
Vomiting	15%	–	–	19.8%
Dizzy symptoms	53%	–	–	36.1%
Neck pain	42%	34%	–	–
Shoulder pain	–	–	–	–
Back pain	53%	–	–	–
Radicular pain	19%	–	–	–
Worsening on valsalva	–	70%	35%	–
Worsening on bending	–	52%	44%	–
Aggravated by physical activity	50%	64%	74%	90% (13.5% occasionally; 32.2% frequently, 44.3% very frequently)
Pulsatile tinnitus	52% (bilateral in two-thirds of these)	64%	26%	–
Daily nonpulsatile tinnitus	23%	–	–	–
Transient visual obscurations	68%	64%	35%	–
Patient reported diplopia	18%	45%	24%	–
Esotropia or 6th cranial nerve palsy	3%	–	–	–
Papilloedema	Yes	Yes	No	No

AZA, Acetazolamide group; CSF, cerebrospinal fluid; ICP, intracranial pressure; IIH, intracranial hypertension.

may serve as a useful 'red flag' for those who investigate children for raised ICP.

PRIOR HISTORY AND FAMILY HISTORY OF HEADACHE

Prior history of headache in the IIHTT was found in 41% [14▪▪], which is similar to Yri *et al.* [6] who found in 45% of their IIH cohort with 25% having prior migraine and 34% having prior tension-type headaches. This is nearly double that of the US female population with 18% having history of migraine [19]. Positive family history was high, with one study reporting up to 68% of those with IIH [20]. These factors may be implicated in the pathophysiology of headache in IIH. What is of importance is the re-examination for papilloedema in those who have a change or escalation in their headache [21].

HEADACHE OUTCOMES IN INTRACRANIAL HYPERTENSION STUDIES

Overall, there are few studies investigating headache; they report different headache outcomes and have a small number of patients (Table 1), and the results of which are not surprisingly conflicting in this rare disease.

HEADACHE SEVERITY AND FREQUENCY

Headache severity in IIH appears to be moderate to severe. In the Birmingham prospective study investigating women with IIH who followed a low-calorie diet for 3 months, severity, as recorded using the visual analogue pain score, was 4.2 (±2.8) and reduced to 1.9 (±2.8), $P = 0.015$, at study end with significantly reduced ICP compared with pressure measured in the 3 months before the diet [22]. Others have reported higher severity of 5.6 (±2.5) [15], and the IIHTT baseline headache severity was 6.3 (±1.9) on a 0–10 scale, with 5.4% reporting 10/10 [9]. Differences could exist because of duration of IIH and medication overuse headache.

Headache frequency in IIH is typically episodic in new onset disease and chronic in more longstanding disease (Table 1). Both severity and frequency have not appeared to correlate with lumbar puncture opening pressure in the IIHTT [14▪▪], and the portions between episodic and chronic could reflect time to enrolment from diagnosis, or onset of raised ICP, or existence of other coexisting headache phenotypes.

HEADACHE DISABILITY SCORE

The Headache Impact Test (HIT)-6 [23], which is a validated for use across headache disorders, is commonly used [24]. Most agree at baseline the HIT-6 measures substantial to severe impact on IIH patients. Headache disability is multifactorial, and comorbid conditions can influence disability for example those with a high risk of sleep apnoea, as determined by the Berlin questionnaire, had a higher HIT-6 score in the IIHTT ($P = 0.04$) [14▪▪].

In the Birmingham weight loss study [22], baseline HIT-6 was 57.5 (±9.0) which significantly improved after weight loss to 46.9 (±10.1) ($P = 0.004$). The IIHTT HIT-6 mean baseline was similar to 59.7 (±9.0) reducing both arms by over 9 points, which did not reach significance [14▪▪]. In an open-label extension of the IIHTT [25], 96 participants were sorted into remaining on acetazolamide ($n = 34$), switch placebo to acetazolamide ($n = 35$), switch acetazolamide to no treatment ($n = 16$) and switch placebo to no treatment ($n = 11$). At month 12, those switched placebo to acetazolamide had significant improvement HIT-6 with −3.70 point reduction ($P = 0.01$). This is an interesting fact; however, caution must be used in interpreting this as headache outcomes are prone to placebo effects and total blinding to treatment allocation is hampered by knowledge of trial arm allocation and through the experience of drug-related side-effects (such as use of acetazolamide and experiencing paraesthesia) [26].

HEADACHE RELATIONSHIP TO INTRACRANIAL PRESSURE

The relationship between headache and degree of ICP elevation is not fully delineated and is likely to be complicated. Younger age ($P = 0.03$) of onset and high lumbar puncture opening pressure ($P = 0.03$) have both been associated with better odds of being without headache or with only infrequent headache (<1 day/month) headache after 12 months [6].

Amongst IIHTT cohort, there was no relationship found between the mean lumbar puncture opening pressure, 343.5 (±86.9) and the presence or absence of headache at baseline [14▪▪]. This potentially suggests an individual threshold of tolerance of differing degrees of ICP and that once elevated other factors may contribute to chronicity. Analogies maybe drawn to posttraumatic headache in which susceptibility is influenced by previous migraine history, childhood migraine and family history of migraine, potentially suggesting an underlying genetic predisposition to headache and not necessarily a clear correlation between degree of trauma. Other investigators have supported theories that headache in IIH is attributed to more complex mechanisms than ICP elevation alone [27].

The IIHTT highlighted that there was no statistical relationship found between headache severity

(0–10 scale) and ICP, at both baseline and trial end. Only half agreed to have a lumbar puncture at 6 months (65 had headache and 20 without) and there was no correlation between HIT-6 and lumbar puncture opening pressure ($r = 0.12$; $P = 0.29$), but the number of headache days weakly correlated ($r = 0.12$, $P = 0.04$). Lumbar puncture opening pressure changed by 112.3 mm cerebrospinal fluid (CSF) in the acetazolamide group and 52.4 mm CSF in the placebo group ($P = 0.002$) and both arms reported headaches (69% acetazolamide and weight loss arm; 68% placebo and weight loss arm) [14▪▪].

In the Birmingham weight loss study, lumbar puncture opening pressure was 38.0 (±5.0) at the start of the diet and 30.0 (±4.9) ($P < 0.001$). HIT-6 significantly improved with this reduction in ICP ($P = 0.004$) and there were significant improvements, by greater than 50%, in headache severity (visual analogue pain score (0–10) from 4.2 (±2.8) to 1.9 (±2.8), ($P = 0.015$), headache frequency from 4.4 (±2.9) to 2.1 (±2.8) days a week ($P = 0.011$), and weekly use of analgesics from 2.2 (±2.5) to 0.2 (±0.4) days a week ($P = 0.007$). Patients' symptoms (headache, tinnitus, obscurations and diplopia) showed significant improvement after the low energy diet ($P < 0.001$, $P = 0.004$, $P = 0.025$ and $P = 0.008$, respectively) One explanation of the difference between this study [22] and IIHTT [14▪▪], in which the magnitude CSF pressure reduction was similar, may be that the Birmingham study assessed the intervention at 3 months, compared with 6 months in the IIHTT.

In children with IIH, Hamedani *et al.* [28▪] retrospectively reported headache characteristics. They detailed headache pattern from clinical records, severity (subjectively determined) and location along with associated symptoms of visual change and nausea. There was no difference between the groups in terms of pain severity, and presence of nausea, despite there being distinct differences in median lumbar puncture opening pressure between definite PTCS (39 cm CSF), probable PTCS (24 cm CSF), elevated opening pressure (35 cm CSF) and normal opening pressure group (23 cm CSF) ($P < 0.001$). It may be that once ICP is over a 'patient specific threshold' headache will occur, but the absolute degree of ICP elevation may not be the primary underlying mechanism.

MANAGEMENT OF HEADACHE IN INTRACRANIAL HYPERTENSION

The 2015 Cochrane review concluded that there is a lack of evidence to guide pharmacological treatment in IIH [29]. There are few published randomised clinical trials [11,12] and a small number of ongoing trials [30,31]. None of these have focused on management of headache. Managing headache in IIH is an essential aspect of patient care and recent consensus guidelines have provided a practical approach to managing them [1▪▪].

MANAGEMENT OF MIGRAINE IN INTRACRANIAL HYPERTENSION

As migraine is the predominant phenotype (Table 1), the use of migraine therapies has been recommended [1▪▪]. Migraine attacks may benefit from triptan acute therapy used in combination with either a nonsteroidal anti-inflammatory or paracetamol and an antiemetic with pro-kinetic properties [32▪]. Their use should be limited to in the region of 2 days/week or a maximum of 10 days/month [32▪]. Where medication overuse coexists, this should be addressed, and if chronic migraine is present, preventive strategies have been recommended [1▪▪,33]. Caution should be observed before selecting drugs that could increase weight such as β-blockers, tricyclic antidepressants, sodium valproate, pizotifen and flunarizine. Care should be taken in those medications that exacerbate depression which is a frequent co-morbidity in IIH, such as β-blockers, topiramate and flunarizine [1▪▪].

A meta-analysis demonstrated that topiramate was effective in reducing headache frequency and was reasonably well tolerated in adult patients with episodic migraine [34▪]. It may have additional benefits of suppressing appetite and have an effect on reducing ICP through carbonic anhydrase inhibition. In-vivo studies demonstrated that both subcutaneous and oral administration of topiramate significantly lowered ICP in rodents, whereas other drugs tested, including acetazolamide, furosemide, amiloride and octreotide, did not significantly reduce ICP [35]. Topiramate utility in IIH reported in an open-label study which randomly assigned 40 patients with IIH to acetazolamide or topiramate and demonstrated treatment equivalence with all experiencing improvement in visual fields [36].

Other preventive therapies, some of which are not licenced for migraine, could include candesartan because of its lack of weight gain and depressive side-effects [37] or potentially non-invasive neuromodulation [38]. Botulinum toxin A, which is a licenced therapy for migraine, could also be useful in those with coexisting chronic migraine [39▪]. Other strategies, such as mindfulness, may suit some patients [40▪].

MANAGEMENT OF MEDICATION OVERUSE HEADACHE

One-third of IIHTT participants overused medication at baseline, on the basis of the last 30-day

history, and had a significantly higher mean HIT-6 score (63.1 ± 6.9) than in those without (58.1 ± 9.4; $P = 0.0007$) [14▪▪]. Other studies found management of medication overuse headache (MOH) a more common issue for IIH patients long term, reflecting the study type [6]. Successfully removing excessive analgesic use significantly improves headaches in other headache disorders. What is yet what is yet to be determined is the effects it has on the course of IIH-related headache [41]. It seems prudent that all IIH patients with headaches are warned about avoiding excessive analgesic use and where MOH exists standard advice of removal given [41,42].

THERAPEUTIC LUMBAR PUNCTURE

Professional bodies in the United Kingdom [1▪▪] and Europe [43] do not advocate therapeutic lumbar puncture as a treatment strategy for IIH. Although lumbar puncture induces a transient reduction of ICP, the effect is typically short lived with pressure rising rapidly after the procedure [44]. There is growing awareness regarding the morbidity of the procedure [45,46]. IIH patients frequently report a negative and emotional experience when they undergo a lumbar puncture [47,48] and the majority of active IIH patients (papilloedema and lumbar puncture opening pressure >25 cm CSF) will face an exacerbation of headache in the week following lumbar puncture [49]. The long-term therapeutic effects of lumbar puncture are not well known.

NEUROSURGICAL TREATMENT OF HEADACHE

CSF shunting to exclusively treat headache in IIH has limited evidence. About 68% will continue to have headaches at 6 months and 79% by 2 years following CSF diversion. A third have been reported to develop iatrogenic low pressure headaches, although this figure may be lower depending on shunt and valve types [50]. There is uncertainty that failure to optimise ICP may render the migraine headaches difficult to treat, and if headache was indicated for CSF shunting, then a period of ICP monitoring preoperatively may be useful to determine the success of the proposed procedure [1▪▪].

INTERVENTIONAL VASCULAR STENTING FOR HEADACHE

The literature detailing dural venous stenting typically does not clearly separate the cohorts of IIH into those with acute visual loss and those with headaches. Many case series are small, nonrandomised, do not detail morphological stenosis type and some do not record the pressure gradient. There are selection bias, differing treatment protocols, poor characterisation of headache phenotype and a lack of long-term follow-up [51]. Additionally, objective validated headache outcome measures are infrequently utilised. Well characterised studies would be welcomed in this area.

MANAGEMENT OF HEADACHES IN THE SHUNTED PATIENT

Shunted patients may have significant headache morbidity and understanding the underlying causes may guide management. It has been recommended that shunt revision should not routinely be undertaken unless there is an assessment of vision for papilloedema and there is a risk of visual deterioration [52]. There is little indication to perform shunt series, as they do not determine shunt failure or overdrainage or change management decisions [53]. As with chronic headaches, removal of MOH [53,54] and migraine treatments should be considered; additionally, ICP monitoring may be informative to direct treatment choices [1▪▪].

CONCLUSION

Migraine phenotype and prior history of headache before a diagnosis of IIH needs to be recognised by clinicians to avoid misdiagnosis. There is an unmet need to treat headaches in IIH. Future studies should consider core outcome measures for headache, as used in migraine trials, which would optimise meta-analysis. Migraine abortive and preventive therapies can be used, but currently there is no high-class evidence to help guide treatment decisions.

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Conflicts of interest

There are no conflicts of interest.

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