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REVIEW ARTICLE

Headache for ophthalmologists: current advances in headache understanding and management

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Abstract

Patients with headache and head pain are often referred to ophthalmologists. These symptoms can either be associated with underlying ophthalmic conditions, or more often are headache disorders unrelated to the eyes. Understanding the phenotype of the headache is critical for advice, safe discharge or onward referral. This review will provide an update on the criteria for common headache disorders that are often seen by ophthalmology and embrace disorders associated with ophthalmic diseases. It will also describe the changing management of migraine and outline recent therapies that are currently available.

Introduction

Headache is very common. The World Health Organisation (WHO) estimates that over half of the global population will have had at least one headache during the past year and within the adult population up to 47% have a general headache disorder [1–3]. Migraine is the commonest primary headache disorder and is ranked the 2nd most disabling disease globally [4]. It is a costly condition both for the individual [5] and the impact on society [6]. The WHO have stated that headaches are under-treated, under-recognised and under-reported [3].

With increasing frequency, eye care professionals are being referred people with headache to rule out sinister causes of headache, such as papilloedema [7]. However, certain headache disorders can themselves present with visual disturbances or autonomic features such as engorged conjunctival vessels or a watery eye. Headache may be a key clinical feature of ophthalmic conditions such as idiopathic intracranial hypertension (IIH) [8]. This review will provide an informed appraisal consistent with the International Headache Society (IHS) criteria for common headaches that frequently present to ophthalmology and present the new advances in the management of migraine.

Approaching headache

Headache is typically classified into primary headache disorders, secondary headache disorders and facial pains or neuralgias. Each headache has been classified by the International Headache Society Classification Criteria (ICHD-3) which are routinely updated for accuracy [9]. The National Institute for Clinical Excellence (NICE) (2012) and the British Association for the Study of Headache have produced guidelines on the assessment of headache and consideration of onward referral in patients [10, 11]. The aetiology of primary headache disorders is more elusive than secondary headaches, which are headache arising from a defined cause. The previous concept that migraine was caused by rebound dilatation of constricted blood vessels in the brain, which was developed by Wolff in the 20th Century, is no longer accepted [12]. Migraine is felt to be primarily a neuronal issue, driven by trigeminovascular activation [13, 14]. Headaches can also arise from traction to the meninges and blood vessels, such as in a space occupying lesion, and through inflammation/infection of the meninges [15].

Pathophysiology in headaches has been extensively studied, but still poorly understood, and a wide variety of

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mechanisms have been proposed, such as plasma protein extravasation and inflammation, release of neuropeptides such as Calcitonin gene-related peptide (CGRP), neuronal sensitisation leading to features such as allodynia, specific central connections and higher order processing [16].

Migraine is by far the commonest primary headache disorder seen, followed by tension headache and then less common disorders such as trigeminal autonomic cephalalgias (such as cluster headache). Secondary headache disorders have an underlying aetiology that likely requires active management and include structural (such as Chiari malformation), trauma, infection, neoplasia, vascular causes or raised intracranial pressure.

Key elements to note in the headache history will help distinguish, to a certain degree, the underlying headache phenotype. Severity of pain can either be documented on a verbal rating scale by the patient (for example between 0 being no pain and 10 being the worst pain); duration of pain; how often the pain occurs; location of the pain; nature of the pain (such as throbbing, pulsing or stabbing); were there prodromal features, occurrence of aura (visual, sensory or motor aura or speech disturbance); during the headache were there associated features of photophobia, phonophobia; osmophobia; nausea or vomiting; aggravation by physical activity. Determining the headache frequency helps distinguish disorders, and prepares for target management plans. A summary of the headache phenotypes and key diagnostic criteria and phenotypes are detailed in Tables 1 and 2 (adapted from ICHD-3 and NICE CKS) [9, 17].

Red flags

There are red flags that may require immediate or urgent investigation, particularly where there may be a secondary cause of the headache. They include new severe, unexpected headache, progressive or persistent headache which has changed dramatically, fever/impaired consciousness, papilloedema, new neurological deficit, features of giant cell arteritis, change in personality, dizziness, visual symptoms, vomiting [17]. The box below has been adapted from the headache red flag mnemonic "SNOOPS", which has been described in 2003 and taught to medical students around the world as an aide memoire for identifying suspicious features in a patient presenting with headache [18, 19]. Updated guidelines have led to the formation of the current SNOOP10 mnemonic in 2018 [19]. This has a more comprehensive list of ten "P"s—which include: pattern change/recent onset of headache, positional headache, precipitated by coughing/sneezing, papilloedema, progressive headache, pregnancy/puerperium, painful eye with autonomic features, posttraumatic onset, pathology of immune system, painkiller overuse or new drug at onset of headache (Box 1).

Box 1 SNOOPS [19] as a useful mnemonic for red flags in headache

- SYSTEMIC SYMPTOMS (e.g. fever, weight loss)
- NEUROLOGIC SYMPTOMS/SIGNS
- ONSET (SUDDEN)
- OLDER AGE (over 50 years)
- PRIOR HISTORY (New Headache)
- SECONDARY ILLNESSES (HIV or history of neoplasia)

There is a temptation for clinicians and patients to elect for routine neuro-imaging for reassurance when headache is a principle symptom for a consultation. However, this is not recommended by NICE [17]. Incidental findings are common, up to 2.7% in one study, however they did not include white matter hyperintensities, silent brain infarcts, brain microbleeds and anatomical variants. They also did not include the difference in fidelity between 1.5 and 3.0 Tesla (T) MRI scanners, where the incidence seen within a 3 T scanner may be much higher. Benign pathology can cause significant concern for the patient, and the non-specialist [20]. Indications for imaging include where there are atypical features and/or abnormal clinical signs on examination suggesting an alternative underlying cause of the headache (Box 1).

Visual disturbances associated with headache and pain

Visual disturbances within in the context of head and eye pain can be wide ranging and include amaurosis fugax, Uhthoff's phenomenon, transient visual obscuration and visual aura (Table 3). Taking an accurate history of both the visual disturbance and headache can aid in formulating a robust differential diagnosis and management plan for workup and treatment.

Monocular transient visual loss (TVL) or amaurosis fugax is usually a medical emergency. There is interrupted blood flow to the central retinal/ophthalmic artery causing the symptom of a blackout in the whole or half of the visual field, possibly starting with a 'curtain' sweeping in from one side of the vision. This is temporary and typically resolves within minutes and lasts no longer than 1 h. It can be caused by thromboembolism originating from an atherosclerotic plaque in the internal carotid artery, or an embolus originating from the heart or aorta. If associated with atheromatous carotid artery disease there is a 2% risk of recurrent stroke at one year and in those with severe internal carotid artery stenosis, the risk of ipsilateral stroke is up to 16% after three years [21]. An embolus can also originate from a carotid artery dissection. Giant cell arteritis (GCA) is another serious cause of TVL that can be associated with headache [22, 23]. Differentiating between

Table 1 Summary of headache classification adapted from NICE CKS [10].

Headache type	Consider if:
Migraine without aura	At least five attacks fulfilling the following criteria: ○ Headache attacks lasting 4–72 h (untreated or unsuccessfully treated). ○ The headache has at least two of the following four characteristics: • Unilateral location. • Pulsating quality. • Moderate or severe pain intensity. • Aggravation by or causing avoidance of routine physical activity (for example walking or climbing stairs). ○ During the headache at least one of the following; nausea and/or vomiting; photophobia and phonophobia.
Migraine with aura	At least two attacks fulfilling the following criteria: ○ One or more of the following fully reversible aura symptoms: • Visual symptoms such as zigzag lines and/or scotoma—visual aura is the most common type of aura. • Sensory symptoms such as pins and needles. • Speech and/or language symptoms such as aphasia. • Motor weakness. • Brainstem symptoms such as vertigo or diplopia. • Retinal symptoms such as monocular scintillations or scotoma. ○ At least two of the following four characteristics: • At least one aura symptom spreads gradually over at least 5 min, and/or two or more symptoms occur in succession. • Each individual aura symptom lasts 5–60 min. • At least one aura symptom is unilateral. • The aura is accompanied, or followed within 60 min, by headache.
Tension-type headache	At least ten episodes fulfilling the following criteria: Lasts between 30 minutes to 7 days. At least two of the following: bilateral location; pressing or tightening (non-pulsating) quality; mild or moderate intensity; not aggravated by routine physical activity such as walking or climbing stairs. There must be no nausea or vomiting and no more than one of photophobia or phonophobia.
Cluster headache	At least five attacks of severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min and associated with at least one of: ipsilateral conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhoea; eyelid oedema; forehead and facial sweating; forehead and facial flushing; sensation of fullness in the ear; or miosis and/or a sense of restlessness or agitation. Attacks occur between one every other day and eight per day for more than half of the time when the disorder is active.
Medication overuse headache	The person has headache occurring on at least 15 days per month and a pre-existing headache disorder. Regularly overused, for more than 3 months, one or more drugs that can be taken for acute and/or symptomatic treatment of headache such as ergotamines, triptans, simple analgesics or opioids.

TVL caused by migraine aura or transient ischaemic attack (TIA) is challenging, particularly in the ≥60 years old age group where TIA's become more common and migraine with aura attacks become more atypical in nature [24].

Transient greying or blacking out in the vision, which may occur when a patient moves/bends down, define transient visual obscurations. These can occur in optic nerve swelling and papilloedema, typically last seconds before the vision returning to normal [25, 26].

The Uhthoff phenomenon is a symptom, typically associated with a blurring of the vision occurring after physical exercise or activities that increase in body temperature, e.g. after a hot shower or bath [27, 28]. It occurs in association with optic neuritis, either as a clinically isolated syndrome or within the context of diagnosed demyelinating disorders such as multiple sclerosis and neuromyelitis optica spectrum disorder. It is thought that increased temperature prolongs inactivation of voltage-gated sodium channels and therefore increases the chance of conduction failure in partially myelinated or incompletely remyelinated axons.

Current thinking suggests cortical spreading depression is the underlying pathophysiology of visual aura [13].

Table 2 Typical headache phenotypes.

Headache feature	Tension-type headache	Migraine (with or without aura)	Cluster headache
Pain intensity	Mild or moderate	Moderate or severe	Severe or very severe
Pain location	Bilateral	Unilateral or bilateral	Unilateral (around the eye, above eye and along the side of the head/face)
Pain quality	Heavy, pressure, tightening (non-pulsating) Can be featureless	Pulsating	Variable (can be sharp, boring, burning, throbbing or tightening)
Effect on activities	Not aggravated by routine activities of daily living	Aggravated by, or causes avoidance of, routine activities of daily living	Restlessness or agitation
Associated symptoms	None	Photophobia, phonophobia nausea and/or vomiting Aura Typical aura symptoms include visual symptoms and/or partial loss of vision; sensory symptoms such as numbness and/or pins and needles; and/or speech disturbance	Ipsilateral: • Hyperaemic and/or watery eye • Nasal congestion and/or rhinorrhea • Eyelid oedema/swelling • Forehead and facial sweating • Miosis/ptosis
Duration of headache	30 min–hours-days	4–72 hours in adults 1–72 hours in young people aged 12–17 years	15–180 min
Frequency of headache	<15 days per month	≥15 days per month for more than 3 months <15 days per month	1 every other day to 8 per day, with remission > 1 month 1 every other day to 8 per day, with a continuous remission < 1 month in a 12-month period
Diagnosis	Episodic tension-type headache	Chronic tension-type headache Episodic migraine (with or without aura)	Episodic cluster headache Chronic cluster headache

The typical clinical history suggests it develops gradually over 5–20 min and last for less than 60 min. It starts in the periphery and there may be a positive scotoma. Migraineurs describe many different symptoms that include phosphenes, and more complex visual hallucinations of fortifications of flashes of light, zigzags, scintillating scotomas and visual illusions like teleopsia or metamorphopsia [29, 30].

Visual disturbances in nonconvulsive epilepsy can be difficult to distinguish from migraine aura and can cause a diagnostic dilemma. One small case series found the localisation and patterns of the symptoms can differ between the two. In epilepsy, positive visual phenomena were centrally located in the visual field of epileptic patients and peripheral in those with migraine. Negative visual phenomena tended to be diffuse in epilepsy and peripheral in migraine aura [31]. The duration of symptoms in epilepsy tended to be extremely short lasting a few seconds whereas discussed migraine aura lasts between 5 and 60 min. The presence or absence of colour does not distinguish the two conditions. Where there is diagnostic confusion an EEG may be helpful in determining the diagnosis.

Migraine

For the diagnosis of migraine to be upheld the IHS have set criteria (ICHD-3), detailed in Table 1 [9, 17].

It is now accepted that there are premonitory symptoms that can occur days before the headache onset. The most commonly reported premonitory symptom is marked fatigue that has been shown to be highly predictive of an ensuing migraine attack [32]. Other premonitory symptoms include mood change, anxiety, irritability, unhappiness, yawning, asthenia, gastrointestinal disturbance, change in appetite, muscle aches, hypersensitivity to light/sounds, difficulty concentrating and confusion [33, 34].

Migraine is also noted to have a phenotypic postdrome, which can be broadly grouped into four areas—neuropsychiatric, sensory, gastrointestinal, and general systemic symptoms. These range from fatigue, difficulty concentrating, excessive yawning, to photophobia, nausea, difficulty with speech and/or writing [35]. These often appear quite similar to the premonitory symptoms and it is theorised that therefore they may share a common neural network [36].

Aura

Aura is defined as a fully reversible cluster of neurological symptoms. Symptoms often spread gradually over 5 or

Table 3 A summary of visual disturbances that can occur with head and neck pain.

	Description of visual disturbance	Unilateral	Bilateral	Length of onset	Maximal time to recovery	Differential diagnosis
Amaurosis fugax	Black out of whole or half of visual field	✓	x	Minutes (typically to 10 min)	No more than 1 hour	Atrial fibrillation Carotid bruit Internal carotid artery dissection or aneurysm Giant Cell Arteritis Vertebral basilar insufficiency Bilateral optic nerve disease (rare)
Visual aura	Zig-zag, flashing, scintillating scotoma	x	✓	Occurs over minutes (typically up to 30 min)	No more than 1 hour	Migraine
Transient visual obscuration	Greying or blacking out of vision	✓	✓	Minutes	Seconds	Papilloedema Optic nerve swelling from other causes Uhthoff phenomenon

more minutes and should resolve fully within 60 min of onset [9]. Aura is experienced in 25–30% of sufferers [37]. Aura may include visual symptoms (as described above), difficulty with speech, paraesthesia, allodynia, confusion and heightened sense of smells [38].

It has been observed that patients who suffer from active migraine with aura are associated with increased risk of major cardiovascular disease (CVD), myocardial infarction, ischaemic stroke, and death due to ischaemic CVD [39, 40]. Thus increased risk of ischaemic stroke is associated with migraine with aura, young age, female sex, use of oral contraceptives and smoking habits [41]. With regards to contraception, as many migraine sufferers are female of childbearing age, it must be carefully considered if their headache is typical of migraine before recommending contraceptive changes. The WHO state that the use of combination oestrogen/progesterone contraception may be considered for women with migraine headache only if they do not experience aura, do not smoke, are otherwise healthy, and are younger than age 35 years [42]. Otherwise, patients should not take oral combined contraceptive pill. The progesterone only pill is safer and not associated with increased stroke risk. Other options include oral desogestrel; the subcutaneous implant etonogestrel; the injection medroxyprogesterone acetate or an intrauterine device such as levonorgestrel.

The risk of stroke is increased by smoking, migraine type and use of hormonal contraception (Box 2) and a consensus statement was made in 2017 by the European Headache Federation and the European Society for Contraception and Reproductive Health [43].

Episodic to chronic migraine

Headache frequency can broadly classify migraine into two types: episodic migraine (less than 15 headache days per month) or chronic migraine (15 or greater headache days per month). The International Classification of Headache Disorders 3rd edition Appendix A1.3 defines chronic

Box 2 Absolute risk of ischemic stroke in women aged 20 to 44 years in relation to the use of hormonal contraception and migraine status (adapted from S Sacco et al. 2017 [43] to show increased risk in comparison to no migraine and no contraception)

	No migraine	Migraine without aura	Migraine with aura
Without hormonal contraception	2.5/100,000	4.0/100,000	5.9/100,000
	–	1.6 fold	2.4 fold
With hormonal contraception	6.3/100,000	25.4/100,000	36.9/100,000
	2.5 fold	10.2 fold	14.8 fold

migraine as greater than or equal to 15 headache days per month for at least 3 months, with at least 8 days per month fulfilling criteria for migraine without aura, in the absence of medication overuse and that cannot be attributed to another causative disorder [9]. Headache frequency is variable and changes over time. Chronic migraine often begins as episodic which increases and worsens in frequency and is often associated with concurrent tension type headache [44]. The yearly incidence of chronic migraine from episodic migraine is 2.5% [45]. Refractory migraine is defined by having failed all of the available preventatives and suffer from at least eight debilitating headache days per month for at least six consecutive months. Migraine has significant financial burden which has been shown across five European countries from the International Burden of Migraine Study 2012 [46]. It showed chronic migraine was associated with greater healthcare cost than episodic migraine, more provider visits, emergency department/hospital visits, and diagnostic tests and three times higher medical costs [46].

Trigeminal autonomic cephalagias

Trigeminal autonomic cephalalgias (TACs) are characterised by strictly unilateral nature, ipsilateral cranial autonomic symptoms and their severity. This group includes Cluster Headache, Paroxysmal Hemicrania, Short-lasting Unilateral Neuralgiform attacks with Conjunctival injection and Tearing (SUNCT) and Short-lasting Unilateral Neuralgiform attacks with cranial autonomic symptoms (SUNA).

Cluster headache

Cluster headache is a primary headache disorder affecting up to 0.1% of the population. It is often misdiagnosed, as those with cluster attacks may seek advice of dentists or indeed eye care professionals. The pathophysiology involves activation of the trigeminovascular complex and the trigeminal-autonomic reflex. There is severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting between 15 min and 2 h [47]. The attacks can include autonomic symptoms such as ipsilateral conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhoea; eyelid oedema; forehead and facial sweating; forehead and facial flushing; sensation of fullness in the ear; or miosis. Those with cluster describe a sense of restlessness or agitation. The attacks can happen up to eight times a day [48]. It is more common in males with a 2.5 male to 1 female ratio [48]. Cluster attacks can be triggered by strong smells and by ingestion of alcohol (with onset within minutes). The first line acute treatments are high flow oxygen or sumatriptan (nasal or subcutaneous).

Other trigeminal autonomic cephalagias

Hemicrania continua, a side locked continuous head pain, has recently been added to the TACs. [49] Paroxysmal Hemicrania attacks are shorter than Cluster headache (2–30 min) and frequency is above 5/day on the majority of episodes. The key to differentiation is the complete response to therapeutic dose to indomethacin (initially at least 150 mg daily). Similarly Hemicrania Continua has absolute response to indomethacin but it is continually present for more than 3 months with exacerbations of moderate-high intensity with associated agitation. The differentiation between SUNCT and SUNA is which autonomic features are present. The SUNCT and SUNA peaks are much shorter lasting 1–600 s as single stabs, groups of stabs or a sawtooth pattern. Multiple cutaneous stimuli have been reported to trigger attacks [50]. They do not have the response to indomethacin that is characteristic of the Hemicranias.

Trigeminal neuralgia

Trigeminal Neuralgia (TN) is characterised by sudden, brief, sharp/excruciating pains within the distribution of the trigeminal nerve, often in response to an innocuous tactile stimulus such as wind on the face, or brushing teeth. It can start infrequently and progress to more frequent episodes of pain. In comparison to SUNCT/SUNA, TN generally has less prominent autonomic features but has a refractory period between attacks, there is however overlap between these conditions. It is more common in females and tends to occur in those over the age of 50 years. Neuroimaging, with intravenous contrast, is important to exclude neuroinflammatory conditions and tumours. A common finding on dedicating neuroimaging is that of a neurovascular conflict. If the chronic pain is refractory to medications, dedicated neurosurgery or stereotactic surgery may be warranted.

Ocular conditions that masquerade as primary headache disorders

The primary headache disorders can mimic many ocular diseases. The pain can be located periorbital and retroorbital and when associated autonomic features such as conjunctival injection, lacrimation, mild ptosis and eyelid oedema. An ophthalmic examination is important in all new onset cases where there are unexplained ophthalmic symptoms or signs. Not infrequently our non-ophthalmic colleagues can mistake sub-acute and acute angle closure as

a headache disorder, particularly if the symptoms are episodic and insidious [51]. Similarly in uveitis and scleritis with pain and photophobia, can be misdiagnosed as although some are easily differentiated with a slit-lamp examination, conditions such as posterior scleritis are not [52].

A diagnosis that requires careful investigation is ophthalmoplegic migraine. It is a rare and is characterised by recurrent bouts of head pain and ophthalmoplegia. The third cranial nerve is most commonly affected. Most patients recover completely within days to weeks, but a minority are left with persistent neurologic deficits [53].

Secondary headaches

Secondary headaches are headaches caused by another medical disorder, and are recognised by the International Classification of Headache Disorders, 3rd edition, and have to fulfil specific criteria, such as a clear temporal relationship between the disease process and headache symptoms, a clear correlation of patient symptoms and symptoms expected in this disease and improvement of headache with improvement of the underlying disease [9]. Headaches may be attributed to a number of different causes that may present acutely to ophthalmology include trauma to the head or neck that may cause a Horner Syndrome, intracranial tumours such as pituitary apoplexy, intracranial haemorrhage from aneurysmal causes, arteriovenous malformations causing visual field disturbances and carotid cavernous fistulas.

In the ophthalmology clinic, there are several key secondary headaches that require active timely investigation and management such as giant cell arteritis, pituitary apoplexy, raised intracranial pressure and IIH.

Giant cell arteritis

New onset headache is a cardinal symptom of GCA, with 67% reporting this symptom [54]. The IHS definition of headache attributable to GCA is a classification system, rather than diagnostic criteria [9]. Caution needs to be applied as improvement in headache with high dose glucocorticoids happens in many secondary headaches, not just those attributable to GCA. The GCA headache characteristics are poorly defined in the literature with few investigating the headache phenotype systematically [22, 23]. It has been reported as continuous in 60% with just under half having paroxysmal headache [55]. Case reports suggest that the headache is severe and unlike prior headaches in those who have had a prior history of headache [56]. However, there is a spectrum of severity of the pain, and one series reported a range from severe (42%), to moderate (37%) and mild (21%) [55]. The location of pain is commonly reported in the temporal artery (TA) region, when the TA is involved and may be more holocranial in nature in others, likely dependent on the arterial involvement of the disease [57]. In one small series 19 cases at a Japanese headache centre reported, as expected, the location of the headache to be temporal [55]. Headache has also being reported to be a common symptom at relapse [58]. The GCA headache phenotype is yet to be fully differentiated. Where headache does not markedly improve on starting glucocorticoids, this should be considered a red flag and an alternative diagnosis to GCA considered.

Pituitary apoplexy

Characterised by infarction or haemorrhage of the pituitary gland leading to localised oedema or bleeding, pituitary apoplexy (PA) is a potentially fatal endocrinological emergency. The majority of PA cases are found to have a co-existent pituitary adenoma, 80% of which were undiagnosed prior to the development of apoplexy [59].

PA presents as a clinical syndrome of acute or subacute headache, vomiting, visual impairment, and decreased consciousness [60]. Sudden onset headache is the most frequent presenting feature, present in 80–93% of patients [61–63]. The characteristics of PA headache are variable. Unilateral frontal headache is most common but retro-orbital, bifrontal, diffuse, temporal, thunderclap and occipital headaches are also recorded in the literature [61, 62]. Vomiting is present in just over half of cases [62]. Visual abnormalities can include loss of visual acuity, cranial nerve palsies III, IV and VI and visual field loss, most commonly bitemporal hemianopsia [64]. Pituitary insufficiency is also a common finding, with corticotropic deficiency present in 50–80% of cases [61].

Although part of the clinical syndrome, the cardinal symptoms can be present infrequently and may not co-exist with each other, with reports of PA presenting initially as isolated cranial nerve palsies without, or prior to, the development of headache [65, 66].

Due to the highly variable presentation of PA, differentiation from other important diagnoses such as subarachnoid haemorrhage or meningism is often difficult if the pathognomonic features are absent. As such CT head imaging is often performed prior to MRI even though the latter is known to have higher sensitivity to detect acute intrasellar haemorrhage or infarction [67].

Cavernous sinus syndrome

This syndrome is caused by any pathology in the cavernous sinus which causes disruption to its contents, resulting in characteristic symptoms and signs. Causes include tumours such as meningioma, inflammatory disease such as

sarcoidosis, trauma, vascular lesions such as intracavernous aneurysm and carotid-cavernous fistula; and infections such as aspergillosis. [68] Commonly there is new onset headache in combination to clinical examination findings such as; ophthalmoplegia—as the cavernous sinus transmits cranial nerves 3, 4 and 6; corneal and facial sensory loss, due to cranial nerve 5a and b involvement; Horner syndrome; proptosis and chemosis.

Vascular lesions such as a carotid-cavernous fistula can present with pain. Direct fistulas are often a result of head trauma, and indirect are often spontaneous and related to atherosclerosis. In addition to the signs listed above, there may be an orbital bruit, increased intraocular pressure, and engorgement 'arterialisation' of the conjunctival vessels and a relative afferent pupillary defect [69]. When suspected the workup should be done urgently, and usually a combination of blood tests for infection/inflammatory markers and directed neuroimaging confirms the fistula.

Idiopathic intracranial hypertension

Idiopathic Intracranial Hypertension (IIH) is characterised by an elevation of intracranial pressure with no identifiable cause [70]. There is a rising incidence in this disease [71], it typically affects women of working age [72] and headache is the predominant morbidity in over 90% [73]. Headache is also the key factor driving reduced quality of life in IIH [74]. Previous characterisation of the typical phenotype of a raised intracranial pressure headache was of a nonspecific headache that is worse on waking [7]. The IIH Treatment Trial (IIHTT) characterised IIH headache in their participants as pressure-like in 47% and throbbing 42%, which is similar to migraine [75]. Photophobia, phonophobia, nausea, vomiting and worsening on physical activity were reported and none of these migraine features separated IIH headache from migraine [75]. Headache severity in IIH appears to be moderate to severe [76]. Headache frequency in IIH appears to be typically episodic in new onset disease and chronic in more longstanding disease [8]. In the IIHTT, both severity and frequency have not appeared to correlate with CSF opening pressure [75], this may seem counter-intuitive but may reflect as a rare disease the numbers needed to find significance is challenging. As the predominant phenotype of headache in IIH is migrainous, the consensus guidelines suggested a practical approach of using abortive and preventative migraine therapies, with the caution of avoiding those medications with side-effects of weight gain [76]. There have been no trials specifically investigating the management of headache in IIH [77]. A recent open label study of 55 patients with IIH in ocular remission (resolved papilloedema) and chronic migraine-like headaches investigated the use of erenumab, a calcitonin gene-related peptide monoclonal antibody. Erenumab reduced the frequency of moderate/severe headache days by 71% and all headache days by 45% from baseline to 12 months. Further, Erenumab significantly increased crystal clear days, reduced analgesic days, reduced severity and reduced absenteeism and presenteeism [78]. A key clinical point from was that treating the headache successfully, then abolished headache as a cardinal symptom of recurrence of disease. This was evidenced by seven patients who had recurrence of papilloedema without headache, suggesting that patients should be warned regarding weight gain, and need to be reassessed by ophthalmology should this occur [79].

Medication overuse headache

Medication overuse headache (MOH) is a treatable phenomenon because the specific treatments that patients take to control headaches actually cause headache. MOH patients often present with chronic headache were the MOH can mask the underlying phenotype of the original headache disorder, making them a diagnostic challenge. There is also evidence that overuse of barbiturates and opiates, but not triptans, has been associated with increased risk of progression from episodic migraine to chronic migraine [80].

ICHD-3 defines MOH diagnostic criteria as having: headache present on >15 days/month, regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, headache has developed or markedly worsened during medication overuse [9].

The commonest medications causing MOH are paracetamol, opioids, aspirin, triptans and NSAIDs. Bigal et al. in 2004 defined medication overuse defined according to the analgesic that is being used [81]:

1. Simple analgesic use (>1000 mg ASA/acetaminophen/paracetamol) >5 days/week;
2. Combination analgesics use (caffeine containing) >3 tablets a day for >3 days a week;
3. Opiate use >1 tablet a day for >2 days a week;
4. Ergotamine tartrate use: 1 mg PO or 0.5 mg PR for >2 days a week.
5. Triptans: overuse >1 tablet per day for >5 days per week.

Patients should be counselled and warned about the risks of MOH [82]. Addressing MOH is medication specific for example drugs such as triptans and NSAIDs can be stopped abruptly; patients should aim to stop taking the offending drug for at least 1 month. Abrupt withdrawal may precipitate withdrawal headache which lasts on average 3.5 days but can be up to 10 days. Other withdrawal symptoms may include gastrointestinal such as nausea and

vomiting, cardiovascular such as hypotension, tachycardia, neuropsychiatric such as sleep disturbances, restlessness, with autonomic overly and can include anxiety and nervousness [83]. The drug overused is responsible for the time taken to improve—triptans or ergots approximately take 7–10 days and simple analgesics 2–3 weeks [83].

The original headache disorder is elicited usually within 2 months of cessation of analgesics. If relapse occurs, behavioural therapy and stress management techniques can be considered. Patients should be provided with written information on 'Painkiller headaches' so that they may understand the process and increase compliance with the management plan [82].

It is also worth considering that MOH is a presumed diagnosis and withdrawing medication may not help the headache, in which case further workup is indicated to reach the diagnosis [83].

Management of migraine

Management of headache aims for effective control of symptoms. Migraine is life-long condition and a cure is unrealistic. The WHO reflected that migraine is under treated [3], and under treated headaches are not cost effective as they cause unnecessary pain, reduce an individual's productivity and led to repeated medical consultations. There are two targets for head pain: acute therapies, which may be non-specific or specific, and preventative treatments. The choice is largely dependent on the frequency of the headache. Lifestyle advice should be given with all headache disorders, as these can have considerable impact on the disease course. Strategies should be implemented to limit caffeine intake, ensure regular meals and adequate hydration, an exercise programme and sleep hygiene. Behavioural and stress management techniques can be implemented such as yoga, cognitive behavioural therapy and mindfulness. Of particular note, there are no currently treatments for aura although a number of treatments have been investigated, often in case series or un-blinded studies, none have proven to be of clinical benefit.

Abortive therapies

These includes non-specific drugs (analgesics and non-steroidal anti-inflammatory drugs—NSAIDs) and specific drugs (ergot derivatives and triptans) [84]. Opiates should be avoided due to the risk of MOH and dependency.

Specific combination therapy should be offered first line, usually an oral triptan (e.g. sumatriptan 50 mg) and an NSAID, or an oral triptan and paracetamol, some are available in melt preparations which dissolve under the tongue for faster action. If the patient prefers monotherapy, this could be either a triptan, NSAID or aspirin (high dose—900 mg 4–6 hourly, maximum dose 4 g daily). An antiemetic can be considered even if nausea and vomiting are not present. Importantly opioids or ergots are not to be prescribed.

Triptans are selective 5-hydroxytryptamine (5HT) receptor agonists, with affinity for the 5HT1B and 5HT1D receptors. 5HT1B receptors are on blood vessels smooth muscle cells and cause vasoconstriction when stimulated. 5HT1D receptors occur on perivascular trigeminal nerve terminals and in the dorsal horn, with activation blocking peptides from the trigeminal and neurotransmitter release in the dorsal horn that convey nociceptive information to the thalamus [85]. Commercially, seven triptans are available—sumatriptan, rizatriptan, eletriptan, naratriptan, zolmitriptan, frovatriptan and almotriptan—with minor differences in pharmacokinetics/dynamics. The first agent has been used since the 1990s. These medications are contraindicated in coronary artery disease, cerebrovascular disease, peripheral vascular disease, and uncontrolled hypertension. Side effects can occur, and include dizziness, drowsiness, dyspnoea, flushing, myalgia, nausea pain, temperature sensation altered, vomiting, angina pectoris, anxiety, arrhythmias, arthralgia, colitis, ischaemic coronary vasospasm, diarrhoea, dystonia, hyperhidrosis, hypotension, myocardial infarction, nystagmus, palpitations, Raynaud's phenomenon, seizure, tremor and vision disorders. Triptans can be taken orally, nasally and subcutaneously. Sumatriptan subcutaneous and nasal preparations have faster onset of action (within 15 min), whereas oral tablets generally take longer to work (30–60 min). Patients should not take ergotamine within 24 h nor monoamine oxidase inhibitors within 14 days of taking triptans. NICE found that overall, triptan plus NSAID combination therapy was ranked the most cost-effective treatment, followed by triptan plus paracetamol, and then triptan monotherapy [10].

New classes of acute abortive treatments are emerging with ditans and gepants (see below) but widespread availability is currently limited. Lasmiditan offers therapeutic efficacy but dizziness can compromise driving acutely [86–88].

Preventative therapies

The aim of preventive treatment is to reduce the frequency, severity and duration of migraine attacks, and avoid medication-overuse headache [47]. This is usually considered if migraines are causing disability regularly, for example, if there are two or more attacks per month that produce disability lasting for 3 days or more [10]. The majority of migraine preventative treatments are repurposed medications such as topiramate and propranolol. These are taken daily. Propranolol is also useful for treating co-existent anxiety and hypertension. Riboflavin taken at 400 mg once a day can also be useful in reducing migraine

frequency. Venlafaxine and angiotensin receptor type 2 antagonists have also been tried.

Botulinum toxin type a (BT-A)/onabotulinumtoxin A

More recently, newer therapies have emerged for the treatment of migraine. NICE have approved Botulinum toxin type A (BT-A) for migraine in specific circumstances. The proposed mechanisms of action are inhibition of muscle spasms aiding headache, a direct or independent and prolonged analgesic action unrelated to skeletal muscle relaxation is believed to underlie the prophylactic efficacy of BT-A in migraine and peripheral and central modulation of pain impulses by BT-A has also been proposed [89].

The NICE eligibility criteria for use of BT-A in migraine are adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine), that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse are eligible. The PREEMPT trials, which compared BT-A with placebo, was analysed by the NICE committee. This showed that the pooled results for the intention-to-treat population indicated a statistically significant reduction in frequency of headache days per month, migraine days per month and cumulative headache hours with BT-A compared with placebo [90]. The main drawback of studies in migraine is the high placebo effect noted in these studies. Treatment with BT-A is longstanding, and many be required for longer than 2 years. Patients need at least two treatment cycles to assess response to BT-A. Subsequently, ~50% of people would continue on treatment, 30% would need 5 cycles before being classified as episodic migraine. The remaining patients would continue to receive treatment for longer than 2 years. Alternatively, if the patient does not respond to BT-A, this should be discontinued and they should receive standard care. A recent Cochrane review found that in chronic migraine, BT-A may reduce the number of migraine days per month by two days compared with placebo treatment. Non-serious adverse events were probably experienced by 60/100 participants in the treated group compared with 47/100 in the placebo group [91–93].

Neurostimulation

Neuromodulation devices are available for headache, which utilise a variety of technologies [94]. Non-invasive stimulation options include supraorbital stimulation (Cefaly), vagus nerve stimulation (gammaCore) and single-pulse transcranial magnetic stimulation (SpringTMS). Invasive procedures include occipital nerve stimulation, sphenopalatine ganglion stimulation and ventral tegmental area deep brain stimulation. Evidence for these therapies is sparse and involve a small number of patients, and often manufacturer-sponsored trials.

Calcitonin gene-related peptide (CGRP) therapies

The need for newer treatments is evident because fewer than 50% of patients on current pharmacological therapy experience 50% reduction in their headache symptoms [95]. CGRP is a neuronal peptide that has been shown to be released during migraine attacks. More than 30 years ago CGRP was demonstrated in trigeminal ganglion pseudounipolar neurons [96]. Two different CGRP blockers have been developed, a small molecule CGRP receptor antagonists and immunoglobulins targeting CGRP or the CGRP receptor. These drugs are generally well tolerated, with the exception that early gepant class drugs had been associated with liver toxicity. CGRP is also found in the vasculature and therefore we can infer that there may be issues in patients with cardiovascular comorbidities.

In 2004, a proof-of-concept study showed that intravenous olcegepant (the first CGRP receptor antagonist) was effective in the acute treatment of migraine [97]. A number of other gepants for the acute treatment of migraine have been studied including: telcagepant, olcegepant, BI 44370, rimegepant (BMS-927711), MK3207 and ubrogepant, some of which have been shown to be superior to triptans for pain relief at 2 h [98]. Further direct comparison studies are required to establish further conclusions [98].

Antibodies against CGRP or the CGRP receptor have been tested as prophylactic treatment of episodic and chronic migraine. Randomised controlled trials investigating four agents, Erenumab, Fremanezumab, Galcanezumab, Eptinezumab have shown high efficacy in prevention of episodic and chronic migraine [99]. Anti-CGRP monoclonal antibody therapies are becoming increasingly utilised internationally, but in some countries are only funded in those who are treatment refractory.

Conclusion

Headache represents a very common clinical symptom and can be associated with a wide variety of clinical conditions, some of which can be lethal. It is important to take a thorough history and examination, with a cautious approach, to identify serious pathology. Cranial nerve examination and peripheral neurological examination may be required. Headaches often present to the ophthalmologist with other ophthalmic signs and symptoms and it is important to be aware of the types of visual phenomenon that can be found in conjunction with headache to help to formulate a differential diagnosis. New treatments are available for headache.

Summary

What was known before:

- Headache morbidity is high in the general population.
- The aetiology of headaches may be primary or secondary.
- Medication overuse headache, a preventable entity, can complicate the investigation and management of headache disorders.

What this study adds:

- Secondary headaches, such as idiopathic intracranial hypertension, mimic migraine-like headaches.
- Botulinum toxin type A for chronic migraine can reduce the number of monthly migraine days by two compared to placebo.
- Therapies targeting calcitonin gene-related peptide (CGRP) have been shown in randomised controlled trials to be safe and effective for both treatment of the acute attack (gepants); and prevention in chronic and episodic migraine (anti-CGRP monoclonal antibodies).

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Compliance with ethical standards

Conflict of interest SPM—Novartis, speaker fees (2020). Invex therapeutics, advisory board (2020). ASJ—Novartis and Allergan Advisory board. Speaker fees Novartis. Invex therapeutics, company director with salary and stock options (2019, 2020). No other authors contributing have a conflict of interest in the subject matter.

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