Primary headache disorders and neuro-ophthalmologic manifestations

Daniel P Schwartz
Matthew S Robbins

Department of Neurology, Montefiore Headache Center, Albert Einstein College of Medicine, Bronx, NY, USA

Abstract: Headache is an extraordinarily common complaint presenting to medical practitioners in all arenas and specialties, particularly primary care physicians, neurologists, and ophthalmologists. A wide variety of headache disorders may manifest with a myriad of neuro-ophthalmologic symptoms, including orbital pain, disturbances of vision, aura, photophobia, lacrimation, conjunctival injection, ptosis, and other manifestations. The differential diagnosis in these patients is broad and includes both secondary, or symptomatic, and primary headache disorders. Awareness of the headache patterns and associated symptoms of these various disorders is essential to achieve the correct diagnosis. This paper reviews the primary headache disorders that prominently feature neuro-ophthalmologic manifestations, including migraine, the trigeminal autonomic cephalalgias, and hemicrania continua. Migraine variants with prominent neuro-ophthalmologic symptoms including aura without headache, basilar-type migraine, retinal migraine, and ophthalmoplegic migraine are also reviewed. This paper focuses particularly on the symptomatology of these primary headache disorders, but also discusses their epidemiology, clinical features, and treatment.

Keywords: headache, migraine, trigeminal autonomic cephalalgias, neuro-ophthalmologic, aura, photophobia

Introduction

Headache is an extraordinarily common symptom and presenting complaint to medical practitioners in all arenas and specialties – particularly for primary care physicians and neurologists, but ophthalmologists as well. A wide variety of headache disorders may manifest with a myriad of neuro-ophthalmologic symptoms, including orbital pain, disturbances of vision, photophobia, lacrimation, conjunctival injection, ptosis, and other manifestations. The differential diagnosis in these patients is broad and includes both secondary, or symptomatic, and primary headache disorders. Awareness of the headache patterns and associated symptoms of these various disorders is essential to achieve diagnostic certainty and therapeutic success.

Secondary causes of headache presenting with neuro-ophthalmologic manifestations have been extensively reviewed elsewhere.[1] Herein, primary headache disorders that prominently feature neuro-ophthalmologic manifestations, including migraine, the trigeminal autonomic cephalalgias (TACs), and hemicrania continua (HC) are reviewed. This review focuses particularly on the symptomatology of these primary headache disorders and the pathophysiology of the neuro-ophthalmologic manifestations, but their epidemiology, diagnosis, and management will also be reviewed.

Correspondence: Daniel P Schwartz
The Montefiore Headache Center, Department of Neurology, Albert Einstein College of Medicine, 1575 Blondell Avenue, Suite 225, Bronx, NY 10461, USA
Tel +1 718 405 8360
Fax +1 718 405 8369
Email dschwar1@yahoo.com

Headache classification

A systematic approach to headache classification is essential for both clinical management and research, which spurred the development of the first edition International Classification of Headache Disorders (ICHD-1) in 1988.[2] The second edition (ICHD-2) revised the first edition and is the current standard for headache diagnosis and classification.[3] The ICHD-2 classifies headache disorders into three major categories: (1) primary headaches; (2) secondary headaches; and (3) cranial neuralgias, central and primary facial pain, and other headaches. This review will focus exclusively on primary headache disorders. Most of the common associated neuro-ophthalmologic symptoms have been incorporated into the diagnostic criteria of various primary headaches, such as photophobia in migraine.

Neuro-ophthalmologic symptoms

A host of neuro-ophthalmologic symptoms may occur in primary headache disorders, and are summarized in Table 1.

Photophobia

Photophobia is the clinical term that may encompass three different phenomena, all of which are common in patients with headache: (1) abnormal sensitivity to light; (2) ocular discomfort; and (3) exacerbation of headache by light.[4] Photophobia is described by 66%–88% of individuals with migraine.[5] Three-quarters of patients with migraine with aura report light as their most common trigger.[6] Light exposure can worsen acute migraine, and affected individuals typically escape to a dark place. Photophobia may also interfere with correct visual and color perception as well as induce visual perceptual distortions.[7]

The presence of unilateral photophobia may be clinically useful in the differential diagnosis of primary headaches. Although photophobia is almost always bilateral in patients with migraine – even in the presence of unilateral head pain, it is more often unilateral – ipsilateral to the side of head pain – in patients with TACs and HC.[8] Only 4% of episodic migraine patients with photophobia experience this symptom unilaterally, while 80% of those with episodic cluster headache (CH) and 55% of those with HC have unilateral symptoms.[8]

Pathophysiology

The exact signaling pathways and neurophysiological features of photophobia are not well understood, but are thought to involve the trigeminal afferent pathways with possible input from the pretectal nuclei, occipital cortex, and thalamus. Irritation to any region supplied by the trigeminal nerve can result in photophobia. Recent studies have suggested that the visual cortex is hyperexcitable and a major contributor to the symptom of photophobia in migraine.[5,9,10] Recent positron emission tomography data indeed note the presence of occipital cortex hyperexcitability during migraine attacks and even after migraine alleviation with triptans utilizing low luminous stimulation.[11]

The most likely anatomical localization of photophobia is at the site where the visual and trigeminal nociceptive pathways converge. The anatomic pathway by which light drives migraine pain has been recently identified in a study of migraine patients who were legally blind but still experienced photophobia with light stimulation.[12] The likely candidate locus for such an interaction is a nucleus in the posterior thalamus, which receives input from non-image forming, intrinsically photosensitive retinal ganglion cells and projects to somatosensory cortices.

Visual aura

A classic neuro-ophthalmologic manifestation of migraine is visual aura. Typical visual aura is classically described as

Table 1 Neuro-ophthalmologic manifestations commonly occurring in primary headache disorders

	Photophobia	Visual aura	Autonomic symptoms (ptosis, myosis, lacrimation, eyelid edema)
Migraine	Common, bilateral	Common, binocular, and homonymous	Common but not prominent, usually bilateral
Basilar-type migraine	Common	Common, occurs simultaneously in temporal and nasal fields	Uncommon
Retinal migraine	Common	Monocular, often ipsilateral to the head pain (commonly occurs in patients who also have migraine with typical visual aura)	Uncommon
Trigeminal autonomic cephalalgias	Common, often unilateral	Uncommon but reported	Prominent, strictly unilateral
Hemicrania continua	Common, often unilateral	Uncommon but reported	Prominent with exacerbations, strictly unilateral; also associated with ipsilateral ocular foreign body sensation[98]

having a hemianopic distribution and expanding in the shape of a crescent with a bright, flickering, ragged edge. This arc of scintillating lights, known as the fortification spectrum, may form into a herringbone-like pattern that expands to encompass an increasing portion of a visual hemifield. Visual distortions such as metamorphopsia (a visual distortion in which straight lines appear curved), micropsia (objects appear to be smaller than their actual size), and macropsia (objects appear to be larger than their actual size) can also occur, but are more common in children.[13–15] "Positive" symptoms such as photopsia (the sensation of unformed flashes of light before the eyes) or phosphenes (simple flashes) are sometimes followed by "negative" symptoms such as a scotoma (partial loss of sight).

The flickering or scintillating quality of aura elements is commonly reported and, according to one study, was described in approximately 70% of visual auras. To measure the perceived rate of flicker (temporal frequency) during visual auras, Crotogino et al asked migraine with aura subjects to match the flickering of their observed auras with the flickering generated by portable devices that contained adjustable light-emitting diodes.[16] To record the rate of aura flicker, subjects were instructed to look directly at the light-emitting diode and to adjust the dial until the temporal frequency of the light-emitting diode matched the flickering in their aura. The mean rate of flicker across individuals was approximately 17 Hz, although considerable interindividual variability was found.

A recent, detailed reappraisal of visual aura in 122 migraine patients across two international centers revealed that aura symptoms may be colored or black and white, have no consistent relationship to the side of head pain, and often simply consist of a visual "shimmering." In addition, the auras are often evolutive, heterogeneous, and pleomorphic.[17]

Pathophysiology

There is growing evidence that cortical spreading depression (CSD) underlies most forms of migraine aura.[18] CSD, originally described by Leao, is an intense depolarization of neuronal and glial membranes accompanied by a massive disruption of ionic gradients, and loss of membrane resistance.[19] It is characterized by cessation of spontaneous or evoked synaptic activity, and massive glutamate and potassium release, causing extracellular potassium concentrations to rise. The marked decrease in membrane resistance also results in an increase in intracellular sodium and calcium. Elevated potassium concentration is a strong

depolarizing stimulus that promotes the contiguous spread of a depolarization wave across neural tissue. Large unregulated release of excitatory amino acids like glutamate and direct intercellular transfer of ions and small molecules through gap junctions facilitate the spread.[20] This intense neuroglial depolarization facilitates the access of hydrophilic molecules to approximate and discharge nociceptive meningeal trigeminovascular afferents.

How CSD is triggered in the human cortex during a migraine attack is uncertain, but it seems clear that CSD can subsequently activate central trigeminovascular neurons.[21,22] Once triggered, CSD slowly propagates (2–5 mm/minute) to adjacent tissues without regard to functional cortical divisions or arterial territories. CSD is associated with characteristic blood flow fluctuations in the cerebral cortex: an initial, small, brief, species-dependent reduction in cerebral blood flow is followed by a profound hyperemia and then by a long-lasting oligemia, which usually lasts up to an hour.[18] In 1958, Milner pointed out the similarity between the velocity of CSD propagation and the march visual aura reported by Lashley.[23,24] The velocity of spread is approximately 3 mm/minute, consistent with the speed of CSD in the human cortex. Recently, functional magnetic resonance imaging detected focal increase in occipital blood flow spreading at a rate of 3.5 mm/minute, retinotopically congruent with a patient's visual aura.[25]

Autonomic symptoms

The signature neuro-ophthalmic feature of the TACs is the association with prominent ipsilateral cranial autonomic features (Table 2). The TACs include CH, paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA).[26] Lacrimation and conjunctival injection are the most common cranial autonomic symptoms followed by nasal congestion or rhinorrhea. Ptosis and myosis are also commonly reported. These autonomic features are typically transient, lasting only for the duration of the attack, with the exception of an interictal partial postganglionic Horner syndrome seen occasionally in patients with CH.

In migraine, patients may commonly possess attack-related cranial autonomic features as well. However, as opposed to the TACs, the autonomic symptoms are more likely to be bilateral, unrestricted to the side of the pain, of a lesser intensity, and occur on a less consistent basis with attacks.[27]

Table 2 Clinical features of the trigeminal autonomic cephalalgias and hemicrania continua

	Cluster headache	Paroxysmal hemicrania	SUNCT	Hemicrania continua
Sex F:M	1:2.5–7.2	1.6–2.4:1	1:1.5	1.8:1
Pain type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp	Throbbing, sharp, pressure
Pain severity	Severe	Severe	Severe	Baseline: mild, moderate, or severe Exacerbations: severe
Pain site	Orbit, temple	Orbit, temple	Periorbital	Orbit, temple, hemicranial
Attack frequency	1/alternate day–8/day	1–40/day (>5/day for more than half the time)	3–200/day	Daily and continuous
Duration of attack	15–180 minutes	2–30 minutes	5–240 seconds	Continuous
Autonomic features	Yes	Yes	Yes	Yes
Migrainous-associated features*	Yes	Yes	One-third	Yes
Alcohol trigger	Yes	One-fifth	No	Yes
Cutaneous triggers	No	No	Yes	No
Indomethacin effect	Variable but usually ineffective	Absolute response	Variable but usually ineffective	Absolute response
Abortive treatment	Sumatriptan injection Sumatriptan intranasal Zolmitriptan intranasal Oxygen	None**	None**	Indomethacin
First-line prophylactic therapy	Verapamil	Indomethacin	Lamotrigine	Indomethacin
Associated functional neuroimaging findings	Ipsilateral posterior hypothalamic gray matter fMRI activation during attacks[101,102]	Contralateral posterior hypothalamic gray matter fMRI activation[103]	Ipsilateral posterior hypothalamic gray matter fMRI activation[104,105]	Contralateral posterior hypothalamic gray matter, ipsilateral dorsal rostral pontine, ventrolateral midbrain, and pontomedullary junction PET activation[106]

Notes: *Photophobia, phonophobia, nausea, vomiting; **attacks too short to treat acutely in paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.
Abbreviations: F, female; fMRI, functional magnetic resonance imaging; M, male; PET, positron emission tomography; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Pathophysiology

The ipsilateral autonomic features in the TACs suggest cranial parasympathetic activation (lacrimation, eyelid edema, rhinorrhea, and nasal congestion) and sympathetic hypofunction (ptosis and myosis). There is considerable experimental animal literature to document that stimulation of trigeminal afferents can result in cranial autonomic outflow, the trigeminal-autonomic reflex.[28] Goadsby and Lipton have suggested that the pathophysiology of the TACs may be related to a central disinhibition of the trigeminal-autonomic reflex.[26]

Diplopia

Diplopia is an extraordinarily uncommon feature of primary headache disorders, and its presence mandates aggressive exclusion of secondary causes through cerebrovascular imaging and cerebrospinal fluid analysis. When diplopia accompanies symptoms of migraine, it is occasionally diagnosed as "ophthalmoplegic migraine." Ophthalmoplegic migraine is actually a rare form of neuralgia as opposed to a migraine subtype and, despite its name, is appropriately not listed as a migraine subtype in the ICHD-2. The condition has been recently reclassified as a demyelinating neuropathy of the ocular cranial nerves. In this condition, which may predominate in childhood, diplopia is often associated with migraine-like headache and periorbital pain.[29] The oculomotor nerve is most commonly involved followed by the abducens nerve and rarely the trochlear nerve. Ophthalmoplegia may last from days to months, usually with spontaneous remission. Magnetic resonance imaging findings include reversible enhancement of the cisternal segment of the oculomotor nerve and focal thickening at the exit of the nerve in the interpeduncular cistern.[30] Single photon emission computed tomography studies during attacks of ophthalmoplegia and migraine have demonstrated reversible reductions in regional cerebral blood flow in the thalamus ipsilateral to the site of ophthalmoplegia.[31] These findings suggest reversible ischemia in the territories of perforating branches of the posterior cerebral artery may accompany ophthalmoplegic migraine and possibly bear some relationship to the clinical features.

Diplopia has also been reported in several patients with CH, and may be related to compression of the oculomotor or abducens nerves by inflammatory and vasodilatory changes that occur within the cavernous sinus during CH attacks.[32] However, in the TACs, the presence of diplopia is the rare exception rather than the rule.

Palinopsia

Visual hallucinations are found in several neurological conditions and migraine is well recognized as a cause of simple visual hallucinations. The experience of retaining a visual image of objects remaining in the field of view after the patient has looked away or returning after a short delay is known as palinopsia (Greek: palin, again and opsis, vision). To investigate the frequency of palinopsia (visual perseveration) in patients with migraine with and without aura, Belcastro et al conducted structured interviews in 118 migraine patients matched with control subjects.[33] Palinopsia occurred in approximately 10% of migraine patients, and was seen more frequently in migraine with aura than in migraine without aura. Visual perseveration consisted of real objects or patterns that were located in the peripheral visual field after looking away, and these were unlikely to be associated with the onset of migraine attacks or an aura.

The mechanisms of palinopsia remain uncertain. A range of symptoms collectively termed palinopsia has been linked to dysfunction within parietal-lobe coordinate systems. Functional magnetic resonance imaging data has shown that the onset of palinopsia is associated with activation of the occipitotemporal region of the nondominant hemisphere. The most likely pathogenetic possibilities are partial seizures, cerebral hyperperfusion adjacent to areas of cortical damage, or hallucination in cases of visual loss.

Migraine
Epidemiology

Migraine is by far the most common primary headache disorder, affecting approximately 28 million people in the United States.[34] In 2004, the largest epidemiologic study of migraine to date – the American Migraine Prevalence and Prevention Study – sampled 120,000 United States' households. Migraine prevalence was approximately 17% among women and 6% among men, a finding which has remained consistent among previous epidemiologic studies. The average female-to-male migraine prevalence ratio is around 2.8, with a peak of 3.3 between age 40–45 years.[35,36] In addition, studies have consistently demonstrated that migraine prevalence is inversely related to household income. As income or education increases, migraine prevalence declines.[35–37]

Diagnostic criteria

Migraine is characterized by recurrent attacks of headache, autonomic nervous system dysfunction, and in a significant minority of patients, by aura.[38] The diagnostic criteria for migraine without aura (section 1.1) in ICHD-2 require at least five lifetime attacks lasting 4–72 hours each, with at least two of four pain features, and at least one of two sets of associated symptoms (Table 3). In children, attacks may be shorter (1–72 hours), and in young children, photophobia and phonophobia may be inferred from behavior. The diagnostic criteria for migraine with aura (section 1.2) require only two lifetime attacks of fully-reversible aura symptoms which are closely followed by headache (Table 4).

The migraine attack itself can be divided into four phases: the premonitory phase or prodrome occurring hours or days before the headache; the aura, neurologic symptoms that usually immediately precede the headache; the headache phase, comprised of headache and associated symptoms; and the postdrome. No single phase is necessary to make a diagnosis of migraine and most patients do not have all four phases.

Neuro-ophthalmologic manifestations

As described, in addition to photophobia, the classic neuro-ophthalmologic manifestation of migraine is visual aura. Migraine aura is defined as a focal neurological disturbance manifest as visual, sensory, or motor symptoms and is seen in about 20%–30% of migraineurs.[3,39,40] Typical aura symptoms develop gradually and last no more than 60 minutes, and visual aura is overwhelmingly the most common.[41] Ninety-nine percent of aura patients experience visual phenomenon in at least some attacks.[42] Headache follows aura 80% of

Table 3 Second edition International Classification of Headache Disorders diagnostic criteria for migraine without aura (section 1.1)

A. At least five attacks fulfilling criteria B–D

B. Headache attacks last 4–72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following characteristics:
  1. Unilateral location
  2. Pulsating quality
  3. Moderate or severe pain intensity
  4. Aggravation by, or causing avoidance of, routine physical activity (eg, walking or climbing stairs)

D. During the headache attack, at least one of the following:
  1. Nausea and/or vomiting
  2. Photophobia and phonophobia

E. Symptoms not attributed to another disorder

Table 4 Second edition International Classification of Headache Disorders diagnostic criteria for typical aura with migraine headache (section 1.2.1)

A. At least two attacks fulfilling criteria B–D
B. Aura consisting of at least one of the following, but no motor weakness:
  1. Fully reversible visual symptoms including positive features (eg, flickering lights, spots, or lines) and/or negative features (ie, loss of vision)
  2. Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
  3. Fully reversible dysphasic speech disturbance
C. At least two of the following:
  1. Homonymous visual symptoms and/or unilateral sensory symptoms
  2. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
  3. Each symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B–D for migraine without aura (section 1.1) begins during the aura or follows the aura within 60 minutes
E. Symptoms not attributed to another disorder

Table 5 Second edition International Classification of Headache Disorders diagnostic criteria for basilar-type migraine (section 1.2.6)

A. At least two attacks fulfilling criteria B–D
B. Aura consisting of at least two of the following fully reversible symptoms, but no motor weakness:
  1. Dysarthria
  2. Vertigo
  3. Tinnitus
  4. Hypacusia
  5. Diplopia
  6. Visual symptoms simultaneously in both temporal and nasal fields of both eyes
  7. Ataxia
  8. Decreased level of consciousness
  9. Simultaneously bilateral paresthesia
C. At least one of the following:
  1. At least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
  2. Each aura symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B–D for migraine without aura (section 1.1) begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

the time and usually begins within 60 minutes of the end of the aura.[41]

Migraine variants with prominent neuro-ophthalmologic symptoms

Aura without headache

Migraine aura without headache, previously referred to as acephalgic migraine or migrainous late-life accompaniments, may be encountered in both older patients with a remote history of migraine as well as patients who also have aura with their migraine attacks as well.[3,43] Ziegler and Hassanein reported that 44% of their patients who had headache with aura experienced aura without headache at some time.[44] Differentiating this benign disorder from transient ischemic attack and occipital lobe seizures may require investigation, especially when it first occurs after age 40 years, when negative features (eg, hemianopia) are predominant or when the aura is of atypical duration.[43]

Basilar-type migraine (BTM)

First described by Bickerstaff, BTM is a migraine subtype in which headache is accompanied by neurological symptoms referable to the brainstem, including dizziness, dysarthria, ataxia, tinnitus, hearing loss, bilateral paresthesia, altered consciousness, and syncope (Table 5).[45] Otherwise typical visual aura, but occurring in both temporal and nasal hemifields, as well as diplopia may be neuro-ophthalmologic features of BTM. The condition is more common in adolescent girls and young women. The historical concern of this representing basilar artery spasm has never been demonstrated, and BTM may

be a variant of migraine with aura with CSD occurring in the brainstem.[46] BTM should be differentiated from demyelinating, inflammatory, vascular, or neoplastic conditions affecting the brainstem, and is ultimately a diagnosis of exclusion.

Retinal migraine

Retinal migraine is a rare migraine variant characterized by attacks of fully reversible monocular visual loss, scintillations, scotomata, or blindness associated with migraine headache.[47] It is most common in women in the second to third decade of life, typically in patients with a history of migraine with aura. Other causes of monocular visual loss including transient ischemic attack, optic neuropathy, mass lesions, retinal detachment, and intermittent angle-closure glaucoma must be ruled out by appropriate investigation. The pathophysiology may relate to CSD occurring in the retina, which has been demonstrated in an animal model.[48] Work by Hanke and de Lima has shown that retinal spreading depression spreads at a rate of 4 mm/minute and its duration in vitro is about 15 minutes.[49] Prophylactic aspirin, antiepileptic drugs, and tricyclic antidepressants have been reported to reduce the frequency of episodes of migraine with and without monocular visual defects.[47] Careful follow-up in retinal migraine patients is paramount because patients may manifest irreversible visual loss with their attacks, akin to migrainous infarction of the retina.[47]

Migraine with unilateral mydriasis

Migraine associated with persistent ipsilateral mydriasis has recently been described in a series of patients.[50] While the

precise mechanism of persistent mydriasis in these patients is unclear, it is thought to be benign and related to migraine-related ciliary ganglion dysfunction. This phenomenon could represent a complicated migraine; a new migraine category; an ophthalmoplegic migraine with selective parasympathy-coparesis; an episodic ciliary ganglionitis with migrainous features; or an association of Adie's pupil and migraine.[50]

Persistent visual aura

Persistent visual aura without infarction is a rare but well-documented condition. According to the ICHD-2 criteria, this disturbance is defined by the persistence of a migraine aura for more than 1 week without radiographic evidence of infarction.[3] This migraine-related complication seems to be more common in women. The pathophysiology of prolonged visual aura is not understood, but several mechanisms are probably involved, including sustained reverberating waves of CSD.[51] There is no radiographic evidence of infarction, but functional neuroimaging studies have demonstrated cortical hypoperfusion in certain cerebral areas.[52] Medications reported as effective include divalproex sodium, intravenous furosemide, lamotrigine, and nimodipine.[51–55]

Visual snow

Visual snow is an increasingly recognized phenomenon that occurs not uncommonly among patients with migraine. Visual snow, a type of positive persistent visual disturbance, is a disorder with continuous visual symptoms consisting of white and black dots in the entire visual field that can persist for years. Schankin et al recently presented results of a retrospective survey of 120 patients who reported visual snow phenomenon.[56] A female-to-male ratio of 1:2.2 was reported and 92% of patients had no response to medication. It appears to be a unique disease entity presenting clinically distinct from visual aura, and is often associated with other visual symptoms including floaters, palinopsia, halos, photophobia, and phosphenes. However, its onset seems to coincide with headache onset, and has a high prevalence among patients who have migraine without and with visual aura. The etiology is unknown.

Migraine with binocular blindness

Binocular blindness with migraine headaches is a very rare occurrence. While BTM can be associated with binocular vision changes including blindness, rarely do migraine patients complain of losing vision in both eyes during an attack of headache. To further characterize migraine-related binocular blindness, Rozen asked 383 migraineurs if they had ever experienced an episode of complete bilateral blindness with their headaches.[57] A total of six patients (1.6%) reported episodes of binocular blindness with their headaches. All affected patients were female and did not have a history of aura. Interestingly, all showed some abnormality in clotting testing – five of the six reported patients had polymorphisms in MTHFR C677T. The MTHFR 677TT genotype has been shown to be associated with an increased risk for the development of migraine with aura. Migraine with binocular blindness appears to be a female-predominant event occurring mostly in migraine patients without a history of aura. This rare migraine-related event may reflect an underlying clotting disorder or be a manifestation of retinal spreading depression. Alternatively, it may reflect activation of the retinal–thalamic–visual cortex pathway.

Treatment

A comprehensive migraine treatment plan includes (1) education and reassurance; (2) identification and avoidance of triggers to prevent attacks; (3) nonpharmacologic treatments such as behavioral interventions, biofeedback, and relaxation exercises; (4) acute medication to abort attacks (used a maximum of 2–3 days a week to avoid medication-overuse headache); and (5) long-term preventive medication to reduce the frequency and severity of anticipated attacks.[58]

Acute therapy

In cases where there is no substantial disability, most people obtain headache relief with nonspecific acute treatments, including simple analgesics such as acetaminophen.[59,60] The nonsteroidal antiinflammatory drugs – namely aspirin, ibuprofen, and naproxen sodium – block neurogenic inflammation by a direct effect on dural blood vessels and have direct antinociceptive effects on neurons.[61]

Patients with more severe migraine and those with lack of responsiveness to nonspecific analgesics should be treated with migraine specific medications, namely triptans, 5-hydroxytryptamine-1B/1D receptor agonists, or ergotamine compounds. Both classes relieve head pain, nausea, photophobia, and phonophobia, and restore the patient's ability to function normally during an acute attack.[62] The effectiveness of triptans is in part due to agonism of 5-hydroxytryptamine-1 inhibitory heteroreceptors on the trigeminal nerve blocking neurogenic inflammation and pain transmission and their direct inhibitory effects on pain transmission in the trigeminal nucleus caudalis.[63–65]

The precise timing of triptan administration in relation to the aura phase of migraine remains controversial.

Several studies have shown that triptan therapy administered during the aura phase of migraine is ineffective in preventing the onset of headache or shortening its duration.[66,67] However, researchers recently demonstrated that treating migraine with triptans within the first 15 minutes of the aura phase proved extremely effective in preempting the onset of migraine headache.[68]

There are seven triptans available in various formulations including oral tablets, orally disintegrating tablets, nasal sprays, and injectable formulations. The most common side effects of triptans include malaise/fatigue, dizziness/vertigo, and nausea. Contraindications to the use of triptans include ischemic heart disease, cerebrovascular disease, or uncontrolled hypertension.[69]

Ergotamine compounds are also appropriate treatment choices but are associated with higher rates of side effects than triptans and may be inferior in efficacy.[70] Dihydroergotamine is an ergotamine derivative that is available in nasal spray and injectable formulations. Because of their inability to tolerate or take oral medications, patients with nausea and vomiting may benefit from dihydroergotamine nasal spray for acute attacks. Contraindications to their use include renal or hepatic failure, pregnancy, hypertension, and coronary, cerebral, and peripheral vascular disease.

Preventive therapy

The major medication groups for preventive migraine treatment include β-adrenoceptor blockers, antidepressants, anticonvulsants, calcium channel antagonists, onabotulinumtoxin A, and medicinal herbs, vitamins, and minerals. Table 6 details the medication classes, individual agents, potential mechanisms of action, and adverse effects.

Trigeminal autonomic cephalalgias (TACs)
Cluster Headache (CH)

CH is characterized by short attacks of strictly unilateral head pain that occurs in association with ipsilateral cranial autonomic features. It is a relatively rare disorder and is more common in adult males, with a reported male-to-female gender ratio of 4.3:1.[71–73] In contrast to the pulsating pain of migraine, the pain of CH is described as sharp, boring, drilling, knife-like, piercing, or stabbing.[74] The pain is so severe it has been described as worse than childbirth and renal colic. Many patients contemplate suicide during attacks – the reason it is sometimes referred to as the "suicide headache." The pain is almost strictly unilateral and typically located over the retroorbital, supraorbital, or temporal regions.[71,72] Interestingly, cluster attacks occur more frequently on the right than the left.[74–76] Pain usually peaks in 10–15 minutes but remains excruciatingly intense for an average of 1 hour within a duration range of 15–180 minutes.[76] During an attack, patients find it difficult to lie still, exhibiting often marked agitation and restlessness.[72]

CH sufferers exhibit cluster attacks, periods, and remissions. A cluster attack is an individual episode of pain that can last from several minutes to a few hours. A cluster period refers to the duration during which recurrent cluster attacks are occurring; it usually lasts from a few weeks to months. In episodic CH, the frequency of attacks ranges from one every other day to eight daily, though 75%–88% of patients have one to two attacks daily.[77] The attacks tend to be less frequent at the beginning and end of a cluster bout. In chronic CH, patients either experience attack-free remissions for less than 1 month annually or no remissions at all.

Another hallmark of CH is its marked circadian and circannual periodicity. Most patients report predictability of attack onset nocturnally, awakening them from sleep, and less so during the day.[75] Ekbom reported that cluster bouts have a seasonal predilection, being more frequent in spring and autumn.[75] Kudrow studied this periodicity in a large series of patients and reported that the frequency of cluster bouts increases with a gradual increase or decrease in daylight hours during the year, with two significant peaks starting 7–10 days after the longest day and the shortest day.[78]

Neuro-ophthalmologic manifestations

The signature neuro-ophthalmic feature of CH is the association with often prominent ipsilateral cranial autonomic features. Lacrimation and conjunctival injection are the most common symptoms followed by nasal congestion or rhinorrhea. Approximately one-third of the patients report ptosis and myosis, though these symptoms are present in two-thirds of patients observed by clinicians during an attack.[76,77] These cranial autonomic features are transient, lasting only for the duration of the attack, with the exception of a partial postganglionic Horner syndrome.

Studies now have indicated that upwards of 20% of patients with CH may have visual, sensory, or language/speech aura – the same percentage of migraine sufferers who have aura.[79] There is no definitive explanation for the aura in cluster patients, but its presence suggests CSD as it occurs

Table 6 Classes of migraine prophylactic agents

Class	Commonly used medications	Mechanism	Side effects	Other
Beta-adrenoceptor blockers	Propranolol, timolol, metoprolol	Inhibition of noradrenaline synthesis and release, blocking $5\text{-}HT2_C$ and $5\text{-}HT2_B$ receptors[107,108]	Reduced exercise tolerance, bradycardia, hypotension, gastrointestinal complaints	
Calcium channel antagonists	Verapamil, flunarizine	Block 5-HT release, interfere with neurovascular inflammation, and interfere with cortical spreading depression[109]	Constipation, dizziness, ankle swelling, bradycardia, hypotension, nausea, fatigue. Flunarizine can also cause galactorrhea and Parkinsonism	May be particularly helpful for migraine with aura
Antidepressants	Amitriptyline, nortriptyline, venlafaxine	Inhibition of serotonin and norepinephrine reuptake, antagonize $5\text{-}HT_2$ receptors[110]	Sedation, dry mouth, constipation, urinary retention	Amitriptyline is the only antidepressant with fairly consistent support for efficacy in migraine prevention[111,112]
Anticonvulsants	Topiramate	Increases GABAergic tone, blocks sodium and calcium channels, inhibits AMPA/kainate receptors, carbonic anhydrase inhibition[113]	Sedation, paresthesia, weight loss, cognitive slowing, angle-closure glaucoma, nephrolithiasis	
	Valproate	Increases GABAergic tone, inhibits NMDA depolarization	Sedation, dizziness, tremor, weight gain, alopecia, hepatitis, thrombocytopenia	
	Gabapentin	Increases GABAergic tone, blocks voltage-gated calcium channels, increases 5-HT concentration	Sedation, dizziness, edema	
Neurotoxins	Onabotulinumtoxin A	Inhibition of pronociceptive, calcium-dependent neurotransmitter (CGRP, acetylcholine) release[114]	Headache, muscle stiffness, weakness, dysphagia, dysarthria, ptosis	Approved for prophylaxis in chronic migraine, not episodic migraine
Medicinal herbs, vitamins, and minerals	Butterbur, Feverfew, magnesium, riboflavin, coenzyme Q10	Varies by compound	Varies by compound	

Abbreviations: 5-HT, 5-hydroxytryptamine; AMPA, 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid; CGRP, calcitonin gene-related peptide; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate.

in migraine aura.[80] Further study is required to elucidate the pathophysiology of aura and its association with CH.

Treatment

Acute therapy for CH includes non-oral triptans, such as subcutaneous or intranasal sumatriptan, and intranasal zolmitriptan. In addition, inhalation of 100% oxygen at 12–15 L/minute is rapidly effective in relieving pain in the majority of sufferers.[81] Oxygen does not seem to act directly on trigeminovascular afferent fibers, but may affect para-sympathetic projections to the trigeminal system that may be particularly activated during CH attacks.[82]

The preventive treatments that are commonly used for CH include verapamil, lithium, methysergide, ergotamine, corticosteroids, and valproic acid. Verapamil is the preventive drug of choice in both episodic and chronic CH.[83,84] The dose

is increased until the cluster attacks are suppressed or side effects intervene, including subclinical electrocardiogram abnormalities such as heart block.[85]

Paroxysmal hemicrania (PH)

PH is an indomethacin-responsive TAC characterized by strictly unilateral, brief, severe attacks of head pain that recur several times per day, typically with prominent ipsilateral cranial autonomic symptoms. The pain in PH is recurrent, short-lasting, and intermittent, generally occurring in brief episodes lasting 2–30 minutes at least five times a day.[26,86,87] The maximum pain is most often centered on the ocular, temporal, maxillary, and frontal regions, and is typically characterized as excruciating in severity, claw-like, throbbing, aching, or boring in quality. PH responds in an absolute fashion to indomethacin, a brain-penetrant nonsteroidal

antiinflammatory drug. This effect is so pathognomonic that indomethacin responsiveness is included in the diagnostic criteria for the disorder.

Neuro-ophthalmologic manifestations

As with the other TACs, ipsilateral cranial autonomic symptoms characteristically accompany attacks, and are typically more prominent than in CH. Lacrimation, conjunctival injection, nasal congestion, or rhinorrhea frequently accompany the headache. Eyelid edema, ptosis, myosis, and facial sweating are less frequently reported. Bilateral autonomic symptoms can occur in a minority of patients. Photophobia and nausea may accompany some attacks, though vomiting and phonophobia are rare.[86]

Aura is not unique to migraine but has also been described in various TACs, including PH. Matharu and Goadsby published a case of posttraumatic chronic PH with sensory and motor aura, and Seidel and Wober published a case of a 17-year old boy presenting with recurrent episodes of isolated visual aura followed infrequently by indomethacin-responsive headache attacks resembling PH.[88,89] Interestingly, in this case a lower dose of indomethacin lead to the abolition of head pain but persistence of both visual aura and autonomic symptoms; however, after titration of indomethacin to a higher dose, the aura and autonomic symptoms also ceased. This observation could suggest a differential dose-response relationship for indomethacin and head pain, aura, and autonomic symptoms. Migrainous aura may be seen with TACs and may represent the expression of an aura-susceptibility gene rather than typical migraine headache biology.

Treatment

PH and HC, by definition, require a therapeutic response to indomethacin. Complete resolution of the headache is prompt, usually occurring within 1–2 days of initiating the effective dose of indomethacin. The most common serious side effect of indomethacin is the development of peptic ulcers. Indomethacin suppositories are occasionally helpful if gastric intolerance is a major problem.[62]

SUNCT/SUNA

SUNCT is a very rare primary headache disorder. The diagnostic criteria require at least 20 high-frequency attacks (3–200 a day) of unilateral orbital, supraorbital, or temporal stabbing or pulsating pain, lasting 5–240 seconds, and accompanied by ipsilateral conjunctival injection and lacrimation.[3] The pain in SUNCT has a neuralgic character, being usually described as stabbing, sharp, burning, pricking,

piercing, shooting, lancinating, or electric-like. The attacks are characteristically dramatic, with moderately severe pain peaking in intensity within 3 seconds and prominent tearing.[90,91] Attacks may be as infrequent as once a day or less to more than 60 per hour.[92] Attacks may be triggered by touching certain trigger zones within trigeminal innervated distribution and, occasionally, even from an extratrigeminal territory, mastication, wind blowing on the face, washing the face, brushing teeth, and movements.[93]

SUNA, a close relative of SUNCT and occurring in both episodic and chronic forms, requires at least 20 high-frequency attacks of unilateral orbital, supraorbital, or temporal stabbing pain lasting from 2 seconds to 10 minutes that are accompanied by either ipsilateral conjunctival injection and lacrimation, nasal congestion and rhinorrhea, or eyelid edema.[3]

Neuro-ophthalmologic manifestations

By definition, SUNCT/SUNA patients usually have extremely prominent ipsilateral conjunctival injection and lacrimation associated with their attacks. Pareja et al studied video records of SUNCT attacks and found dramatic conjunctival injection involving mostly vessels of the palpebral territory stemming from superior and inferior palpebral vessels that supply the tarsal conjunctiva and most of the ocular conjunctiva.[94] Ptosis, eyelid edema, rhinorrhea, nasal congestion, and sweating are less commonly reported. It is the prominence of the autonomic symptoms that helps distinguish SUNCT/SUNA from trigeminal neuralgia of the ophthalmic nerve, where autonomic symptoms are entirely absent.

Treatment

The treatment of SUNCT/SUNA is entirely prophylactic, as attacks are generally too short for any abortive treatment to be effective. Lamotrigine has been reported to be highly efficacious in treating the disorder, although randomized, controlled studies are lacking.[95]

Hemicrania continua (HC)

HC is an indomethacin-responsive primary headache disorder characterized by daily and continuous strictly unilateral headache with ipsilateral cranial autonomic features.[96] While technically not considered a TAC, being classified under other primary headaches (section 4) in the ICHD-2, one might argue for its inclusion in this category based on clinical similarities and overlapping patterns of activation with the TACs on functional imaging studies.[97] As is the case with PH, there is by definition an absolute and exquisite response to therapeutic

doses of indomethacin. The pain in HC is continuous, moderate to severe, and unilateral, varying in intensity – waxing and waning without disappearing completely.

Neuro-ophthalmologic manifestations

Ipsilateral cranial autonomic symptoms including ptosis, myosis, tearing, and sweating characteristically accompany attacks in HC.[96] Patients with HC have also described symptoms of ocular discomfort, at times premonitory. Some patients report an "ocular foreign body" sensation, described as a feeling of "sand in the eye," which may be specific for HC.[98] Peres et al published four cases of typical visual aura accompanying or preceding HC attacks. Indomethacin provided complete relief for both the headaches and the visual symptoms, suggesting that the auras might be pathophysiologically related to the headaches in HC.[99]

Treatment

Like PH, HC by definition requires a therapeutic response to indomethacin, and a therapeutic trial of oral indomethacin is undertaken in a similar fashion. In patients who cannot tolerate indomethacin, other prophylactic agents including conventional migraine prophylactic medications like topiramate and even melatonin may be effective.[100]

Summary

Primary headache disorders as a whole are common, and commonly feature prominent neuro-ophthalmologic symptoms. Migraine, TACs, and HC are the main primary headache syndromes associated with neuro-ophthalmologic manifestations including orbital pain, photophobia, visual aura, and autonomic features. The key to effective management of these disorders is a differential diagnosis through a thorough headache and medical history, a general physical, neurological, and ophthalmologic examination. Specific neuroimaging studies are indicated when the presentation is atypical, to exclude other underlying etiologies for the headache and ocular symptoms. Pharmacologic management is highly individualized and specific to the primary headache disorder diagnosed, and may include abortive and prophylactic medications.

Disclosure

The authors report no conflicts of interest in this work.

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