Case Studies of Uncommon and Rare Headache Disorders

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KEYWORDS

• Status migrainosus • Cervical artery dissection
• Spontaneous intracranial hypotension • Hemicrania continua • Migraine with aura
• Limb pain and migraine • Cluster headache • Trigeminal neuralgia

KEY POINTS

- Status migrainosus often lasts a few weeks and may not respond to emergency department treatment.
- Cervical artery dissection can mimic migraine and present with headache and/or neck pain only.
- Spontaneous intracranial hypotension can present with a variety of headaches and be difficult to diagnose.
- Hemicrania continua and cluster headaches are commonly misdiagnosed.
- There are a diverse number of migraine auras.
- Migraine can cause limb pain with or without headache.

About 20% of the practice of the general neurologist consists of seeing patients with headaches, most of whom have primary headache disorders, mainly migraine. These case studies may be of benefit when the uncommon or rare headache disorder presents.

CASE 1. A 12-DAY MIGRAINE WITH RECURRING AURA?

Case 1 is a 60-year-old man with a history of migraine with and without aura since his 40s up to 25 days per month, decreased to about 5 per month on gabapentin 600 mg 3 times a day previously followed for 3 years. The headaches could be at the back of the head or generalized or occasionally with bitemporal pressure with an intensity of 3 to 10/10 associated with light and noise sensitivity but no vomiting relieved by eletriptan

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in 2 hours. He would occasionally have a visual aura of flashing lights in both eyes for 20 minutes before the headache.

He presented with a 12-day history of a right temporal, behind the right eye and occasionally right back of the head, sharp pain with an intensity of 4/10 at onset and 7 to 9/10 since associated with nausea, light, and noise sensitivity but no vomiting on a daily basis lasting 2 to 8 hours with ibuprofen or eletriptan. He reported blurred vision with things missing in the right eye intermittently for 3 to 5 hours daily from the day of onset of the headache for 10 days. He had no fever. His primary care physician had placed him on a methylprednisolone dose pack without help. Examination by an ophthalmologist was normal. Neurologic examination was normal.

Question: What is your diagnosis?

Perhaps he has migraine status, which is migraine lasting longer than 72 hours. The headache is different than prior migraines but seems to fit migraine criteria: the headache is unilateral associated with nausea, light, and noise sensitivity. In addition, he has been having daily episodes of blurred vision in the right eye, which may be a migraine aura.

The prevalence of migraine status is uncertain but is probably rare. In a retrospective French study of 25 patients with status migrainosus seen in a tertiary care center (of 8821 migraineurs over 11 years), the demographics were as follows: mean age at first episode, 39 years; male:female ratio, 4:21; duration 4.8 weeks (3–10); relapse of status migrainosus, 32%; and delay of relapse, 61.5 months.[1] Precipitating factors included the following: stress/anxiety, 69%; menses, 31%; and lack of sleep, 6.3%. The great majority of patients had the same attack frequency before and after the status, and most cases occurred in those with low-frequency migraine attacks.

Question: What treatments are effective for migraine status in the emergency department?

Adequate IV hydration is important as indicated, and nonopioids are preferred because the emergency department (ED) visit may be longer than with use of nonopioids[2] and risk of habituation and abuse. Medication use may be guided by comorbidities, which are contraindications to use (such as cardiovascular, cerebrovascular or cerebrovascular disease, history of gastrointestinal bleeding, and pregnancy), prior response to medications, and medications taken before the ED visit. There are a variety of potential adverse events with the medications, including movement disorders with dopamine receptor antagonists.[3]

Little has been published on treatment of migraine status in the ED. Rozen[4] reviewed ED and inpatient management of migraine status.

The Canadian Headache Society performed a systemic review of 44 studies of acute treatment of migraine in the ED and found many were of poor quality and lacking in comparator trials.[5] The Society strongly recommended the use of prochlorperazine IV, metoclopramide IV, sumatriptan subcutaneous, and ketorolac intramuscular. The Society recommended strongly against the use of dexamethasone IV and haloperidol IV.

Persistent or recurrence of migraine without status is common after the ED visit. In a study of 186 migraineurs who presented for treatment to the ED with headaches present with a median duration of 24 hours (12–72 hours), 31% had moderate or severe headache present within 24 hours of ED discharge.[6] Although no data are available, ED treatment of migraine status may not be adequate, and some patients may need to be admitted for longer treatment. In the French study of 25 patients with status migrainosus, 60% required hospitalization for a mean of 6 days and were given IV amitriptyline (not available in the United States). Dihydroergotamine

with an antiemetic is commonly used in the United States when there are no contraindications.[1]

However, because migraine is a diagnosis of exclusion and the headache was different than his prior migraines, a migraine mimic or secondary cause needed to be excluded, including temporal arteritis and cervical arterial dissection.[7]

Neuroimaging

Erythrocyte sedimentation rate was 2 mm/h. MRI scan of the brain on the day of the office visit showed small acute/subacute mid and anterior right centrum semiovale white matter infarcts. Magnetic resonance angiography (MRA) of the brain and neck showed a right internal carotid artery dissection (ICAD) extending from distal to the right carotid bulb to the proximal petrous segment with about 60% stenosis.

Questions: How often is headache and/or neck pain the only manifestation of cervical artery dissection? What are the incidence, factors associated, and other symptoms and signs with dissection?

Headache and neck pain were the only symptoms of spontaneous cervical artery dissection (CAD) in 8% in a prospective French series of 247 patients[8] and 20% in a prospective Russian series of 161 patients[9] and can mimic migraine with and without aura and migraine status (**Box 1**). The headache has a thunderclap onset in about 20% of cases. Two percent of all ischemic strokes are due to CAD, but occur in 8% to 25% of strokes in those less than 45 years of age.[10] The mean age is 44 to 46 years affecting men and women equally.

Box 1
Features of headaches due to cervical artery dissection

Carotid artery
Initial manifestation in 47% and present in 60% to 95% of cases
Ipsilateral pain in 91% of cases
Most commonly frontotemporal, occasionally hemicranial or occipital
50% with facial, dental, or orbital pain
25% with unilateral upper anterolateral neck pain
Can have nausea and vomiting
Partial Horner in 25% with ptosis and miosis
Median duration is 3 days with a range of 1 hour to 4 years (90% resolve within 1 week)
Median interval from onset of pain to neurologic symptoms is on average 9 days (range, 1–90 days)
Vertebral artery
Presenting symptom in 70% of cases and present in 88% of cases
Typically a severe ipsilateral occipital or posterior neck throbbing or steady and sharp pain but
Can be bilateral
Rarely frontal or generalized with rare nausea, vomiting, light and noise sensitivity
Mean duration 8.3 days (range 2–35 days)
Median interval from onset of pain to other symptoms is about 2 weeks (range 0.5 hour to 30 days)
Easily and often misdiagnosed as musculoskeletal pain or tension headache

There are numerous factors associated with CAD, including the following: major and minor cervical trauma; arterial hypertension; young age; current use of oral contraceptives; migraine; fibromuscular dysplasia; ultrastructural connective tissue abnormalities; vascular subtype of Ehlers-Danlos syndrome; Marfan syndrome; Turner syndrome; Williams syndrome; familial cases; hereditary hemochromatosis; osteogenesis imperfect type I; α1-antitrypsin deficiency; 677T genotype MTHFR; hyperhomocysteinemia; cystic medial necrosis of intracranial vessels; styloid process length; autosomal-dominant polycystic kidney disease; infections; Moyamoya disease; lentiginosis; and vessel redundancies (coils, kinks, loops), especially if bilateral.[11] Migraineurs such as this patient have a 2-fold increased risk of CAD, which does not appear to significantly differ by migraine aura status or gender.[12]

The incidence of spontaneous cervical ICAD is about 2.6/100,000 per year. Headache is the initial manifestation in 47% and occurs in 60% to 95% of those with ICAD preceding other neurologic symptoms and/or signs by a mean time of 4 days. The pain of ICAD, which is ipsilateral in 91% of cases, is typically unilateral frontemporal, facial, dental, or orbital area, 25% one side of the anterolateral neck, and occasionally hemicranial or occipital and is more often aching than throbbing.[13] ICAD can have migraine features, including nausea and vomiting. The median duration of the headache is 3 days with a range of 1 hour to 4 years with 90% resolving within 1 week.

ICAD can mimic migraine with aura with a visual aura only or a march of symptoms (such as visual then sensory then dysphasia) associated with a migraine-like headache.[14,15] In occasional cases where migraine with aura criteria are met in those with a prior history of migraine, the dissection could be incidental or could be a trigger for the migraine with aura episode.

This patient had asymptomatic acute/subacute right hemisphere infarcts on MRI and was also having daily ischemic visual episodes of the right eye. After the onset of pain, the median time to the appearance of neurologic symptoms is on average 9 days (range, 1–90 days).[13] Cerebral or retinal ischemic symptoms have been reported in 50% to 95% of patients in the past, although the frequency has decreased over the years.[16] Rarely, permanent blindness occurs as a result of ischemic optic neuropathy or central retinal artery occlusion.

A partial Horner syndrome occurs in about 25% of cases with ptosis and miosis. About 12% of patients with ICAD have cranial nerve palsies, most commonly involving the lower cranial nerves, especially the hypoglossal, although the oculomotor, trigeminal, and facial nerves may be involved.[17] Twenty-five percent report pulsatile tinnitus.

CASE 2. A MIGRAINEUR WITH A NEW CONSTANT HEADACHE FOR 1 MONTH

Case 2 is a 35-year-old woman with a history of occasional migraine with visual aura as a teen, and migraine without aura since her 20s occurring 1 to 2 times per month, described as a bifrontal aching with light and noise sensitivity relieved with ibuprofen.

One month before, she looked behind the seat in the car and developed a mild crick in her neck. A few hours later, she developed a constant nuchal-occipital and generalized pressure and throbbing without associated symptoms with an intensity of 9 to 10/10. Her primary care physician gave her sumatriptan tablets and an isometheptene mucate, dichloralphenazone, and acetaminophen combination, which helped a little. Over a couple of weeks, the headaches were only bifrontal. After 1 month, the headaches were still constant, bifrontal and right temporal, with an intensity of 3 to 10/10. Neurologic examination was normal.

Question: Does she have migraine status?

Just as in case 1, suspicion is raised because the headache is different than prior migraines, and migraine-associated features are not present, so testing was performed.

Neuroimaging and Follow-up

MRI of the brain showed no ischemic lesions. MRA of the neck suggested a dissection of the proximal to mid left vertebral artery. Computerized tomographic angiography was also suggestive but not diagnostic of a left vertebral dissection. A cerebral arteriogram showed a left vertebral artery aneurysm at the C6 level with a pseudoaneurysm just distal to the narrowing with 50% stenosis.

She was treated with heparin and then warfarin for 3 months. A repeat MRA showed recanalization, and she was placed on daily aspirin. The headache persisted daily with an intensity of 3 to 10/10 and lasting most of the day. The headaches persisted fairly constantly for 7 months as a bifrontal and sometimes nuchal-occipital aching and pressure and occasional throbbing with light and noise sensitivity but no nausea or aura with an intensity ranging from 4 to 10/10 with an average intensity of 5/10. She was placed on topiramate titrated up to 100 mg daily and given bilateral greater occipital nerve blocks with 1% lidocaine, and the headaches decreased to every 1 to 2 days, lasting 30 minutes to 2 hours and not requiring medication after 3 months. After 4 months, the headaches increased to 5 days a week and lasted all day. She was placed on desvenlafaxine 50 mg daily; topiramate was discontinued, and the headaches decreased to 2 to 3 monthly. Three years later, on desvenlafaxine, the headaches were occurring about once a month, lasting a few hours with acetaminophen.

Questions: How often are headaches associated with cervical vertebral artery dissection, and where is the headache in vertebral artery dissection? Can dissection cause new daily persistent headache? How often is the imaging indeterminate in diagnosing dissection? Is antiplatelet or anticoagulation treatment preferred?

Headache is a presenting symptom in about 70% of cases, is reported in 88% of cases, and is typically a severe ipsilateral occipital or posterior neck throbbing or steady and sharp pain but can be bilateral and rarely frontal or generalized (see **Box 1**).[18] The headache is rarely associated with migraine features, such as nausea, vomiting, photophobia or phonophobia, and visual aura.[19,20] The pain can easily be and is often misdiagnosed as being of musculoskeletal origin when the pain is in the back of the neck or a tension headache when in the back of the head and neck. The mean duration of the headache is 8.3 days (range 2–35 days).[13]

As this case illustrates, cervical arterial dissection is a rare secondary cause of new daily persistent headache, which is more common after ICAD.[21]

Transient ischemic attack (TIA) has been variably reported as occurring in 7% to 75% of cases and stroke in 10% to 89% of cases.[22] Rarely, cervical radiculopathy (most often at the C5-6 level), spinal epidural hematoma, and cervical spinal cord ischemia can occur. The median interval from the onset to pain onset to other symptoms is about 2 weeks (range 5 hours to 30 days).[13]

The incidence of spontaneous cervical vertebral artery dissection is about 1.5/100,000 per year. As discussed in case 1, there are numerous factors associated with cervical dissection, including prior mild or trivial trauma estimated to be antecedent in 12% to 36% of cases.[23] In this case, did she develop the dissection from looking in the back seat (unlikely) or did she recall the initial pain from the dissection (the crick in her neck) after the unrelated movement?

Seemingly forever (although the first description of spontaneous CAD was 100 years ago),[24] neurologists have debated the best medication treatment for cervical

dissections (the jury is still out on the benefit of endovascular therapy). Now we may have the best answer that we may have for many decades.

The Cervical Artery Dissection in Stroke Study was a randomized trial at hospitals with specialized stroke or neurology services (39 in the United Kingdom and 7 in Australia) of 250 patients with 118 extracranial carotid or 132 extracranial vertebral dissections with onset of symptoms within the prior 7 days with a mean age of 49 years (range 18–87).[25] Presenting symptoms in the 250 patients were as follows: ischemic stroke, 195; TIA, 29; headache, 22; neck pain, 22; Horner syndrome, 4. Patients were randomly assigned to antiplatelet (aspirin, dipyridamole, or clopidogrel alone or in combination) or anticoagulant drugs (unfractionated heparin or low-molecular-weight heparin followed by warfarin aiming for an international normalized ratio of 2–3) for 3 months with the specific treatment decided by the local clinician. In the antiplatelet group, 22% received aspirin alone; 33% received clopidogrel alone; 1% received dipyridamole alone; 28% received aspirin and clopidogrel; and 16% received dipyradomole. In the anticoagulant group, 90% received heparin and warfarin and 10% received warfarin alone.

The diagnosis of dissection could not be confirmed on central imaging review in about 20% of participants despite evidence of dissection on angiographic imaging or cross-sectional imaging through the vessel wall. In some cases, imaging was of poor quality. In others, alternative diagnoses were suggested, including atherosclerosis with an atretic artery, a narrowed artery, or adherent thrombus without dissection.

Excluding patients wherein dissection could not be confirmed, ipsilateral stroke or death occurred in 3 of 101 patients in the antiplatelet group (3%) versus 1 of 96 patients (1%) in the anticoagulant group (odds ratio 0.346, 95% confidence interval 0.006–4.390; $P = 0.66$). There was one subarachnoid hemorrhage in the anticoagulant group. All stroke events occurred in the first 10 days after randomization. There were no deaths in the total population. In the intention-to-treat population, ipsilateral TIA occurred in 1% of the antiplatelet group versus 3% of the anticoagulant group.

There was no difference in efficacy of antiplatelet and anticoagulant drugs and preventing stroke and death. The overall risk of stroke was low.

The study might not have enrolled a small high-risk group, those with early recurrent strokes.[26] Any future trials of newer oral anticoagulants and to detect small effect size may require 5000 participants and require 500 sites and 10 years to complete recruitment.

CASE 3. AN ORTHOSTATIC HEADACHE

Case 3 is a 41-year-old man with no prior headache history with a 2-month history of fairly constant daily back-of-the-head throbbing pain with an intensity of 9 to 10/10 when upright and 1/10 when supine associated with intermittent nausea and occasional vomiting. Past medical history was negative. No history of trauma. Neurologic examination was normal.

Question: What are the causes of orthostatic headaches? What tests should be ordered?

The most common cause of an orthostatic headache is a cerebrospinal fluid (CSF) leak, most commonly iatrogenic after a dural puncture. Other than iatrogenic, CSF leaks can be traumatic or spontaneous (**Box 2**).

Spontaneous intracranial hypotension (SIH) has an estimated annual incidence of 5/100,000 with a female-to-male ratio of 2:1. The peak incidence is around the age of 40 years. SIH is usually due to a spontaneous CSF leak into the epidural space through

Box 2
Cause of cerebrospinal fluid hypovolemia or cerebrospinal fluid leaks

- True hypovolemic state, when total body water (including CSF) is reduced
- Overdraining CSF shunts
- Traumatic CSF leaks
  - Obvious major injuries (eg, from motor vehicle accidents, sports injuries)
  - Brachial plexus injuries (eg, nerve root sleeve tears, avulsions)
  - Iatrogenic (eg, following dural punctures or epidural catheterizations)
  - Postsurgical (eg, after cranial, spinal, sinus, or ear surgeries)
- Spontaneous CSF leaks (major etiologic challenge)
  - Unknown cause
  - Pre-existing dural sac weakness, supported by one or more of the following:
    - Presence of meningeal diverticula, often, but not always, multiple
    - Ectasia of dural sac
    - Surgical anatomic observations of attenuated to near-absent dural zones
    - Clinical stigmata of disorders of the connective tissue matrix
      - Marfan syndrome or marfanoid features
      - Joint hypermobility
      - Retinal detachment at young age
      - Abnormalities of elastin/fibrillin in dermal fibroblast cultures
      - Familial occurrence of the leaks
      - Personal or family history of arterial dissections, aneurysms, or nonrheumatic valvular heart disease, such as bicuspid aortic valve
  - Trivial trauma (perhaps becoming relevant in the setting of a pre-existing dural weakness)
- Herniated discs or spondylotic spurs piercing or weakening the dura[13,14]

Data from Mokri B. Spontaneous intracranial hypotension. Continuum (Minneap Minn) 2015;21(4 Headache):1086–108, 1088; and Mokri B. Spontaneous CSF leaks: low CSF volume syndromes. Neurol Clin 2014;32(2):397–422.

a defect in the thecal sac at the thoracic or cervicothoracic junction due to spontaneous dural dehiscence and dural tears caused by degenerative causes.

An MRI of the brain with contrast may demonstrate diffuse pachymeningeal enhancement in 80% of cases.[27] Other abnormal abnormalities may include subdural fluid collections, engorgement of venous structures, pituitary hyperemia, and sagging of the brain (including descent of the cerebellar tonsils). An MRI of the spine without contrast may detect the leak. If the study is negative, an MRI myelogram with gadolinium may find the leak.[28]

Routine lumbar puncture may not be helpful. In a series of 106 patients with SIH, the lumbar puncture opening pressure was normal in 61%.[29] In some cases, the location of the leak cannot be located despite extensive spine imaging.[30]

There are other causes of orthostatic headaches.[31] Orthostatic headache can be the most prominent feature of postural orthostatic tachycardia syndrome.[32] Occasionally following decompressive surgery for Chiari malformation, an orthostatic headache may occur with a CSF leak.

Following large decompressive craniectomies for life-threatening cerebral edema, orthostatic headaches may occur that can improve with cranioplasty.[33] Individuals with increased compliance of the dural sac (especially with large lumbar dural sacs and stigmata of connective tissue disease) may develop orthostatic headaches.[34] Finally, orthostatic headaches can be present with colloid cysts of the third ventricle[35] and a supratentorial meningioma.[36]

Neuroimaging Results

An MRI of the brain showed diffuse pachymeningeal enhancement. MRI of the spine without contrast showed a small ventral epidural CSF collection at the C8-T1 level.

Question: What types of headaches occur in spontaneous intracranial hypotension?

The most common headache and clinical manifestation of SIH is an orthostatic headache, which may appear with the upright position or be relieved with recumbency within a few minutes but may be longer.[37] The headache is usually but not always bilateral and may be frontal, fronto-occipital, generalized, or occipital and is often throbbing but may be a pressure with an intensity ranging from mild to severe. In some chronic cases, the orthostatic features may disappear. Associated symptoms may include neck and/or interscapular pain, nausea, vomiting, diplopia, tinnitus, dizziness, change in hearing, cognitive symptoms, and unsteady gait.

Other headaches that may occur with SIH include the following: nonorthostatic headaches from the start; exertional (and Valsalva induced) headaches; acute thunderclap onset of orthostatic headaches; second-half-of-the-day headaches (often with some orthostatic features); paradoxic orthostatic headaches (present in recumbency, relieved when upright); intermittent headaches associated with intermittent leaks; and acephalgic or no headaches presenting with other clinical manifestations.[38]

Questions: Are patients with spontaneous intracranial hypotension without Ehlers-Danlos or Marfan at risk for vascular abnormalities?

Schievink and Deline[39] recommend screening for 2 vascular abnormalities, which occur with a higher frequency in those with SIH than in the general population: intracranial saccular aneurysm and aortic root dilatation, based on single studies.

MRA scans of the brain were performed in 93 patients (mean age 42.2 years, 70% women) with SIH finding 8.6% intracranial saccular aneurysm (mean age 51.4 years).[40] None of the patients with aneurysms had a recognized systemic connective tissue disorder or family history of aneurysm. In a control population of 291 patients (mean age 54.8 years, 56% women), 1% had intracranial aneurysms. Study limitations included not obtaining MRA scans on all patients with SIH and not matching study and control patients for important risk factors.

In a study of 50 consecutive patients with SIH aged 12 to 67 years,[41] 9 had cardiovascular abnormalities with dilatation of the aortic root in 6. The investigators recommend that patients with SIH without a connective tissue disorder may benefit from baseline echocardiographic screening. For those with evidence of a dilated thoracic aorta, they suggest a yearly follow-up for the first 3 to 4 years to determine the risk of progression and rupture. For those with an initial normal study, follow-up examinations in 2- and 5-year intervals are recommended. They also recommend confirmation of their findings in larger cohorts.

CASE 4. A UNILATERAL HEADACHE

Case 4 is a 48-year-old woman seen for a third opinion with a 20-year history of only menstrual headaches always preceded by a visual aura followed by a generalized throbbing with an intensity of 5 to 6/10 associated with light and noise sensitivity but no nausea. The headache would last 2 to 3 days with ibuprofen.

For 3.5 months, she had a daily constant headache, daily since onset, described as a left-sided pressure or throbbing with an intensity ranging from 1 to 10/10 with an average of 6/10 associated with light and noise sensitivity but no nausea, aura, or cranial autonomic symptoms (CAS). She had no triggers.

She had seen 2 headache specialists previously. She had tried sumatriptan orally and subcutaneously, diclofenac powder, ketorolac orally and intramuscularly, and

dihydroergotamine nasal spray, and had an occipital nerve block without benefit. Gabapentin and pregabalin did not help. She was placed on indomethacin 75 mg sustained release once a day for 8 days without benefit. Prednisone 60 mg daily for 10 days did not help. An IV dihydroergotamine regimen for 5 days did not help.

An MRI scan and MRA of the brain and cervical spine and magnetic resonance venogram of the brain were negative. Blood tests were normal. She had a past medical history of asthma. Neurologic examination was normal.

The author placed her on an increasing dose of indomethacin to 75 mg 3 times a day with omeprazole, and she became pain free. She has been followed for almost 3 years. The pain resolved for 9 months without medication and then recurred and has been controlled with indomethacin 75 mg daily.[7]

Question: What is the diagnosis, and why might the case be misdiagnosed?

The diagnosis is hemicrania continua (HC), which is an easy diagnosis to miss as in this case because of the similarity to migraine and to new daily persistent headache, which can be unilateral in 11% of cases. She did not have CAS, which are absent in about 25% of cases of HC but are also present in about 50% of migraineurs.

In a study of 52 patients with HC, 52% were misdiagnosed with migraine and 40% met migraine criteria during HC exacerbations.[42] The mean time until correct diagnosis was 5 years. Other studies have reported a delay until diagnosis of 86.1 months to 12 years[43] and up to 70% meeting migraine criteria during exacerbations.[44] The average number of physicians seen before the correct diagnosis was 4.6 with misdiagnoses by a variety of specialists including neurologists and headache specialists. Indomethacin may be underdosed during an indomethacin challenge, which can also lead to misdiagnosis. Patients with HC also may undergo unnecessary dental extractions, temporomandibular disorder, or sinus surgery.

HC is a rare disorder that may have a prevalence of up to 1% of the population. HC is more common in women than men, 1.6:1. The onset is often during the third decade of life with a range from the first to seventh decade.

The pain is almost always unilateral, although occasionally the pain can switch sides, and rare bilateral cases have been reported.[45] The pain is throbbing in 69%, and exacerbations of pain have the following triggers: stress, 51%; alcohol, 38%; irregular sleep, 38%; bright lights, 36%; exercise, 31%; warm environment, 28%; skipping a meal, 23%; strong smell, 15%; weather change, 13%; tiredness, 13%; and period, 10%.[46] Similar to chronic migraine, 75% have exacerbations of severe throbbing or stabbing pain lasting 20 minutes to several days, which can be associated with photophobia (59%), phonophobia which is often unilateral (59%), nausea (53%), and vomiting and pain awakening in one-third (24%). A visual aura can rarely occur.[47]

Cranial autonomic features are present in up to 75% with tearing and then conjunctival injection the most common complaints compared with 56% of migraineurs. A prior history of migraine is common. Primary stabbing headache or jabs and jolts are reported by 41% especially in exacerbations and about 40% of migraineurs.

HC can be labeled unremitting when daily and continuous for at least 1 year without remission periods of at least 1 day and remitting when the pain is not daily or continuous but is interrupted by remission periods of at least 1 day without treatment. In one series, 82% of cases had chronic (unremitting) HC, which was chronic from the onset in 69%.[8] Evolution from the episodic form occurred in 28% after a latency of 7.9 years (range of 2 weeks to 26 years). Some of the patients with the initial episodic form had headaches that were not daily initially, and one patient had about 10 headache days per month. Fifteen percent of patients had the episodic form, which was episodic from the onset in 33% and evolved from the chronic form in 66%.

Indomethacin responsiveness defines HC during an indomethacin trial with complete headache freedom in divided doses from 50 to 300 mg daily, usually 150 mg/d or less. There are rare reports of response at 300 mg daily. Most patients will respond to an indomethacin trial of increasing the dose if not completely headache free as follows: 25 mg 3 times a day for 3 days, 50 mg 3 times a day for 3 days, 75 mg 3 times a day for 3 days,[48] and 100 mg 3 times a day for 3 days.[49] Charlson and Robbins[50] recommend titrating up from 75 mg daily to 150 mg daily to 225 mg daily with each dose tried for 5 days.

The lowest effective dose of indomethacin should be used because of the risk of side effects, including abdominal pain, dizziness, nausea and/or vomiting, diarrhea, ulcer disease, renal impairment, and association with adverse cardiovascular thrombotic events. Some patients may respond to doses as low as 25 to 50 mg daily. One study found benefit from a median dose of 61 mg daily when the patients were asked to taper the doses down to lowest effective dose after 6 months of treatment.[51] Because of the risk of gastroduodenal mucosal injury, indomethacin is typically taken with a proton pump inhibitor.

For patients who respond to indomethacin but have tolerability issues or have contraindications to indomethacin, there are other options that, unfortunately, are not nearly as effective. In one series, greater occipital nerve block and IV dihydroergotamine were effective as a short-term treatment in 35% and 33%, respectively, and topiramate was effective in 41% for prevention,[8] with 100 to 200 mg daily used in different reports. Melatonin 9 to 15 mg at bedtime, ibuprofen 1600 to 2400 mg daily, celecoxib 200 mg twice a day, onabotulinumtoxinA, verapamil 120 to 480 mg daily, gabapentin 600 to 3600 mg daily, pregabalin 150 mg daily, IV methylprednisolone, Boswellia serrata extract 750 mg to 3375 mg daily divided into 3 doses,[52] occipital nerve stimulation, radiofrequency ablation of the C2 ventral ramus, C2 dorsal root ganglion, or sphenopalatine ganglion have been reported as effective in case reports.[11,53]

CASE 5. MIGRAINE WITH AURA AND LIMB PAIN WITHOUT HEADACHE

Case 5 is a 25-year-old woman with a history of headaches since childhood occurring about twice a week described as a left-sided throbbing with an intensity of 6 to 8/10 associated with nausea, light and noise sensitivity but no vomiting relieved in about 2 to 3 hours with an acetaminophen, aspirin, and caffeine combination. For 6 months, she had episodes about once a month; she sees heat waves in the left field for about 30 minutes followed by a typical headache. On 2 occasions, the visual symptoms were followed by mixing up her words for about 10 minutes. On one occasion, she had the visual symptoms followed by numbness of the right arm and then right face and then trouble mixing up words all lasting about 45 minutes followed by a typical headache.

For the last 3 months, she has had episodes about twice a month of tingling and throbbing pain with an intensity of 5/10 of the right upper extremity, which spreads to the right lower extremity without visual symptoms, dysphasia or dysarthria, paresis, or headache lasting about 2 hours. Past medical history is negative. Neurologic examination is normal. She was only taking the combination pain medication.

She saw an ophthalmologist with a normal examination. She saw a vascular neurologist and had normal testing including an MRI of the brain and cervical spine, MRA of the head and neck, 2-dimensional echocardiogram, Holter monitor, and extensive blood tests, including for vasculitis and coagulopathy. An electroencephalogram was normal. Propranolol and amitriptyline were not effective for prevention of the headaches.

Question: What are the manifestations and how common are the various types of migraine with aura? How often does the aura have onset during the headache?

Case 5 has a history of migraine without aura since childhood and a 6-month history of migraine with visual aura and migraine with visual aura and dysphasia and migraine with a visual and sensory aura and dysphasia.

In the United States, the 1-year period of prevalence of migraine with aura is 5.3% in women (30.8% of female migraineurs) and 1.9% in men (32% of male migraineurs).[54] Up to 81% of those with migraine with aura also have attacks of migraine without aura.[55]

The reported age of onset ranges from a mean of 11.9 years (range 4–17)[56] to a mean of 21 years old (range 5–77).[57] In one study, 54.9% of patients suffered from less than one attack per month and 9.7% suffered from more than 3 attacks per month.[58] In another study, the mean of migraine with aura episodes per year per patient was reported to be 29 (ranging from less than one to 156).[59]

In a study of 362 patients with migraine with aura with a mean age of 46 years (range 12–90), at least in some attacks, 99% of patients had a visual aura, 54% had a sensory aura, and 32% had an aphasic aura.[60] Most patients had a combination of aura symptoms as follows: 28% had a visual and sensory aura; 25% had a visual, sensory, and an aphasic aura; 6% had a visual and aphasic aura; and 39% had a visual aura exclusively. When more than one aura symptom occurred, they occurred in succession in 96% and simultaneously in 4% of patients, and 91% had a gradual onset of visual aura symptoms.

The "classic" visual aura is the fortification (looks like a fortified town as viewed from above) spectra or teichopsia ("seeing fortifications"), which is a jagged figure with fortification lines arranged at right angles to one another beginning from a paracentral area, which usually spreads outward leaving visual loss behind. There are often scintillations that may be white, gray, or have colors similar to a kaleidoscope in a semicircle or C-shape surrounding the scotoma or area of visual loss. Scintillating scotomas are typically in one hemifield with visual field defects beginning around fixation and spreading outward. The symptoms reported by patients may be quite variable, however.

Approximately 50% of patients report that the visual auras begin in the periphery and 50% in or adjacent to the center of the visual field. In a series of 122 clinic patients,[61] the laterality of the visual auras was reported as follows: always on the same side of vision (right or left), 22.1%; one sided, but not always on the same side, 23.8%; always on both sides of vision, 23.8%; and sometimes on one side, sometimes on both sides, 29.5%.[17] The color of the visual auras was reported as follows: always black-and-white, 30.3%; always black-and-silver, 20.5%; always colorful, 18.0%; both black-and-white and colorful, 22.2%; and have no color, 9.0%. The visual phenomena were described with the following characteristics and percentages of patients: blurred vision, 54.1%; small bright dots, 47.5%; zigzag lines, 41.8%; flashes of bright light, 38.5%; "blind spots", 33.6%; flickering light, 30.3%; "like looking through heat waves or water", 24.6%; blindness in half of a visual field, 23.8%; white spots, 22.1%; colored dots/spots of light, 19.7%; curved or circular lines, 18.9%; small black dots, 17.2%; beanlike forms, like a crescent or C-shaped, 16.4%; black spots, 14.8%; and tunnel vision, 9.8%. Less common and rare visual auras include corona phenomena, palinopsia,[62] metamorphopsia, macropsia, micropsia, telescopic vision, teleopsia, mosaic vision, and multiple images.

According to the International Classification of Headache Disorders, 3rd edition, beta edition criteria (ICHD-3),[63] migraine aura is considered to be of typical duration when lasting between 5 and 60 minutes. The criteria label aura as lasting longer

than an hour and less than a week as probable migraine with aura. Visual aura has been reported as lasting more than 1 hour in 6% to 10% of patients.[64] Other aura symptoms can also last more than 1 hour as follows: somatosensory aura in 14% to 27% and aphasic aura in 17% to 60% of patients.

A sensory aura consists of numbness, tingling, or a pins-and-needles sensation. The aura, which is usually unilateral, commonly affects the hand and then the face, or it may affect either one alone.[65] Paresthesia of one side of the tongue is typical. Less often, the leg and trunk may be involved. A true motor aura is rare, but sensory ataxia or a heavy feeling is often misinterpreted as weakness. Patients often report a speech disturbance when the spreading paresthesias reach the face or tongue. Slurred speech may be present. With involvement of the dominant hemisphere, paraphasic errors and other types of impaired language production and comprehension may occur. Rarely, other aura symptoms may be described, including déjà vu and olfactory and gustatory hallucinations.

Migraine aura is considered by many to be a distinct phase of the migraine attack preceding the headache. However, in a prospective study of 861 attacks of migraine with aura from 201 patients, during the aura phase, 73% of attacks were associated with headaches with 54% of the headaches fulfilling migraine criteria during the first 15 minutes within the onset of aura.[66] Aura follows headache in about 3% to 8% of cases.[16] The headache may be contralateral to the side of the visual aura, ipsilateral in up to 62% of patients for some attacks,[17] or bilateral.

Question: How do you distinguish migraine aura from cerebral ischemia and seizures?

Unlike symptoms due to cerebral ischemia, migraine visual or sensory auras typically have a slow spreading quality whereby symptoms slowly spread across the visual field or body part followed by a gradual return to normal function in the areas first affected after 20 to 60 minutes.[67] Cerebral ischemic events typically have a sudden onset with an equal distribution in the relevant vascular territory, although the affected area can expand stepwise if blood flow drops in additional vessels.[68] The progression in partial seizures is typically much more rapid. The return of function in areas first affected while symptoms are occurring in newly affected areas occurs in migraine aura but not in ischemia or seizures. As noted, when more than one aura type occurs, the auras almost always are reported as occurring one after the other, in contrast to cerebral ischemia wherein multiple neurologic symptoms typically occur at the same time. Finally, migraine aura often begins with positive phenomena, such as shimmering lights, zigzags in the vision, or tingling and then followed in minutes by negative symptoms, such as scotoma, numbness, or loss of sensation, which can also occur during seizures but with a typically faster progression of symptoms. This progression from positive to negative symptoms is not typical of cerebral ischemia.

Question: How common are late-life migraine accompaniments and migraine aura without headache?

Fisher[69] reported new onset "late life migrainous accompaniments" in 85 patients ages 40 to 73 years with episodes resembling TIAs similar to the 120 patients he had previously described.[70] Most had visual symptoms occurring alone (44/205) or combined with other aura symptoms. Headache was associated with the episodes in 40% of cases. Subsequent studies have found that accompaniments are not rare, with visual symptoms the most common, followed by sensory, aphasic, and motor auras.[71] There are no randomized controlled studies for prevention. The usual migraine drugs are used for prevention as indicated.

In the Framingham study, visual migrainous symptoms were reported by 1.23% of subjects (1.33% of women and 1.08% of men) with onset after age 50 years in 77%

with the following characteristics: stereotyped in 65%; never accompanied by headaches in 58%; the number of episodes ranging from 1 to 500 with 10 or more in 69% of subjects; and lasting 15 to 60 minutes in 50%.[72] In a study of 1000 patients presenting for a comprehensive eye examination in Alabama,[73] 6.5% reported visual symptoms consistent with migraine aura without headache, 8.6% women, and 2.9% men with risk factors, including female gender, a history of migraine headaches, and a history of childhood motion sickness.

A retrospective study of 100 aura patients[74] compared those with onset at ages of 45 years or older with those with onset before age 45 and found no differences in gender distribution, family or personal history of migraine without aura, type of aura symptoms, or imaging findings. Aura symptoms were mostly visual. The aura duration was similar in both groups with duration in those with late onset aura as follows: less than 20 minutes, 47.8%; 20 to 60 minutes, 39.1%; greater than 60 minutes, 13%. Headaches were associated with auras less often in those with older onset. The patients with onset age 65 or older were similar to those with onset age 45 or older.

Question: What are the features of migraine with brainstem aura?

Migraine with brainstem aura is the term now used rather than basilar-type migraine because involvement of the basilar artery is unlikely. Migraine with brainstem aura is a rare disorder that usually occurs from ages 7 to 20 years and rarely presents in patients older than 50 years.[75] In one study, the following aura symptoms were reported: vertigo, 61%; dysarthria, 53%; tinnitus, 45%; diplopia, 45%; bilateral visual symptoms, 40%; bilateral paresthesias, 24%; decreased level of consciousness, 24%, and hypacusis, 21%. Visual symptoms, which usually take the form of blurred vision, shimmering colored lights accompanied by blank spots in the visual field, scintillating scotoma, and graying of vision, may start in one visual field and then spread to become bilateral. The median duration of aura was 60 minutes (range of 2 minutes to 72 hours) with 2 or more aura symptoms always occurring.

Question: What are the features of retinal migraine?

Retinal migraine is rare with a mean age at onset of 25 years presenting with fully reversible monocular positive and/or negative visual phenomena lasting less than 1 hour (**Box 3** provides the criteria).[76] Typically, patients report flashing rays of light and zigzag lightning and less often, bright-colored streaks, halos, or diagonal lines. Negative phenomena may be blurring, "gray-outs," and "blackouts" causing partial or complete blindness. Elementary forms of scotoma are perceived as blank areas, black dots, or spots in the field of vision. Visual field defects can be altitudinal, quadrantic, central, or arcuate. The headache is usually ipsilateral to the visual loss. Almost 50% have a history of migraine with visual aura. Some patients who report monocular visual disturbance have hemianopsia, which they are not aware of because they do not do a cover/uncover test. This diagnosis is a diagnosis of exclusion of other causes of transient monocular blindness. Retinal migraine can lead to permanent monocular visual loss.

Question: What is Alice in Wonderland syndrome?

Alice in Wonderland syndrome, a term coined by Todd in 1955,[77] is a rare migraine aura where patients usually experience distortion in body image characterized by enlargement, diminution, or distortion of part of or the whole body, which they know is not real. The syndrome can occur at any age but is more common in children. The cause may be migrainous ischemia of the nondominant posterior parietal lobule. Other causes include medications (topiramate,[78] cough syrup with dihydrocodeine phosphate, and DL-methylephredrine hydrochloride), Epstein-Barr virus and other infections,[79] depression, seizures, and a right medial temporal lobe stroke.

Question: What is persistent visual aura and visual snow?

Box 3
International Classification of Headache Disorders, 3rd edition (beta version) criteria for retinal migraine

A. At least 2 attacks fulfilling criteria B and C

B. Aura consisting of fully reversible monocular positive and/or negative visual phenomena (eg, scintillations, scotomata, or blindness) confirmed during an attack by either or both of the following:
   1. Clinical visual field examination
   2. The patient's drawing (made after clear instruction) of a monocular field defect

C. At least 2 of the following 3 characteristics
   1. The aura spreads gradually over 5 minutes
   2. Aura symptoms last 5 to 60 minutes
   3. The aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and other causes of amaurosis fugax have been excluded.

From Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808.

Rarely, migraineurs may have persistent visual aura.[80,81] This aura usually consists of simple, unformed hallucinations in the entire visual field of both eyes with a persistent typical migraine aura with oscillation, scotoma, and fortification in one hemifield. ICHD-3 describes persistent aura without infarction as aura symptoms persisting for 1 week or more without evidence of infarction on neuroimaging.

Visual snow is a rare distinct entity whereby patients complain of uncountable flickering tiny dots in the entire visual field of both eyes akin to television snow with often continuous symptoms that can persist for years.[82] Patients also have 2 of the following 4: palinopsia; enhanced entoptic phenomena; photophobia; and impaired night vision. Visual snow occurs more often in migraineurs but also occurs in nonmigraineurs.

Question: What is the cause of the limb pain in the patient presented?

The patient reported episodes twice a month of tingling and throbbing pain of the right upper extremity that spread to the right lower extremity without headache or other symptoms lasting about 2 hours. In 1873, Liveing[83] reported limb pain associated with migraine. Paresthesias and pain of the upper and lower extremity as well as the face have been reported in pediatric and adult migraineurs with and without headache lasting seconds to 4 days.[84–86] Autosomal-dominant familial limb pain associated with migraine has been reported occurring with or without headache.[87] The pain may be due to upregulation of central convergent pathways in the brainstem, cervical cord, thalamus, and cortex.

The pain occurs more often in the upper extremity alone than the in upper and lower extremity than in the lower extremity alone and can be described as throbbing, shooting, stabbing, burning, tearing, or pressing of variable intensity. The frequency can range from daily to occasional. Typical migraine triggers may be reported. The diagnosis is one of exclusion. Migraine-preventive medications may be effective and triptans might be effective acutely. Similar limb pain has also been reported in cluster headache.[88]

CASE 6. NOCTURNAL HEADACHES

Case 6 is a 52-year-old woman with a 5-year history of facial pain that only occurs at night awakening her from sleep about 2 in the morning. She describes a burning or

pressure pain in the right upper teeth with an intensity of 10/10, which then spreads to the entire right face associated with nausea, vomiting once, light and noise sensitivity, but no eye redness or tearing, nares congestion or drainage, ptosis or miosis. The pain lasts about 20 to 30 minutes. During an attack, she feels like she cannot lie down and has to get up and move around. The pain may recur a second time within a 2-hour span. The pain may occur daily for 6 to 8 weeks and then go away for about 6 to 9 months before recurring. She saw a neurologist and was diagnosed with trigeminal neuralgia before seeking another opinion.

Question: What is the diagnosis?

There are many primary (cluster, chronic, and episodic paroxysmal hemicrania, hypnic, migraine, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and secondary headaches (medication overuse, nocturnal seizures with postictal headache, obstructive sleep apnea with headache, nocturnal hypertension, pheochromocytoma, temporal arteritis, primary or secondary tumor, subdural hematoma, communicating hydrocephalus, and elevated intracranial intracranial pressure) that can cause nocturnal headaches.

This patient has episodic cluster headache (at least 2 cluster periods lasting from 7 days to 1 year [when untreated] and separated by pain-free remission periods of $\geq$1 month). Cluster headache is misdiagnosed more than 80% of the time when first seeing a physician and even when seeing a neurologist especially in a case like this where there are atypical features.[89]

The duration of each headache (untreated, cluster has a duration of 15–180 minutes), nocturnal awakening, and duration of the bouts are all typical of cluster.

In one study, migrainous symptoms of light and noise sensitivity were reported by 70% and vomiting or nausea in more than 20%.[90] Perhaps 14% of cluster patients report an aura including visual and paresthesia.[47] Gaul and colleagues[90] found headaches occurring between 1 to 6 AM in about 75% of patients.

There are 2 less common features in this case. She does not have associated CAS. In a series of 95 cluster headache patients, 95% had CAS with the following: conjunctival injection and/or lacrimation, 95%; conjunctival injection, 62%; lacrimation, 95%; nasal congestion and/or rhinorrhea, 77%; nasal congestion, 45%; rhinorrhea, 65%; eyelid edema, 21%; and forehead/facial sweating, 57%.[91] Gaul and colleagues' study of 209 consecutive patients with episodic and chronic cluster headaches found at least one CAS in 99.5%.

The ICHD-3 beta criteria[64] for cluster require either or both of at least one CAS or a sense of restlessness or agitation. Gaul and colleagues found restlessness in 83% of cases as in this case.

Question: And the distribution of pain?

Gaul and colleagues found periorbital pain location reported by more than 75% of patients followed by occipital neck region and orofacial pain. They note that the orofacial localization and some patients reporting toothache-like pain (40%) may lead to unnecessary dental treatments, including extractions. Based on other series, the pain is behind the eye in about 90%, over the temple in 70%, and over the maxilla in 50%.[92] The pain is often described as sharp, stabbing, piercing, burning, or pulsating. About 15% report that the pain shifts sides between bouts of attacks and, less often, during a bout, but never during a single attack.

Question: What are the features of trigeminal neuralgia?

By ICHD-3 beta criteria, the duration of each paroxysm of pain has a duration of a fraction of a second to 2 minutes. In a prospective series of 158 patients with classical trigeminal neuralgia, the average age of onset was 52.9 years with 60% women affecting the right side of the face in 56%, left side 41%, and bilateral 3%.[93] Pain

was reported in the following distributions: V1, 4%; V2, 17%; V3, 19%; V1+V2, 10%; V2+V3, 33%; and V1+V2+V3, 13%. Thirteen percent had a duller persistent pain at the onset of the disorder ("pretrigeminal neuralgia"), while 87% had stabbing paroxysmal pain. The paroxysmal pain was rated on average 10/10 by 58% of the patients. Forty-nine percent of the cohort reported concomitant persistent pain along with the paroxysmal pain.

Forty percent suffered from more than 10 paroxysms of pain per day. Painful awakening at night because of pain attacks at least occasionally was reported by 49%. Trigger factors were reported by 91%, including the following: chewing, 73%; touch, 69%; brushing teeth, 66%; eating, 59%; talking, 58%; and cold wind, 50%. During attacks of pain, 31% experienced ipsilateral autonomic symptoms, most commonly conjunctival tearing or injection. Of the surgery-naïve patients, 29% had sensory abnormalities on examination, most commonly hypesthesia confined to the painful area of the face. Most patients (63%) had periods of remission with the average number per year of disease of 44 with 37% having months of remission and 63% experiencing years of remission.

Question: What is the significance of neurovascular contact in trigeminal neuralgia?

A consecutive series of 135 patients (61% women) with unilateral classical trigeminal neuralgia underwent 3.0 T MRI scans.[94] Neurovascular contact was prevalent on both the symptomatic and the asymptomatic side (89% vs 78%), usually the root entry zone, while severe neurovascular contact was much more prevalent on the symptomatic side compared with the asymptomatic side (53% vs 13%). Severe neurovascular contact that causes displacement or atrophy of the trigeminal nerve is caused by arteries in 98%. Severe neurovascular contact is more common in men (75%) than women (38%) and the odds in favor of being on the symptomatic side are 5.1 times higher in men compared with women.[95]

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