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Neurologic Manifestations of Systemic Disease (D Lapides, Section Editor)

Headache as a Neurologic Manifestation of Systemic Disease

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Abstract

Purpose of Review This is an update of headache attributed to systemic disease and current therapeutic strategies. Clinical scenarios are discussed.

Recent Findings The diagnosis of headache attributed to metabolic or systemic disorder appears in the Appendix of International Classification of Headache Disorders, Third Edition, and requires further evaluation and validation. However, recent studies characterizing headache appear in the literature. Specific treatment includes addressing underlying systemic disorders, managing concurrent primary headache, and treating comorbidities that may exacerbate headache. Evidence for specific treatment trials for headache as a symptom is lacking, including headaches post-COVID19 infection. Calcitonin gene-related peptide receptor antagonists and 5-HT_{1F} receptor agonists are attractive options for migraine with vascular comorbidities, but long-term studies are needed.

Summary Headache is commonly encountered as a manifestation or complication of systemic disease. Further research is needed to validate headache associated with systemic disorders and to determine optimal treatment strategies.

Introduction

Currently, headache attributed to a systemic disorder appears in the Appendix of the ICHD-3, thus requiring further research and validation. The goals of this review are to discuss important systemic diseases that may manifest with headache, with focus on their epidemiology, diagnostic criteria, recent findings, and current treatment strategies. The review pays special attention to migraine and systemic diseases. We will also discuss the management of complex clinical scenarios relevant to neurology practice (Table 2).

Systemic disease is defined as one that affects several organs and tissues, or the body as a whole. Moreover, headache may occur commonly as a manifestation secondary to numerous systemic conditions and to their therapies. Both primary and secondary headache disorders are diagnosed according to the International Classification of Headache Disorders-3 (ICHD3), published in 2018 [1].

It is helpful to have an anatomical and functional understanding of pain producing structures of the cranium or cranio-cervical region (i.e., dura, venous sinuses, intracranial arteries) that contribute to pain in systemic disease and lead to trigeminovascular activation. Secondary headache may present with a spectrum of clinical phenotypes that resemble primary headache disorders. There are specific indicators that are helpful for identifying secondary headaches such as temporal association and parallel severity, but these are less helpful for systemic disease–induced headaches.

General Considerations

Diagnostic Evaluation: Ruling Out Secondary Disorders

The first objective in the diagnostic evaluation of a headache presentation is the determination of whether the symptom is due to a primary or secondary condition. A detailed and methodical clinical history must be actively elicited from the patient, with specific attention to red flag warning signs (SNNOOP10) [2] in Table 1 and medications known to cause headache. A neurologic examination should be performed, with vital signs, and a general exam focused on systemic complaints. Diagnostic investigations will depend on the suspected underlying disorder.

Headache and Systemic Disorders: Primary Versus Secondary

The presence of "green" flags is reassuring for confirming the diagnosis of primary headache disorders such as migraine, tension-type, and cluster headache. In addition, a history of pre-existing or a family history of headache is helpful for the diagnosis. It is important to note that although migraine is a central nervous system disorder, it can be associated with widespread systemic manifestations due to migraine. Migraine is defined by the presence of a moderate to severe throbbing head pain, hypersensitivities, and gastrointestinal symptoms. However, during the premonitory phase, patients may report fatigue as well as several homeostatic alternations including thirst, frequency of urination, and appetite changes that are possibly associated with the hypothalamus and locus coeruleus [3].

Table 1 Ruling out secondary causes of headache using SNNOOP10

Red Flags	Orange Flag	Green Flag
Systemic symptoms (fever, weight loss, etc.)	Awakens from sleep	Family history of primary headache
Neoplasm in history,	New onset side-locked	Exacerbated by menses
Neurologic deficit (*including decreased consciousness)	Fever in isolation	Established, stable pattern > 6 months
Older age of new headache > 65 years		Return to baseline between episodes
Abrupt onset < 3 months (thunderclap)		Normal neurological exam
Papilledema		Migraine history
Pattern change or recent onset new headache		Fulfill ICHD3 criteria
Postural change		Variable location
Precipitated by Valsalva (sneezing, coughing, or exercise)		Consistent triggers (hormonal cycle, specific foods, specific sensory input such as light, sound, changes in weather, etc.)
Pregnancy or puerperium		
Pathology of immune system (HIV, etc.)		
Posttraumatic onset		
Progressive or atypical		
Painful eye with autonomic features		
Pain medication overuse		

Red flags are concerning signs for secondary disorders and require further investigation and close follow-up. Orange flags are alarming when it occurs with other orange or red flags. Green flags are reassuring for primary headache disorder. Do TP, Remmers A, Schytz HW, Schankin C, Nelson SE, Obermann M, et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology. 2019;92(3):134-44. https://doi.org/10.1212/WNL.0000000000006697

Table 2 Clinical scenarios cases representative of headache in systemic disease

Clinical case scenario	Diagnostic evaluations	Diagnoses: systemic and headache	Treatment recommendations	Teaching point, suggested reading
22-year-old woman presents with new visual disturbance and severe headache meeting migraine criteria, followed by lupus flare; normal neurological exam	Autoimmune panel shows positive ANA titers MRI brain shows multiple small periventricular white matter lesions on FLAIR sequence	Systemic lupus Migraine with aura	Steroids Triptans PRN NSAIDs PRN	Lupus flares may present with migraine with aura. If abnormal neurologic examination, consider CVST, CNS infection, or vasculitis
38-year-old woman diagnosed with migraine without aura, presents with status migrainosus in setting of menorrhagia; normal neurological exam	CBC, iron studies reveal iron deficiency anemia Ultrasound if indicated per GYN referral	Menorrhagia Menstrual migraine	Long acting triptan PRN NSAIDs PRN Magnesium supplementation Consider combined OCP Iron supplement as indicated	Review of treatment options [83]
29-year-old man with ulcerative colitis and chronic migraine with daily attacks	Review of medication use reveals twice daily fioricet	Ulcerative colitis Chronic migraine Medication overuse headache	Avoid NSAID PRN given overuse and medical contraindication Consider triptan through non-oral route (nasal, subcutaneous injection), gepant, 5-HT1F receptor agonist Start preventive	Consider onabotulinumtoxinA for prevention of chronic migraine [84]
76-year-old man with severe left temporal headache, jaw claudication, shoulder and hip pain, weight loss	ESR, CRP elevated. CBC with mild anemia Temporal artery biopsy shows granulomatous panarteritis with mononuclear cell infiltrates and giant cell formation within the vessel wall	Temporal arteritis Unclassified secondary headache	Steroids Tocilizumab	New FDA-approved treatment for temporal arteritis [85]
22-year-old woman with postprandial pain, chronic nausea and vomiting, and severe migraine attacks. History of asthma, hypotension, and constipation	Abnormal gastric emptying study	Gastroparesis Chronic migraine	Triptans, anti-emetics, NSAIDs PRN: Non-oral routes of administration acutely. Consider *onabotulinumtoxinA*	Oral migraine medications rely on gastrointestinal tract absorption, which may be affected in the presence of migraine-associated gastric stasis [86]

Table 2 (continued)

Clinical case scenario	Diagnostic evaluations	Diagnoses: systemic and headache	Treatment recommendations	Teaching point, suggested reading
54-year-old woman with hypertension, palpitations, and migraine with frequent triptan use; now with an episode of severe chest pain	EKG with non ST elevation infarction Abnormal stress-testing	Coronary artery disease. Prinzmetal angina Myocardial infarction Migraine	Gepants (CGRP small molecule antagonists) Ditans (5HT1F receptor agonists) Avoid triptans and NSAIDs	Migraine specific non-vasoactive agents, FDA statement 2019
30-year-old morbidly obese woman with chronic migraine, diabetes, hypertension; she is not using retinoids, vitamin A, exogenous hormones, tetracycline, or quinolones	MRI brain with empty sella. Fundoscopy with papilledema Lumbar puncture with elevated opening pressure	Metabolic syndrome. Idiopathic intracranial hypertension	Weight loss Topiramate OnabotulinumtoxinA CGRP monoclonal antibodies Avoid TCA, VPA due to obesity	Rule out endocrinological disorders (Addison, hypoparathyroidism, PCOS) Strategies for weight loss in migraine: Avoid fasting, meal-skipping as this may trigger attacks; cognitive behavioral methods; exercise outside of acute attacks
46-year-old man presents with 1-h episodes of L orbital pain with conjunctival injection and rhinorrhea	MRI pituitary gland shows pituitary adenoma Pituitary function tests positive for elevated growth hormone levels	Pituitary adenoma: functional or non-functional. Secondary cluster headache	Triptan PRN Tumor-specific treatment: Cabergoline if prolactinoma, etc Verapamil	Neuroimaging should be considered in all patients with chronic cluster headache [87] Triptans may be effective [88]
27-year-old male with Marfanoid body habitus presents with sudden-onset severe headache and neck pain with postural worsening and tinnitus. Joint hypermobility on exam	Beighton Scoring System consistent with hypermobility CT myelography shows CSF leak at T6 level. MRI brain with and without contrast shows classic signs of intracranial hypotension	Ehlers-Danlos Syndrome Spontaneous intracranial hypotension CSF leak	Targeted epidural blood patch Advanced surgical treatments	SEEPS are warning signs of low-pressure headache (subdural fluid collections, enhancement of the pachymeninges, engorgement of venous structures, pituitary hyperemia, sagging of the brain[89]) Update on diagnosis and treatment of spontaneous intracranial hypotension [62]

Table 2 (continued)

Clinical case scenario	Diagnostic evaluations	Diagnoses: systemic and headache	Treatment recommendations	Teaching point, suggested reading
60-year-old man with obesity, COPD, diabetes presents with low-grade daily headache that became persistent within 2 days along with cough, loss of taste, smell, fever, and shortness of breath	COVID testing positive Viral panel negative CXR shows mixed ground glass opacities MRI brain if any red flags	COVID-19 New daily persistent headache (NDPH)	Targeted COVID treatment as indicated, remdesivir Avoid medication overuse Trial of onabotulinumtoxinA	Viral illness is the most common trigger for NDPH [90]. Treatment should follow phenotype
35-year-old pregnant woman at gestational week 24 with hypertension, seizure, and headache	MRI brain with symmetrical FLAIR hyperintensities posteriorly MRA head acceptable CMP with transaminitis	Posterior reversible encephalopathy syndrome (PRES)	Blood pressure control Magnesium	Among pregnant women admitted inpatient with headache, about one-third have secondary headache [91]
54-year-old man with obesity and diabetes presents with new-onset migrainous headache and substernal pressure occurring during physical exercise	EKG acceptable Cardiac enzymes only mildly elevated Stress test abnormal	Cardiac cephalalgia Coronary artery disease Angina pectoris	Reperfusion: Sublingual nitroglycerin, percutaneous coronary intervention Control vascular risk factors Avoid triptans, ergots	This is a migraine mimic of cardiac etiology that should not be missed. There is not always concomitant angina pectoris. Coronary angiography may be performed depending on acuity [92] [93]
39-year-old woman presents with headache attacks lasting < 15 min with maximal intensity instantly, accompanied by palpitations and sweating. Blood pressure and heart rate is elevated during attack	Urinary metanephrines, catecholamines elevated Abdominal imaging reveals adrenal mass	Pheochromocytoma Secondary thunderclap headache	Control hypertension and volume expansion [94] Symptomatic headache treatment	Headache episodes will resolve after removal of this rare neuroendocrine tumor [95]
17-year-old man with sickle cell disease presents with chronic migraine headaches. Normal neurological exam	CBC reveals low hemoglobin	Sickle cell disease Migraine	Recent advances in sickle cell disease	The FDA-approved Oxbryta (voxelotor), developed by Global Blood Therapeutics, 10 days after Adakveo, on November 25, 2019 [96]

Table 2 (continued)

Clinical case scenario	Diagnostic evaluations	Diagnoses: systemic and headache	Treatment recommendations	Teaching point, suggested reading
54-year-old man with chronic back pain, asthma also suffers episodic migraine headaches	Abnormal pulmonary function tests, MRI brain and without contrast shows mild parasinus disease	Comorbid pain Respiratory disease	Control low back pain Close management of sinusitis, allergies	When pain and respiratory conditions occur together, there is greater risk of progression form episodic to chronic migraine [3]
72-year-old woman previously diagnosed with breast cancer metastatic to bone presents with worsening headache, confusion, and vertical double vision	MRI brain reveals abnormal enhancement of meninges diffusely CSF with malignant cells on cytology	Carcinomatous meningitis	Analgesics and possibly steroids	Manage intracranial pressure [97]
45-year-old male with PTSD, insomnia, and high-frequency episodic migraine without aura with recent stressors. Noticed worsened sleep and increase in migraine frequency	Screening for depression negative Screening for OSA positive	Insomnia and OSA Chronic migraine	Sleep hygiene Cognitive behavioral therapy Consider TCA, VPA	Targeted behavioral sleep intervention may result in reversion from chronic to episodic migraine [98]
33-year-old woman who underwent atrial-septal defect (ADS) closure presents with migraine and frequent aura	Hypercoagulable labs work-up negative Cardiac echo bubble study negative	ASD Migraine with aura	Antiplatelet medication	New-onset or exacerbated migraine with aura is described following percutaneous closure of ASD, possibly due to nickel allergy or platelet activation, and may respond to antiplatelet therapy [99]
39-year-old woman with migraine headache becomes pregnant and develops new onset hypertension		Pregnancy induced hypertension Migraine	Start beta-blockers if migraine frequency is disabling. Avoid VPA, TCA. For acute treatment, avoid NSIADs. Triptans may be considered if	Beta-blockers can be considered for migraine prophylaxis. Patient should be monitored closely to rule to secondary headaches and worsening hypertension

Table 2 (continued)

Clinical case scenario	Diagnostic evaluations	Diagnoses: systemic and headache	Treatment recommendations	Teaching point, suggested reading
64-year-old woman with rheumatoid arthritis and severe neck pain and radiating headaches that are throbbing and worse with lateral rotation of the neck	Positive rheumatoid factor. Cervical spine MRI brain shows pannus formation	Cervicogenic headache, rheumatoid arthritis	Disease-modifying therapy and biological agents have been known to reduce pain [100]. Symptomatic relief with COX-2 inhibitors may help reduce inflammation. Serial imaging may be needed to monitor for cervical instability and progressive myelopathy	Cervicogenic headache, while RA is not validated as a cause of headache [13], may meet criteria due to clinical and imaging evidence
68-year-old man with history of migraine and hypertension presents with daytime somnolence, morning headache. Bed partner reports snoring	STOP-Bang questionnaire score high Polysomnogram reveals apnea–hypopnea index 20	Obstructive sleep apnea Secondary headache Hypertension Migraine	CPAP Weight loss Migraine prophylaxis	CPAP may improve headache but should be treated with concomitant acute or prophylactic medication if migraine attack frequency is problematic [101]

MRI magnetic resonance imaging, *NSAIDs* nonsteroidal anti-inflammatory drugs, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TCA* tricyclic antidepressant, *VPA* valproic acid, *PRN* as needed

Migraine, as a primary headache, may be associated with comorbidities including systemic disease with a worse prognosis. Several systemic conditions may act as risk factors for transformation from episodic to chronic migraine [4]. This is important because longitudinal cohort studies such as the Chronic Migraine Epidemiology and Outcomes (CaMEO) and American Migraine Prevalence and Prevention (AMPP) studies have established more severe headache-related disability in those with chronic versus episodic migraine, with up to a 3.63 times greater rate of disability days per month [5, 6]. In a further analysis of the CaMEO study, when comparing individuals with migraine and the highest comorbidity burden with the subgroup with the fewest, there was a greater proportion of individuals with severe disability [7]. Further research is needed to assess prognostic and biological differences in migraine management based on comorbidity profiles. Based on the literature, we discuss several systems in which headache may be associated with systemic disorders or associated with primary headache, most commonly migraine.

Gastrointestinal Disorders

Individuals who regularly experience gastrointestinal symptoms have a higher prevalence of headache [8]. ICHD-3 does not define headache secondary to gastrointestinal disorders. However, nausea and vomiting are defining features of migraine, and both abdominal pain and cyclic vomiting are migraine subtypes that are often misdiagnosed. Patients with irritable bowel syndrome have been shown to have increased risk of coexisting headache; the comorbidity may be explained by shared pathological mechanisms of migraine [9]. Gastroparesis has also been reported with migraine [10]. The benefits of probiotics are understudied for migraine.

For systemic disease, a small study found that a gluten-free diet in four patients with celiac disease decreased reported migraine frequency, duration, and intensity; this may suggest a shared pathogenic relationship but needs further investigation [11]. In inflammatory bowel disease, a heightened immune response increases levels of pro-inflammatory cytokines which may contribute to the increased prevalence of headache among these patients [12]. In terms of medications, proton pump inhibitors, notably esomeprazole and lansoprazole, may cause headache especially in susceptible individuals.

Cardiovascular Disorders

Acute and Chronic Arterial Hypertension

Headache is common in hypertensive urgency, occurring in 42% of patients in one study [13]. According to ICHD-3, headache should be attributed to hypertension only if measured systolic blood pressure ≥ 180 mm Hg and/or diastolic pressure ≥ 120 mm Hg, and there is evidence of causation by either

development in temporal relation to the onset of hypertension or significant worsening or improvement in parallel with relative worsening or improvement in blood pressure.

Regardless of the underlying reason for the hypertensive crisis, the headache is often bilateral in location and pulsating in quality [1], and the mechanism causing head pain during acute hypertension is thought to be the same. Pathologic changes occur at the limit of compensatory cerebrovascular vasoconstriction, which acts to prevent hyperperfusion as blood pressure rises [14]. This presentation may be complicated by posterior reversible encephalopathy syndrome (PRES). One prospective study found headache occurred in 73% of PRES cases [15].

Based on ambulatory blood pressure monitoring correlations with headache diaries, blood pressure variations in those with mild and moderate chronic arterial hypertension did not correlate with occurrence of headache [16, 17]. In a recent prospective study of 29,040 women without hypertension with a mean follow-up for 12.2 years, women with migraine were found to have a higher relative risk of developing hypertension (with aura 9%, without aura 21%, past history 15%) than those without migraine [18]. In the Northern Manhattan Study, hypertension, predominantly uncontrolled and of long duration, was associated with migraine with and without aura, in a predominantly Hispanic community–based cohort [19]. In addition, headache is an adverse side effect of cardiovascular medications use to treat angina and hypertension, including nitrates (nitroglycerin), calcium channel blockers, and angiotensin-converting enzyme inhibitors; these often display a dose-dependent effect.

Autonomic Dysfunction

Headache is a common symptom of autonomic dysregulation. When headache occurs in a patient with complete or incomplete spinal cord injury, the patient should be presumed to have autonomic dysreflexia until proven otherwise. Headache can also be a presentation of autonomic dysfunction as seen in orthostatic hypotension, including postural orthostatic tachycardia syndrome (POTS).

A coat-hanger distribution of pain affecting the neck and shoulders may be indicative of orthostatic hypotension. In one study of patients with POTS, two-thirds of patients interviewed experienced orthostatic headache, more so in those less than 30 years old; almost all patients interviewed experienced migraine headache [20]. Another study found that in adolescents with headache and lightheadedness referred for tilt table testing, headache type did not predict POTS diagnosis, although new-onset motion sickness and dizziness preceding orthostatic headaches were significantly associated with presence of POTS [21]. In patients presenting with these features, this diagnosis should be considered; and the comorbid headache in those with POTS should be managed accordingly. Treatment includes a high-salt diet, propranolol, fludrocortisone, midodrine, and possibly exercise training. Patients with comorbid migraine may particularly benefit from beta-blockers [22].

Migraine and Cardiovascular Disease

Migraine has been associated with an increased risk of cardiovascular disease; it is estimated there are approximately 2.6 million adults with episodic migraine and one or more cardiovascular event, condition, or procedure in the USA [23]. The risk of ischemic stroke in individuals with migraine with aura is doubled; the underlying risk factors may be due to endothelial dysfunction, thromboembolism, hormonal influences, and genetic disposition.

An individual's risk of vascular events should be considered when prescribing migraine prevention and abortive treatments. Treatments may be chosen to target both disease processes; in hypertensive patients, the use of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers for migraine prophylaxis may be helpful.

According to label, triptans are contraindicated in uncontrolled arterial hypertension, coronary artery disease, and after a cerebrovascular event. However, $5HT_{1F}$ and CGRP antagonists are new specific and non-vasoconstrictive acute medications that may be safer for treating migraine in individuals with high cardiovascular risks. For example, in one study, there was no statistical difference in lasmiditan efficacy or frequency of likely cardiovascular adverse events based on presence of cardiovascular risk factors [24]. For CGRP antagonists, also known as gepants, both ubrogepant and rimegepant are migraine specific acute treatment options, while rimegepant and atogepant are approved for prevention [25]. With regard to prevention using antibodies against CGRP or its receptor, although CGRP plays a role in regulation of blood pressure [26], no serious cardiovascular concerns have been disclosed with any of these drugs [27]; still, erenumab has been linked with new-onset or worsening hypertension. A recent review outlines potential risks of migraine treatment in vascular disease and discusses these options in detail [28].

Gynecological

Pregnancy and Puerperium

In any woman presenting with headache during pregnancy or the puerperium, it is imperative to first consider secondary etiologies although primary headache is common. In one retrospective analysis of women presenting to a tertiary care center, 73% were diagnosed with a secondary headache disorder. The most common was a post-dural puncture headache, followed by postpartum preeclampsia and other cerebrovascular disorders.

Headache is considered one of the most common neurologic manifestations of hypertension in pregnancy and is important to further evaluate given the tendency for hypertensive disorders lead to significant morbidity and mortality [29]. In one case–control study, headache was significantly more frequent in those with pre-eclampsia than in controls (OR 4.95) [30].

Headache has also been found to be the most frequent symptom (87%) preceding stroke in a review of preeclampsia pregnancy-related deaths [31]. The headache that occurs is usually bilateral in location, pulsating in quality, and aggravated by physical activity [1]. Treatment of the pre-eclampsia or eclampsia will result in resolution of the headache. Meta-analyses and prospective studies suggest occurrence of headache does not portend adverse outcomes and should not be used as a diagnostic "severe feature" [32, 33].

Other Gynecological Considerations

Estrogen-containing medications, including oral contraceptives, patch, vaginal ring, and hormone replacement, although can improve headache in some cases is known to cause or worsen headache in susceptible patients. On the other hand, valproic acid used for migraine prevention can lead to polycystic ovarian syndrome.

Pulmonary Disorders

Headache can be commonly seen with a number of respiratory disorders such as OSA, asthma, and COPD. In addition, when respiratory disease and psychiatric disorder coexist, high rates of chronic migraine are observed [7]. We focus on OSA, a condition that commonly presents in neurology clinics.

Sleep Apnea Headache

Obstructive sleep apnea (OSA) may be the cause of a headache present on awakening from sleep, with usually a bilateral location, pressing quality, and a duration of less than 4 h. Headaches recur on at least 15 days per month and are not usually accompanied by nausea, photophobia, or phonophobia [1]. The prevalence is 12–18% in those with sleep apnea [34]. Other sleep-related respiratory disorders and primary sleep disorders may also present with headache upon awakening and should remain in differential diagnosis.

The prevalence of morning headache has been shown in some studies to be higher in those with severe compared to moderate OSA based on apnea–hypopnea index (AHI) grading [35, 36]. Others have not found significant increased risk of morning headache based on AHI, blood oxygen saturation parameters, or arousal index [35, 37]. suggesting that oxygen desaturation alone cannot explain the pathophysiology of this secondary headache disorder [34]. Both headache and sleep disorder may be manifestations of the same systemic dysfunction of homeostasis, attributed to hypoxia and/or hypercapnia, although this remains to be elucidated [38].

Headache associated with OSA may resolve after treatment initiation after diagnosis with a polysomnography [39]. In one study, CPAP therapy improved both sleep apnea and headache in only a third of participants [40], although in another, nasal CPAP resolved headache in 90% of participants [36].

Migraine and OSA

OSA appears to occur at the same rate in migraine as the general population [41], but is worth addressing in migraine patients as it is a modifiable vascular risk factor [42]. Snoring and other sleep disorders are risk factors for migraine progression [43]. Screening, diagnosis, and management of these sleep disturbances may be a crucial component of the therapeutic plan for migraine management.

Metabolic and Endocrine Disorders

Headache can be associated with multiple endocrine disorders and can vary in phenotype and pathophysiology such as intracranial hypertension or worsening migraine. Endocrinopathies should be considered in cases of chronic cluster headache or other trigeminal autonomic cephalalgias [44].

Headache can be associated with both hyperthyroidism, hypothyroidism, and Hashimoto's thyroiditis. Headache secondary to hypothyroidism occurs in about one-third of patients diagnosed with the endocrinological derangement [45] A prior history of migraine is more frequent in these patients [45, 46]. The underlying mechanism for headache attributed to hypothyroidism remains unclear.

Patients with headache as a component of their manifestations of hypothyroidism will not differ clinically with respect to the remainder of symptoms compared to those without headache (with the exception of hoarseness which was more frequent in those with headache) [46]. Presenting complaints including fatigue, constipation, cold intolerance, skin changes, decreased concentration, and examination may reveal bradycardia, diminished pules, increased BMI, or delayed relaxation of deep tendon reflexes.

Correction of the hormone derangement with levothyroxine will result in relief or complete remission of headache in the majority of patients; headache has shown to decrease in intensity and duration within the first 2 weeks of treatment [45]. The degree of hypothyroidism (subclinical versus overt disease) does not seem to affect potential for improvement with levothyroxine treatment [46].

Metabolic syndrome may be associated with migraine [47], but not diabetes [48]. Individuals with migraine who are obese or overweight may be at risk of experiencing increased frequency of attacks and progressing from episodic to chronic migraine. In the CaMEO study, chronic as opposed to episodic migraineurs were 34% more likely to be obese. As obesity is a potential modifiable risk factor, clinicians should consider weight management as a particularly useful component of the migraine treatment plan. Therapy should include nutritional and dietary education, exercise strategies, and behavioral interventions. Weight loss may be challenging in some patients with systemic disorders such as PCOS. If migraine and obesity are comorbid, weight neutral drugs such as topiramate should be considered and common drugs associated with weight gain (valproate, amitriptyline, propranolol, etc.) avoided.

For pseudotumor cerebri, headache is a direct consequence of increased intracranial pressure. However, systemic inflammation associated with obesity can be migraine-triggering so treating with migraine prophylaxis and specific therapies is beneficial. Weight loss, correction of metabolic disturbance, removal of the inciting agent, or treatment of the underlying causative disorder may not be sufficient to normalize the high intracranial pressure. Additionally, diuretics are often required to relieve headache and other symptoms and to prevent vision loss.

Rheumatologic Disorders

Headache is a common manifestation of autoimmune disorders, with focused or systemic inflammation. Conditions that may cause headache may vary from systemic lupus erythematosus (SLE) and related conditions, vasculitis which may be primary or secondary, or systemic vasculitides. Treatment with steroids of immunomodulators may not be enough to treat headache; systematic treatment with analgesics are often needed. Migraine has previously been shown to be more prevalent in patients with primary Sjogren's syndrome, scleroderma, SLE, and rheumatoid arthritis as compared to controls; there may be a significant association between Raynaud's phenomenon and migraine [49]. In addition to steroids (and analgesics), steroid-sparing agents are often necessary for prolonged remission.

Temporal Arteritis

Temporal arteritis should be considered in older patients greater than 50 with new-onset headache. Temporal arteritis is commonly associated with polymyalgia rheumatica and jaw claudication. The headache of temporal arteritis is sometimes missed because the headache be present beyond the temples, also involving the frontal, vertex, and occipital regions [50]. In addition to blindness, patients may have vascular complications such as ischemic stroke if not effectively treated with steroids urgently. We suggest an initial treatment with the equivalent of prednisone 1 mg/kg (maximum 60 mg/day) administered in a single daily dose and pulse intravenous methylprednisolone for patients at risk of with established visual loss [51].

Systemic Sarcoidosis and Neurosarcoidosis

Neurologic manifestations are relatively rare in the multisystem granulomatous disorder of systemic sarcoidosis, but patients may develop headache and stroke-like symptoms during presentation [52] and reported migraine headache more commonly than healthy controls [53].

In neurosarcoidosis, headache was the second most commonly reported feature (32%) after cranial neuropathy (55%) [54]. For patients in which

headache was the presenting manifestation of neurosarcoidosis, half had clinical characteristics suggestive of Tolosa-Hunt syndrome while in the remainder headache was tension-type and without other neurologic symptoms [55]. Classical imaging finding include leptomeningeal, pituitary, hypothalamic, and the brain parenchymal involvement. Steroids are first-line treatment, which may improve secondary headache, and the addition of steroid-sparing agents is often necessary [56].

Systemic Lupus Erythematosus

Headache attributed to SLE may occur but is not considered as a presenting or prominent symptom of the disease and is not sufficiently validated to be defined in the ICHD-3. Still, headache is commonly one of the nonspecific symptoms with which an SLE patient may present. Some studies reveal migraine, especially with aura, is more common in patients with SLE than controls [57], although others show no significant difference [58]. In a cohort of 1732 patients, there was no association between headache and immunosuppressant drugs or the presence of specific autoantibodies [59]. Importantly, SLE patients may be hypercoagulable and are therefore at risk of cerebral venous sinus thrombosis (CVST). There is insufficient data on headache treatment, but acetazolamide may be considered as well as standard migraine treatments (i.e., tricyclic anti-depressants, topiramate, onabotulinumtoxinA injections, SNRIs). In SLE patients, serious headache may be an important indicator of CNS infection or cerebral vasculitis.

Aseptic Meningitis

Rheumatologic diseases including sarcoidosis, Behcet's disease, Sjogren's syndrome, SLE, and granulomatosis with polyangiitis may result in headache due to meningeal involvement, though aseptic meningitis can also be due to other etiologies such as drug-induced (most commonly due to NSIADs, antibiotics, IVIG, and monoclonal antibodies) or neoplastic processes [60]. Patients may suffer accompanying nausea, neck stiffness, and photophobia. CSF reveals pleocytosis with no evidence of bacterial infection, fungal infection, or malignancy; MRI may reveal meningeal enhancement [61]. In the case of CSF high pressures, serial lumbar punctures, acetazolamide, or topiramate may be helpful. This condition may be self-limiting; however, shunting may be necessary in severe cases of chronic meningitis with impending blindness.

Other Rheumatological Disorders: Connective Tissue Disease and CSF Leaks

In US populations, connective tissue disorders are a common (16–38%) cause of for patients found to have spontaneous intracranial hypotension

[62]. In Marfan syndrome, Ehlers-Danlos syndrome, autosomal dominant polycystic kidney disease, and benign joint mobility syndrome, dural weakness may predispose to CSF leakage. Therefore, one should evaluate for subtle manifestations of a variety of connective tissue disorder in these cases and if present an epidural blood patch may be therapeutic [63]. An updated diagnostic criteria for this headache was proposed in 2017 [64]. In those already diagnosed with a connective tissue disease, postural headaches should raise suspicion of spinal meningoceles with or without CSF leak [65].

Hematological Disorders

Iron Deficiency Anemia

Patients with iron deficiency anemia (IDA) have a high frequency of headache, and specifically migraine; one questionnaire-based study revealed almost 80% of IDA patients had headache during their lifetime and 36% met criteria for migraine [66]. A recent case–control study found an association between IDA, hemoglobin levels, and serum ferritin levels and the incidence of migraine in female but not male patients [67]. One randomized controlled trial found a significant improvement in headache after iron supplementation in iron-deficient blood donors [68].

Sickle Cell Disease

Headache and facial pain may be common in patients with sickle cell disease (SCD); primary etiologies are common, but secondary etiologies must be investigated given potential for significant morbidity and mortality. Secondary causes of headache and facial pain in SCD include vascular etiology, bone infarcts (including facial, skull, and subperiosteal), orbital compression syndrome, osteomyelitis, dental and periodontal, PRES, and neuropathic pains [69]. At least in children with SCD, headache or migraine was associated with lower hemoglobin and higher pain event rates, but not silent cerebral infarction [70]. In a large case–control study, headache was of increased prevalence in children but not adults with SCD. Regular blood transfusions have not been shown to reduce headache frequency [71].

Other Hypercoagulable States

Patients with suspicion for a hypercoagulable state who present with headache must be evaluated for secondary causes of headache. The most common presenting feature of CVST is headache (up to 89.4%) [72]. The headache in CVST is most frequently subacute, diffuse, and increases in intensity over time; it worsens with maneuvers that increase ICP and may be refractory to common analgesics [73]. In one large population-based case–control study, those

with the combination of headache and high intrinsic coagulation protein levels were shown to have an increased risk of ischemic stroke than was based on the effect of headache or high levels alone [74]. Estrogen-containing oral contraceptives should be avoided as well as non-steroidal anti-inflammatory drugs with concomitant anti-coagulation use.

Infectious Etiologies

Headache may present as a manifestation of systemic or CNS infection, including rhinosinusitis, influenza syndromes, meningitis, encephalitis, or brain abscesses. Headache attributed to infectious meningitis or encephalitis should be suspected when associated with fever, neck stiffness, light sensitivity, nausea, and vomiting. The ICHD-3 recognizes headache attributed to systemic infection or new daily persistent headache (NDPH), which becomes continuous within 24 hours of onset and is commonly preceded by a viral prodrome. The treatment of NDPH may be challenging but includes including muscle relaxants, triptans, tricyclic antidepressants, onabotulinumtoxinA, SSRIs/SNRIs, and antiepileptic drugs [75].

SARS-CoV-2 (COVID-19)

In recent reports of hospitalized patient diagnosed with COVID-19, headache was reported in 11–34% of hospitalized patients [76]. The CDC includes headache in an expanded list of possible symptoms. One hospital found COVID-19-related headaches to be of new onset, moderate to severe intensity, and bilateral with a pulsating or pressing quality in the temporoparietal, forehead, and periorbital regions; headache was poorly responsive to common analgesics and was limited to the active phase of illness [76]. Based on others' experience, in the acute phase, headache can appear as attributed to systemic viral infection, associated with cough headache, or tension-type; headache may emerge during a second phase of cytokine storming [77]. In patients with prior diagnosis of migraine disorder, severe persistent headache may be an early symptom [78]. Headaches associated with personal protective equipment among frontline healthcare workers may occur as a new onset or an exacerbation of a pre-existing headache disorder [79]. Remdesivir is indicated for moderate to severe COVID-19 infection with respiratory compromise; however, headache specific recommendations are lacking. Initially, renin-angiotensin system inhibitors, for hypertension and migraine prevention, were thought to potentially complicate outcomes; however, new studies suggest no evidence of harm. NSAIDs were also advised to use with caution; however, there is no evidence to support and may provide analgesia for severe headaches. Furthermore, mechanistic and therapeutic studies are needed for better management of persistent headache along with other symptoms, also known as long COVID or post-acute sequelae SARS-CoV-2 infection.

Lyme

In acute stage of Lyme disease, many patients have nonspecific symptoms including headache, fatigue, arthralgia, and myalgia. Recent-onset headache occurred in more than half in a study of patient's hospitalization for neurologic Lyme disease; with the majority of these meeting criteria for meningitis or encephalitis with abnormal CSF evaluations [80]. There have been cases published of Lyme disease presenting with Raeder paratrigeminal neuralgia [81, 82]. In the chronic stage, nonspecific symptoms such as persistent headache do not indicate active infection [83]. Persistent headache due to lyme may be difficult to treat and may respond to NSAIDs, anti-depressants, SNRIs, or anti-convulsants. Stabbing headache if present may respond to gabapentin, pregabalin, or NSAIDs.

Human Immunodeficiency Virus

Headaches are the most commonly reported form of pain among patients with human immunodeficiency virus (HIV) [84]. The etiology of headache in patients with HIV infection may be multifactorial; a secondary etiology for headache can occur at any time during infection. Headache related directly to

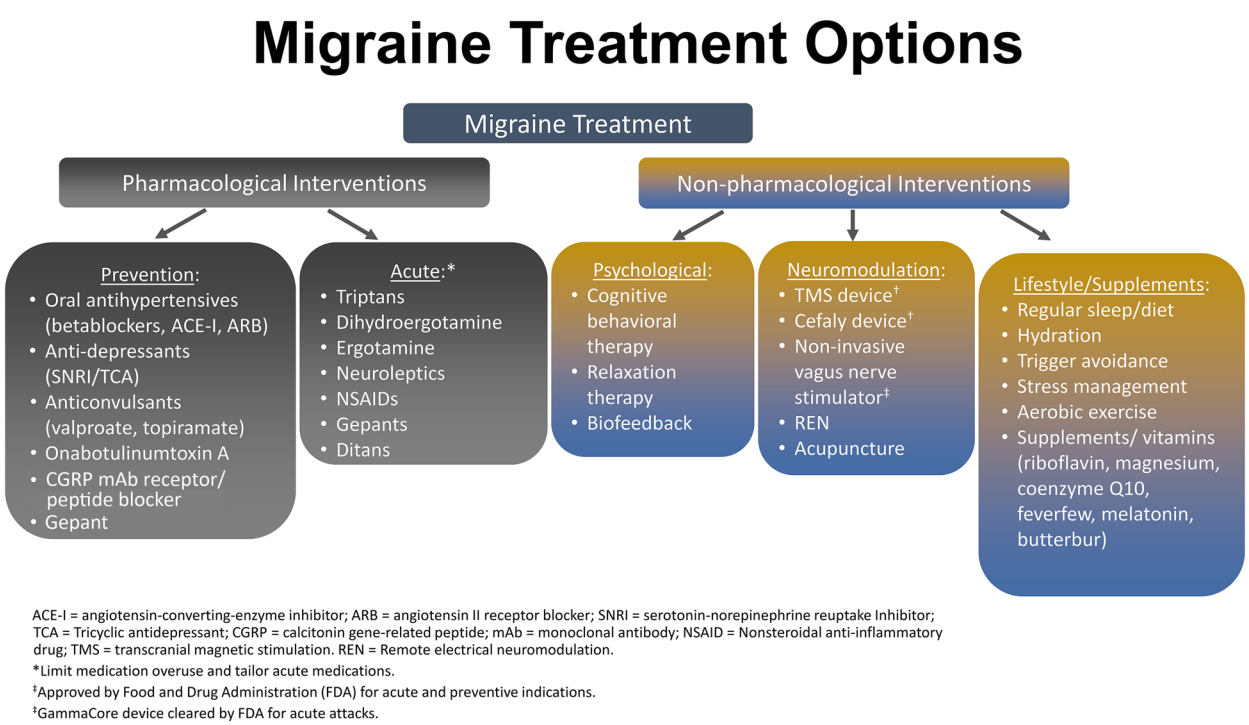

Fig. 1 Headache attributed to systemic disease is best treated by addressing the underlying disorders and treating headache symptomatically. When headache persists, migraine treatments may be helpful if migraine co-exists or if the phenotype resembles migraine. The description of pain may be useful to guide treatment such as the presence of neuropathic symptoms which may indicate use of anti-convulsants, tricyclic anti-depressants, or serotonin norepinephrine reuptake inhibitors.

the HIV infection includes an acute meningitis seen during seroconversion, during symptomatic HIV, and after an AIDS-defining illness. Alternatively, headache may be a manifestation of an underlying opportunistic process, infection-related malignancy, medications used for treatment, and immune restoration inflammatory syndrome [85]. In patients with migraine and HIV, triptans should be used cautiously as they may interact with antiretroviral therapies.

Management Considerations

Headache associated with systemic disorder may be due to new-onset headache, an exacerbation of pre-existing headache disorder, or treatment. When treating the systemic disorder does not resolve headache, the treatment approach should be based on the phenotype it most resembles and management of underlying primary headache disorders such as migraine (Fig. 1) [25]. Treatment may vary between acute and preventive pharmacological options depending on disability but are considered off label. Lifestyle (physical activity, sleep hygiene, dietary factors) or non-pharmacological interventions such as relaxation therapy, cognitive behavioral therapy, or neuromodulation devices should be considered.

Many complex systemic disorders that are associated with headache are often excluded in clinical trials; real-world studies are needed to determine safe and efficacious treatment options. Overlapping conditions can contribute to increased cumulative disease burden, and treatment of headache may improve outcomes and quality of life. A comprehension approach with coordination of care is essential.

Compliance with Ethical Standards

Conflict of Interest

Teshamae Monteith has received personal compensation for serving on advisory boards for Biohaven, Allegan/Abbvie, Lundbeck, Amgen, Teva, and Impel Neuropharmaceuticals. She has also served as a site principal investigator without direct compensation for Teva, Eli Lilly, Electrocore, Amgen, and Novartis. She has received grant support from Abbvie and Amgen and compensation for educational or writing activities from Massachusetts Medical Society, Neurodiem, and Medscape. Alexandra Cocores does not have any conflicts of interest.

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