

Ruling Out Secondary Headache

A careful history and high degree of suspicion are needed for accurate diagnosis.

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Secondary headache disorders are categorically recognized in the International Classification of Headache Disorders, 3rd edition (ICHD-3), with specific criteria related to establishing a temporal relationship between the implicated pathophysiology and the headache.¹

Establishing improvement of the headache with treatment is no longer a criterion in the ICHD-3 criteria, which allows for diagnosis earlier in the clinical course. Population-based data indicate that certain secondary headaches are somewhat common. For example, 72% of adults experience a hangover headache at least once in their life.² However, secondary headaches that are life-threatening are relatively less common, with significant neuroimaging abnormalities noted in only 1% of patients presenting to a clinic with headache and only 3% to 8% of patients presenting to the emergency department with a headache.³⁻⁵ Predictors of intracranial pathology include being over age 50, having abnormal neurologic examination findings, and having an acute-onset headache. Screening mnemonics, such as “SNOOP” (Box 1), appropriately incorporate these features to enable detection of secondary etiologies most likely to result in morbidity and mortality. However, identification of less imminently threatening secondary disorders (eg, headache attributed to hypothyroidism) remains critically important to successful management of patients with headache, including those who initially seem to have refractory headaches.

Clinical Appraisal of the Headache Syndrome

There are a limited number of headache phenotypes (eg, migraine-like, cluster-like), and description of secondary headaches often resembles that of migraine (eg, traumatic brain injury); tension-type headache (eg, glioma); or a trigeminal autonomic cephalalgia (eg, pituitary adenoma.)⁶⁻⁸ Therefore, recognition of a secondary headache requires deliberate appraisal of patient specific risk-factors, such as age and comorbidities; associated symptoms like pulsatile tinnitus; and specific presentation of the headache in relationship to the context in which it occurred, for example, a thunderclap headache during micturition. It is important

to elicit a detailed account of the circumstances surrounding the onset and progression of the headache. A pattern of daily headache that was daily from the initial onset requires a more thoughtful evaluation for secondary etiologies, such as cerebral venous sinus thrombosis, than a headache that was initially episodic and gradually became daily.⁹ How the features of headache evolved may also be important. For example, headache of spontaneous intracranial hypotension may lose the orthostatic component after several months.¹⁰ Clinical suspicion for a secondary headache cause based upon patient history should prompt a careful physical examination and diagnostic workup (Table). In some instances, patients may have a history of episodic migraine which has become chronic in a specific context, such as sleep apnea, hypothyroidism, or analgesic overuse.¹¹ In these cases, consider an independent headache diagnosis.

Red Flags and The SNOOP Mnemonic

The widely utilized mnemonic of “SNOOP” helps detect causes of secondary headache with significant morbidity and mortality (Box 1). It is important to ask specifically about these symptoms, as patients often do not volunteer them.¹² The presence of systemic disorders such as cancer, HIV, or symptoms of systemic disease, for example fever or weight

Box 1. The SNOOP mnemonic may catch potentially life-threatening headaches

- S**ystemic signs and disorders
- N**eurologic symptoms
- O**nset new or changed & patient >50 years old
- O**nset in thunderclap presentation
- P**apilledema, Pulsatile tinnitus, Positional provocation, Precipitated by exercise

loss, necessitate further evaluation of headache for causes such as meningitis, giant cell arteritis (GCA), or brain metastasis (Box 2). Neurologic symptoms or abnormal neurologic signs should prompt immediate evaluation for a focal nervous system lesion. Onset of a new or changed headache after age 50 should prompt consideration of malignancy and GCA. *Thunderclap onset* refers to a headache that peaks in intensity in less than 1 minute, often “less than 1 second,”¹³ but occasionally, patients report peak headache intensity within 5 minutes.¹⁴ Asking about the temporal features of the headache is more specific than asking if it was the “worst of [someone’s] life.” Finally, papilledema, pulsatile tinnitus, positional provocation and Valsalva- and/or exertion-related precipitants are further red flags. Headaches aggravated by lying flat might suggest intracranial hypertension, and those precipitated by orthostasis might suggest intracranial hypotension. Headaches precipitated by (in contrast to aggravated by, which is typical of migraine) valsalva require intracranial imaging to rule out structural pathology, such as a mass lesion or Chiari-malformation. Headache precipitated by exertion should prompt consideration for referred pain of cardiac origin, especially in the setting of vascular risk factors and older age.¹⁵

Yellow Flags and a Hypothesis-Driven Physical Examination

It is also important to be aware of relative yellow flags, features that would not be unexpected for a primary headache disorder, but could also be clues to a secondary pathology. One example is the headache chronotype. Morning-predominant headaches may indicate a sleep disorder (eg, restless leg syndrome, which is also known as Willis-Ekbom disease). Headaches with nocturnal waking can be seen with medication-overuse headache (MOH), as the analgesic wears off during sleep; cervicogenic pathology, as the patient extends their neck with recumbency; or elevated intracranial hypertension. Side-locked headaches are not uncommon in primary headache disorders but can also raise suspicion for a structural pathology. Ear pain, if a predominant feature, has a diverse differential diagnosis, including cranial, cervical and thoracic visceral pathology.¹⁶

A hypothesis-driven physical exam can provide important clues to diagnosis. The examination of a patient with headache should include an assessment of the vital signs, a neurologic examination with direct funduscopy, and a focused head and neck examination. Abnormalities of oral temperature may be seen in a variety of conditions such as GCA and hypothyroidism. Moderate to severe hypertension raises the possibility of hypertensive encephalopathy, and orthostatic hypotension can be a cause of secondary headache. An elevated body mass index may raise suspicion for idiopathic intracranial hypertension. On the neurologic exam, papilledema,

TABLE. FINDINGS INDICATIVE OF SECONDARY CAUSE OF HEADACHE.	
FINDING	RULE OUT
Vital Signs	
Elevated temperature	Infectious causes, GCA
Elevated blood pressure	PRES, CVD
Tachycardia	Orthostatic hypotension, POTS
Bradycardia	Hypothyroidism
Body mass index > 25	Idiopathic intracranial hypotension
General	
Wasted appearance	HIV, Malignancy GCA
Joint hypermobility Skin laxity	Intracranial hypotension Intracranial aneurysm Cervical artery dissection
Hair loss, Dry skin, Edema, Hoarse voice	Hypothyroidism
Diaphoresis, Rhinorrhea, Mydriasis, Restlessness, Yawning, Tremor	Opioid withdrawal
Cardiac	
Temporal artery tenderness/ induration Diminished/asymmetric pulse Aortic regurgitation	GCA
Neurologic	
Papilledema	Intracranial hypertension
Horner’s sign	Carotid artery dissection
Trigeminal sensation loss	Trigeminal neuropathy
Abducens paresis	Intracranial hypertension Other focal lesion
Oculomotor paresis and/or mydriasis	Intracranial aneurysm, ION Other focal lesion
Head and Neck	
Trochlear tenderness aggravated by vertical duction	Trochlear headache
Tympanic vesicles	Herpes zoster
Hard papule near frenulum or adjacent to 2nd upper molar	Sialolithiasis
Restricted neck rotation	C2/3 facet arthropathy
Pericranial and/or occipital nerve tenderness	Trigeminal branch or occipital neuralgia
Limited TMJ range of motion	TMJ syndrome

Abbreviations: CNS, central nervous system; CVD, cerebrovascular disease; GCA, giant cell arteritis; ION, ischemic ocular neuropathy; POTS, postural orthostatic tachycardia syndrome; PRES, posterior reversible encephalopathy syndrome; TMJ, temporomandibular joint.

Box 2. A 64-year-old woman with multifactorial intracranial hypertension

History

A 64-year-old woman with a past medical history of stage IV adenocarcinoma of the lung presented for further evaluation of a 3-month history of new daily-from-onset headaches. The headaches began when she was hospitalized for a superior vena cava syndrome and right internal jugular thrombosis (IJT). Headaches were described as severe, bifrontal, throbbing, and aggravated by lying flat. Head pain was associated with nausea, intermittent horizontal diplopia, and right-sided pulsatile tinnitus. She was treated with stent placement and anticoagulation, with rapid improvement in headache intensity. The positional headaches and right-sided pulsatile tinnitus were noted to have become progressively intense over the 3 weeks prior to presentation. An MRI of the head with and without gadolinium contrast showed mild enlargement of the third and lateral ventricles, suggestive of early communicating hydrocephalus. At the time of consultation, her examination disclosed bilateral papilledema, but no recurrent facial or upper extremity edema. A repeat MRI showed increasing ventricular enlargement. MR venography results were normal. Lumbar puncture was performed demonstrating an opening pressure in excess of 50 cm H₂O, with normal fluid

indices, including cytology. Catheter angiography was urgently performed and ruled out recurrent IJT. A diagnosis of leptomeningeal carcinomatosis was considered clinically as the most likely explanation. She was admitted to hospice, where she died.

Comment

The clinical history of a new daily-from-onset headache in an older adult, especially in the context of systemic malignancy, is immediately concerning for a secondary etiology. The additional clinical features of aggravation with lying supine, pulsatile tinnitus, diplopia, and papilledema all suggest an elevation in intracranial pressure. The evaluation of intracranial hypertension involves a careful search for a mass lesion, cerebral venous sinus thrombosis, or a leptomeningeal process. The physician suspected that this patient's intracranial hypertension resulted from sequentially impaired hematologic (IJT) and cerebrospinal fluid (leptomeningeal carcinomatosis) dynamics. Intracranial hypertension is thought to be uncommon in patients with IJT, but has been reported in patients with both unilateral and bilateral obstructions.^{17,18} The case also highlights the uncommon possibility of an extracranial mechanism as a potential cause of and contributor to intracranial hypertension.

Horner's sign, extraocular misalignment, and trigeminal sensorimotor impairment are of particular importance. The head and neck examination should include assessment of cervical range and temporomandibular joint range of motion, pericranial and occipital nerve tenderness, and temporal artery abnormalities. Headache syndromes due to a cranial neuralgia should be considered when there is a focal topography to the pain syndrome in the distribution of a sensory nerve.

Cranial neuralgias may present with a non-lancinating, continuous-type pain requiring specific landmark palpation to aid in the diagnosis.¹⁹ Pain elicited with palpation over the trochlear region may be due to infratrochlear neuralgia or a trochlear headache, the latter being distinguished by aggravation with vertical ductions.^{20,21} Trochlear headache may be due to trochleitis, which is not uncommonly secondary to inflammatory and/or neoplastic pathologies.²⁰

Diagnostic Evaluation of Suspected Secondary Headache Syndromes

The diagnostic evaluation of a suspected secondary headache syndrome should also be hypothesis-driven, noting that incidental findings are not uncommon.²² In select situations, the specific next best test is algorithmic. For example, the American College of Emergency Physicians specifically recommends a CT scan in the evaluation of thunderclap headache, and following that up with a lumbar puncture, if CT findings are negative.²³ In general, as recommended

by the American Headache Society, with the exception of emergency scenarios, MRI is preferable to CT.²⁴

Apart from overt radiographic lesions such as stroke or tumor, radiologists might not comment on subtle radiographic findings of papilledema²⁵ or CSF pressure syndromes,^{10,26} which in certain cases now form components of diagnostic criteria. Neurologists evaluating patients with headache and a prior diagnosis of Chiari malformation should consider the possibilities of both intracranial hypertension and hypotension, where tonsillar descent can be observed. In intracranial hypertension, flattening of the posterior sclera, widening of the optic nerve subarachnoid space, vertical tortuosity of the optic nerve, partial or empty sella, and a protruding optic nerve papilla with or without enhancement can all be observed (Figure). With the exception of enhancement, these features carry a false-positive rate of approximately 5%. Bilateral tapering of the transverse sinuses is also characteristic. If there is suspicion for intracranial hypotension, the characteristic finding of pachymeningeal enhancement would be overlooked without gadolinium. It is important to also recall that a secondary pain generator may not be appropriately imaged with a MRI of the head if the pain syndrome localizes to either the V2/V3 or C2/C3 dermatomes, where dedicated imaging of the face and/or neck should be considered.²⁷

Laboratory testing may be useful in the assessment of suspected GCA, hypothyroidism, pheochromocytoma, and pre-eclampsia (ie, proteinuria).²⁸

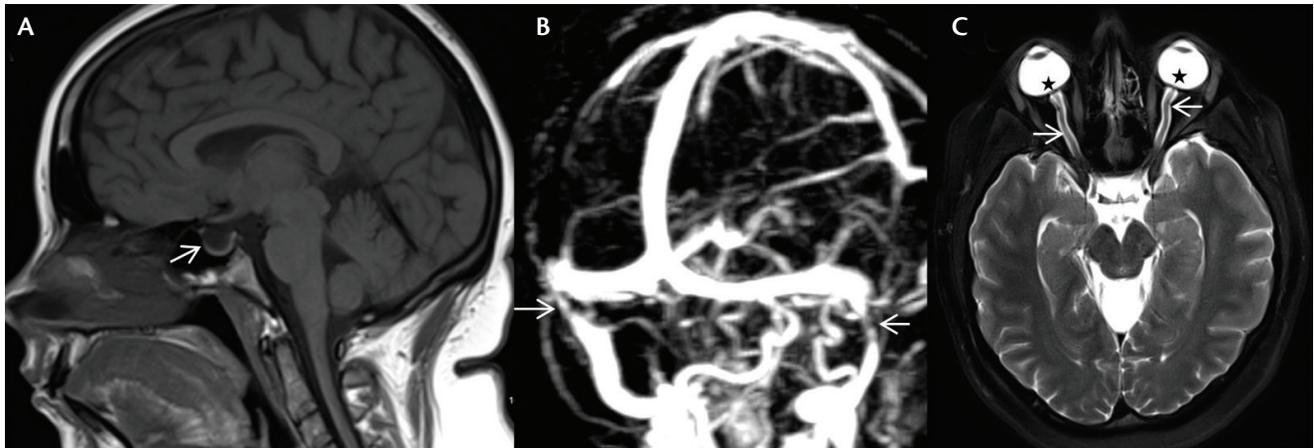


Figure. Imaging findings in idiopathic intracranial hypertension. Four radiographic features can suggest the diagnosis of IIH in the absence of papilledema²⁶: Empty sella, arrow (A), bilateral transverse sinus stenosis, arrows (B), and flattening of the posterior globe (stars) and distention of the perioptic subarachnoid space, arrows (C).

Selected Secondary Headache Syndromes

Giant Cell Arteritis

Giant cell arteritis (GCA) requires a high index of suspicion in patients over 50 years old with new-onset or changed headache pattern that should prompt ordering of an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).²⁹ Approximately 15% to 20% of patients will develop visual loss, which occurs only rarely in treated patients. Serum inflammatory markers poorly correlate with disease activity. Recently, a prospective cohort evaluating relapses in GCA found that inflammatory markers were normal in approximately 20% of patients at the time of relapse.³⁰ A median of 2 (range, 1-6) symptoms were present at the time of relapse, most commonly headache and polymyalgia rheumatica. Headache was only rarely seen (3 of 128 patients) as an isolated symptom at relapse and never in the absence of elevated inflammatory markers. Therefore, treatment decisions should not rely on ESR and CRP alone.

On the other hand, interleukin-6 (IL-6) levels appear to be much more strongly associated with disease activity in GCA.²⁹ Recently, a large phase 3 trial demonstrated efficacy and safety of tocilizumab (TCZ), a humanized monoclonal antibody targeting IL-6.³¹ In this study, the primary outcome of 52-week glucocorticoid-free remission in 53% to 56% of patients was achieved with either weekly or biweekly subcutaneous injections of TCZ plus tapered prednisone compared to 14% to 18% of patients treated with placebo plus tapered prednisone. The overall rates of adverse events were similar between trial arms. Following this trial, TCZ became the first GCA treatment approved by the Food and Drug Administration (FDA).

Patients with GCA are often managed longitudinally by rheumatologists with neurologists and a headache specialist playing a consulting role. If there is complex headache his-

tory, clarifying these nuances to the rheumatologist can be helpful, in order to avoid falsely diagnosing a GCA relapse.

Headache Attributed to Hypothyroidism

Headache attributed to hypothyroidism (HAH) is recognized in the ICHD-3 as a headache that develops in temporal relation to onset of hypothyroidism, and it either worsens in parallel or improves with treatment. The headache should have at least 1 feature of being bilateral, nonpulsatile, and/or constant over time.¹ A prospective study of 213 patients with recent-onset hypothyroidism for 1 year found that 73 (34%) patients reported HAH, and 140 (66%) did not.³² Among those with HAH, there was higher incidence of migraine history (53% vs 38%, $P = 0.04$). Signs and symptoms of hypothyroidism were similar in both groups, and no differences were seen between those with clinical vs subclinical hypothyroidism. Of the 64 patients who completed the 12-month follow-up period, 50 (78%) reported improvements in headache with levothyroxine, with no difference among those with clinical versus subclinical hypothyroidism. The study highlights an important and likely overlooked diagnostic and therapeutic consideration among those with worsening migraines and signs and symptoms of hypothyroidism (eg, somnolence, weight gain, dry skin, edema).

Although hypothyroidism is typically managed by primary care physicians, specific education may be needed regarding the association with headache, as patients with subclinical hypothyroidism may not otherwise be offered treatment.

Medication-Overuse Headache

The diagnostic criteria for MOH have been simplified in ICHD-3. Currently, a headache occurring on at least 15 days of each month in a patient with a pre-existing headache disorder, along with regular overuse for at least 3 months

of at least 1 drug that can be taken for acute treatment of headache is required.¹ A final criterion of the headache “not being better accounted for by another ICHD-3 diagnosis” is where a clinical assessment by the practitioner becomes especially important. In contrast to previously published criteria, establishing either parallel worsening of headaches with medication overuse and/or resolution with withdrawal is no longer formally required. Not surprisingly, the revised ICHD-3 criteria are associated with improved sensitivity.³³ However, this emphasis on sensitivity has not been uniformly welcomed, citing that not all patients improve with withdrawal of the overused drug, and that overdiagnosis of MOH may lead to unnecessary suffering and increased stigmatization and blame toward patients.³⁴ In practice, the clinician must always weigh the possibilities of the overused analgesic being the culprit versus not. Anecdotally, attribution of MOH to simple analgesics such as nonsteroidal anti-inflammatory drugs, may be overdiagnosed, as these drugs are known to exert preventive properties against the development of chronic migraine and in the treatment of episodic migraine.^{35,36} Conversely, combination analgesics containing caffeine appear to be commonly implicated. Remarkably, these over-the-counter analgesics have been marketed aggressively for acute migraine treatment without sufficient warning on labels regarding risk of MOH.

In December 2017, the FDA responded positively to a citizen petition written and submitted by the author and Drs. Robert Shapiro, Robert Cowan, William Young, and Ivan Garza. Citizen petitions are an opportunity for public engagement in federal decision making, where individuals or groups can submit regulatory requests to the FDA. The submitted petition becomes available for public comment, and in our case, a review process in excess of 2.5 years. Labels for these products will now include the statement: “Medication overuse headache warning: Headaches may worsen if this product is used for 10 or more days per month” (<https://www.regulations.gov/document?D=FDA-2015-P-0633-0020>). This approval comes in the context that simple advice may provide effective primary prevention and treatment for MOH.³⁷⁻³⁹

Currently underway is the Medication Overuse Treatment Strategy Trial, which is a Patient-Centered Outcomes Research Institute-funded trial to compare effectiveness of migraine prophylactic therapy with or without discontinuation of an overused analgesic in patients with chronic migraine and medication overuse. The study aims to enroll 1,280 subjects and be completed by January 2021.

Patients with MOH should be followed closely by the headache specialist with more rigidly scheduled follow-up appointments to promote treatment adherence and avoid relapse. Specific communication regarding the diagnosis of MOH is often needed if the overused analgesic is being prescribed by another physician. ■

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