Diagnosing Serious "Cannot Miss" Causes of Non-traumatic Headache—Thunderclap Headache and Beyond

Nicole M. Dubosh, MD[a,b,*], Jonathan Edlow, MD[a,b]

KEYWORDS

• Acute headache • Thunderclap headache • Subarachnoid hemorrhage
• Lumbar puncture

KEY POINTS

- Most emergency department patients who present with a headache have a primary, non-serious cause that can be treated and managed in the outpatient setting.
- A small proportion of emergency department patients with headache have a serious etiology, which if missed, can result in significant morbidity and mortality.
- It is imperative for emergency physicians to identify through a careful history, consideration of epidemiologic factors, and physical examination which patients require extensive testing to identify a serious cause of headache.

INTRODUCTION

Headache accounts for 2% to 3% of emergency department (ED) visits.[1] Most of these patients have primary headache disorders such as tension-type headache and migraine; however, a small minority have "cannot miss" secondary causes of headache that while oftentimes treatable, can result in poor outcomes if not identified and managed early (**Box 1**).[2] Of all ED patients with headache, 3% to 7% have a "cannot miss" diagnosis.[3,4] The majority of serious diagnoses include subarachnoid hemorrhage (SAH), other types of intracranial hemorrhage (ICH) including subdural hematoma (SDH), strokes, and meningitis.

These data illustrate the classic emergency medicine "needle in the haystack" phenomenon—identifying patients with common presenting symptoms who have

[a] Department of Emergency Medicine, Beth Israel Deaconess Medical Center, One Deaconess Road, Rosenberg 2, Boston, MA 02215, USA; [b] Department of Emergency Medicine, Harvard Medical School, Boston, MA, USA
* Corresponding author.
E-mail address: ndubosh@bidmc.harvard.edu

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Abbreviations

ACEP	American College of Emergency Physicians
CO	carbon monoxide
CSF	cerebrospinal fluid
CT	computed tomography
CVST	cerebral venous sinus thrombosis
ED	emergency department
GCA	giant cell arteritis
ICH	intracranial hemorrhage
ICP	intracranial pressure
IIH	idiopathic intracranial hypertension
LP	lumbar puncture
ONSD	optic nerve sheath diameter
PCR	polymerase chain reaction
POCUS	point-of-care ultrasound
PRES	posterior reversible encephalopathy syndrome
RBC	red blood cell
RCVS	reversible cerebral vasoconstriction syndrome
SAH	subarachnoid hemorrhage
SDH	subdural hematoma
SIH	spontaneous intracranial hypotension

Box 1
Causes of "cannot miss" causes of acute headache

Vascular Conditions
- Subarachnoid hemorrhage
- Reversible cerebral vasoconstriction syndrome
- Acute ischemic and hemorrhagic stroke
- Cranio-cervical artery dissection
- Cerebral venous sinus thrombosis
- Hypertensive crisis
- Posterior reversible encephalopathy syndrome

Infectious causes
- Meningitis
- Encephalitis
- Brain abscess
- Epidural empyema

Mass lesions
- Tumors and cysts
- Subdural and epidural hematoma
- Pituitary apoplexy
- Brain abscess and epidural empyema

CSF pressure-related causes
- Idiopathic intracranial hypertension
- Spontaneous intracranial hypotension

Miscellaneous
- Giant cell arteritis
- Carbon monoxide poisoning
- Narrow angle closure glaucoma

low-frequency, high-risk diagnoses. This article focuses on the approach to ED patients presenting with headache in order to minimize misdiagnosis of patients with serious secondary causes.

MISDIAGNOSIS AND GENERAL APPROACH

Misdiagnosis or delayed diagnosis can result in poor patient-centered outcomes. One potential strategy to eliminate misdiagnosis would be to "test all" patients with brain imaging and lumbar puncture (LP). This approach is neither logistically feasible nor intellectually desirable and might even lead to worse outcomes from increased radiation exposure, and adverse effects from evaluating incidental and LP results. A selective approach that leverages history, epidemiologic context, and physical examination to identify patients at higher risk for serious causes of headache is the best approach. Some general considerations include:

Red Flags

Clinicians need to maximize the clinical information in order to thoughtfully decide which patients need evaluation. Most patients simply require treatment of symptoms and appropriate follow-up. Elements of the history including epidemiologic context, supplemented by the physical examination, are key in deciding whether to do additional diagnostic tests in the ED.[5] These elements are often referred to as "red flags" (**Table 1**).

Papilledema

Although we believe that examining for papilledema is best practice, looking for it using an ophthalmoscope can no longer be considered "standard of care."[6] Reasons included infrequent use, lack of training, poor confidence in the findings, technical difficulties, and the frequent need for pharmacologic dilation of the pupil.[7] When fundoscopy is performed, papilledema is rarely found.[8]

Point-of-care ultrasound (POCUS) of the optic nerve sheath diameter (ONSD) is an alternative method for detecting elevated intracranial pressure (ICP) and a skill that many emergency physicians possess. Using a reference standard of physical measurement of the ICP, the area-under-the-curve for POCUS measurements of the ONSD is 0.94.[9] POCUS is now widespread in most EDs and its use should be considered as a surrogate for detecting papilledema.

Response to Analgesics

The American College of Emergency Physicians (ACEP) clinical policy emphasizes that favorable response to analgesic medications does not equate with a benign diagnosis.[10] In one report, patients with such diverse causes of headache including brain tumors, cervical artery dissection, cerebral venous sinus thrombosis (CVST), SAH, ICH including SDH had substantial or complete pain relief after various analgesics.[11] Various classes of "analgesics" were used including non-steroidal anti-inflammatory agents and triptans which should not be considered migraine-specific. While it is important to adequately treat pain, its relief from medications should not be used as evidence of a benign etiology.

Limitations of Brain Imaging

Computed tomography (CT) has important limitations. For instance, a CT will nearly always be normal in patients with giant cell arteritis (GCA), often be normal in reversible cerebral vasoconstriction syndrome (RCVS) and may be normal in late-presenting

Table 1
Red flags and situations suggesting the need for evaluation beyond history and physical examination

Red Flag	Significance
History—headache characteristics	
Rapid onset	Rapid (thunderclap) onset suggests a specific group of diagnoses, most notably SAH and RCVS
Evolution over time	Progressive increase over days or weeks suggests some type of mass lesion or infection
Headache worsens with standing up	Spontaneous intracranial hypotension (or post-dural puncture headache)
Headache worsens with lying down, cough, or Valsalva	Brain tumor, Chiari malformation
Headache worsens with bright light exposure	Acute narrow angle closure glaucoma
Other neurologic symptoms also present	Serious secondary diagnoses
Recent head or neck trauma	Subdural hematoma or arterial dissection
History of fever	Meningitis, encephalitis, brain abscess, or subdural empyema
Changes in pre-existing headache pattern	Any secondary cause in a patient with a pre-existing primary headache diagnosis
Epidemiologic context	
Increasing age	ICH, GCA
History of systemic cancer	Metastatic tumor
Pregnant or post-partum	RCVS, CVST, PRES, pre-eclampsia/eclampsia, post-dura puncture headache, pituitary apoplexy
Immunocompromised state	Opportunistic infections
Hypercoagulable state	Cerebral venous sinus thrombosis
Obesity and female sex	Idiopathic intracranial hypertension
Anticoagulant use	ICH
Clustering of multiple cases	Carbon monoxide poisoning, or rarely meningitis
Recent lumbar puncture	Post-dural puncture headache
Known pituitary adenoma	Pituitary apoplexy
Family history of cerebral aneurysms or SAH	SAH

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Table 1
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Red Flag	Significance
Physical examination	
Fever on examination	Same as history of fever
Hypertension	Hypertensive crisis, PRES, preeclampsia, or any pathology causing elevated ICP
Abnormal temporal artery	GCA
Meningismus	Meningitis or SAH
Any new neurologic deficit	Any secondary cause
Extraocular muscle abnormalities	3rd nerve palsy—aneurysm 6th nerve palsy—elevated ICP or IIH Multiple cranial nerve lesions—cavernous sinus pathology
Dilated pupil	Posterior communicating artery aneurysm
Fixed misposition pupil, limbal flush, and corneal edema	Acute narrow angle closure glaucoma
New ptosis	Horner syndrome
Meiosis	Horner syndrome
Horner syndrome	Carotid dissection, lateral medullary stroke
Fundoscopic ONSD POCUS shows papilledema	Papilledema or absent venous pulsations—elevated ICH, subhyaloid hemorrhage—SAH or ICH

Abbreviations: CVST, cerebral venous sinus thrombosis; GCA, giant cell arteritis; ICH, intracranial hemorrhage; ICP, intracranial pressure; ONSD, optic nerve sheath diameter; POCUS, point-of-care ultrasound; PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; SAH, subarachnoid hemorrhage.

$SNOOP_{10}$

Note: Some authors have proposed $SNOOP_{10}$ to as an aid to remembering headache red flags:[101]

S, systemic symptoms including fever; N, neoplasm history or neurologic deficit; O, onset (sudden); O, older age (different studies use different age cut-offs); P1, pattern change compared to prior episodes; P2, positional headache; P3, precipitated by sneezing, coughing, or exercise; P4, papilledema; P5, progressive headache; P6, pregnancy or post-partum state; P7, painful eye with autonomic features; P8, post-traumatic; P9, pathology of the immune system; P10, painkiller overuse.

cases of SAH. MRI is as good or better than CT for most pathologies but MRI is not perfect, nor are the clinicians interpreting them. Nearly 7% of patients with acute ischemic stroke will be MRI negative with a strong predilection for the posterior circulation.

Thunderclap Headache

One prospective case series of 4536 ED patients with headache reported that 644 (14.2%) patients had a thunderclap headache,[12] which the International Headache Society defines[13] as a headache that

1. Is severe in intensity,
2. Abrupt in onset, peaking in intensity in less than1 minute,

3. Lasts longer than 5 minutes, and
4. Cannot be accounted for by another diagnosis.

This rigid time criterion is problematic. Patients may misjudge brief periods of time. Would you not evaluate a patient who describes a severe headache reaching peak intensity in 3 minutes? 5 minutes? 20 minutes? Furthermore, in a series of 2131 neurologically intact ED patients with thunderclap headache (defined as a severe headache peaking within 1 hour), of the 6 of 132 SAH patients with a SAH reported the time to peak intensity being 1 hour.[14] For these reasons, we evaluate patients with acute onset severe headaches without using a rigid time cut-off.

CEREBROVASCULAR CAUSES

Subarachnoid Hemorrhage

However one defines thunderclap headache, there are many causes (**Table 2** and **Fig. 1**), the most serious of which is SAH. Of non-traumatic SAHs, 80% are caused by ruptured cerebral aneurysms, 10% are from venous bleeding where the blood is localized to the area anterior to the pons, called perimesencephalic SAH, and the rest are due to a variety of vascular causes such as Moya-Moya, CVST, arteriovenous malformations and others.[15]

Studies of neurologically intact ED patients with thunderclap headache have found the incidence of SAH to be approximately 6% (**Table 3**).[12,16,17] When non-SAH diagnoses were reported, 85% to 90% of patients had benign causes. While a full evaluation for SAH is indicated, most patients with thunderclap headache have benign causes.[12]

Missed or delayed diagnosis of aneurysmal SAH can lead to worse patient outcomes due to rebleeding, vasospasm, and hydrocephalus.[18] Misdiagnosis rate ranges from 5% to 20% and mostly occur in lower acuity patients,[19] who otherwise have the best outcomes when correctly diagnosed. Another 2018 study queried a Medicare database.[20] They estimated "missed diagnostic opportunities"—ED visits in which patients were discharged but later came back with a SAH. They found that 3.5% of SAH patients had a prior visit in the 45 days prior to the SAH hospitalization, in which the observed discharges exceeded the expected number. This study, however, cannot tell us if these patients could have been diagnosed using standard protocols or if some presented in a highly atypical manner.

Who to evaluate for subarachnoid hemorrhage?

The Ottawa SAH rule has been developed[14] and validated[21] to help clinicians decide which ED patients with headache should be evaluated for SAH (**Box 2**). The rule approaches 100% sensitivity but has poor specificity. The Ottawa SAH rule only targets SAH, not other serious secondary causes of headache and one still needs to consider individual patient characteristics (eg, family history of SAH) or atypical presentations (**Table 4**).

Once the decision to evaluate for SAH is made, what is the evaluation? All patients with thunderclap headache should have a brain CT.[10,22] In interpreting the results of any diagnostic test for SAH, it is important to recognize that timing of the test is critical. The circulation of cerebrospinal fluid (CSF) is brisk. This leads to a rapid dilution of blood in the subarachnoid space and decreases the sensitivity of detecting blood on CT over time.

Brain imaging

Non-contrast CT diagnoses most patients with SAH, and essentially all patients with SAH who are scanned within 6 hours of symptom onset (**Fig. 2**).[22–24] There are

Table 2
Causes of thunderclap headache

Condition	Comments
Common Causes	
Subarachnoid hemorrhages	Can be isolated headache or neck pain, often with vomiting or transient loss of consciousness. 40% will have headache with an otherwise normal physical examination.
Reversible cerebral vasoconstriction syndrome[a]	Multiple short-duration (several hours) thunderclap headaches, usually with some precipitating trigger. Physical examination may be normal
Migraine, cluster headache and primary thunderclap headache[a]	These are diagnoses of exclusion that should never be made without an extensive evaluation for secondary causes
Uncommon causes	
Arterial dissection[a]	Occurs in ~ 3–5% of carotid dissections and ~ 10% of vertebral dissections. Physical examination may be normal
Cerebral venous sinus thrombosis[a]	Occurs in ~10% of venous sinus thromboses. Physical examination may be normal
Acute stroke[a]	Can occur with ischemic (usually posterior circulation) or hemorrhagic stroke. Usually with a neurologic deficit
Acute subdural hematoma	Other findings are usually present
Retroclival hematoma	Cranial neuropathies may be present
Hypertensive encephalopathy[a]	Associated with elevated blood pressure and evidence of end-organ dysfunction (not any specific blood pressure)
Posterior reversible encephalopathy syndrome[a]	Usually not thunderclap. Seizure precedes the headache. Visual symptoms are common. Most cases have hypertension
Pre-eclampsia/eclampsia[a]	Can occur post-partum
Pituitary apoplexy[a]	Often in setting of a preexisting pituitary adenoma, often with ophthalmoplegia and bitemporal hemianopsia. Physical examination may be normal
Spontaneous intracranial hypotension[a]	Thunderclap headache in ~15% of cases. Headache is usually positional (worse standing, better lying down)

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Table 2
(continued)

Condition	Comments
Sphenoid sinusitis	
Rare causes, mostly described in isolated case reports	
Meningitis or encephalitis	
Unruptured aneurysm[a]	Rare, from acute expansion, thrombosis or dissection of a preexisting aneurysm
Colloid cyst of the third ventricle	Often a history of multiple prior headaches over years
Spontaneous retroclival hematoma	
Giant cell arteritis[a]	Most patients are > 60 y of age
Myocardial infarction[a]	
Aortic dissection[a]	

[a] These causes may be associated with a normal non-contrast brain CT scan and lumbar puncture depending on timing of CT (ischemic stroke) or if the opening pressure is measured on the lumbar puncture (spontaneous intracranial hypotension).

important caveats when applying the "6 hour rule" (**Box 3**).[25] For patients who are scanned after 6 hours, or those for whom one of those caveats apply, controversy exists as to the next diagnostic step. The time-honored, traditional recommendation is to do an LP.[20] The combination of a negative CT and normal CSF excludes the diagnosis of SAH.[26]

Two recent studies representative of ED populations (incidence of SAH 5.3% and 6.5%) reported sensitivities of CT at 24 hours from symptom onset.[16,17] One prospective study of 3268 consecutive ED patients with headaches that reached peak intensity within 1 hour showed an overall CT sensitivity for patients scanned more than 6 hours after symptom onset to be 94.5%.[17] The sensitivities at different time intervals were

- 6 to 12 hours, 99.5%,
- 12 to 18 hours, 94.1%, and
- 18 to 24 hours, 75.0%.

The second study was a retrospective study of 3227 consecutive patients with acute headache "suspicious for SAH". In the 3071 patients with negative CT, 2 of 39 (5%) scanned between 6 and 24 hours were diagnosed by LP.[16] Furthermore, in the original derivation study of the 6 hour rule, 17 of 119 patients with SAH were missed by CT when imaged beyond 6 hours, resulting in a the sensitivity for CT for these patients of 85.7%.[27] It is also clear that occasional interpretation errors by radiology trainees, general radiologists and even neuroradiologists occur.[27–29] For all these reasons, we do not support extending the time window for excluding a SAH on CT scans beyond 6 hours from symptom onset.

Some studies differentiated non-aneurysmal from aneurysmal SAH. Most of these are perimesencephalic SAHs (**Fig. 3**) caused by venous bleeding. Although the outcomes of this form of SAH are better than those with aneurysmal SAH, some of these patients do have complications, with approximately 14% having acute hydrocephalus that occasionally requires drainage.[30] Angiographic vasospasm occurs although

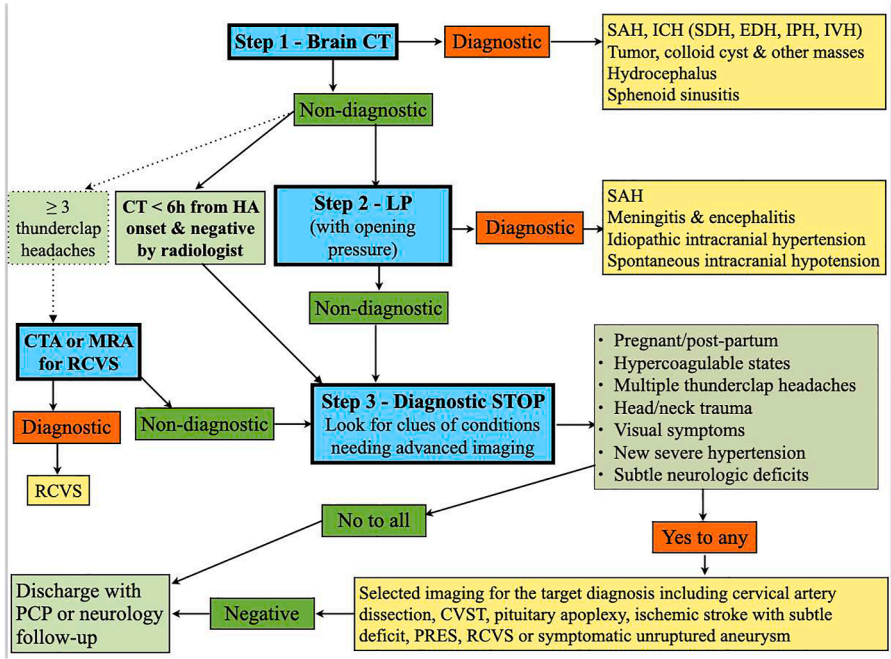

Fig. 1. Diagnostic algorithm for thunderclap headache. *Step 1*: The first diagnostic step is non-contrast brain CT. Although ischemic stroke is often listed in the differential diagnosis of TCH, this would be associated with neurologic deficits. Sphenoid sinusitis is a rare cause of TCH that may be found on CT. *Step 2*: For most patients, the next step is LP, but there are two exceptions. The first group is patients whose CT is negative within 6 hours of headache onset. In these early presenting patients, CT is nearly perfect sensitivity and one can directly go to Step 3. The other exception is patients who present with ≥ TCHs, in which case, go directly to CTA or MRA of the head to diagnose RCVS (remembering that angiography can be falsely negative in the first week). *Step 3*: If there is no diagnosis yet, perform a diagnostic "STOP" to intentionally consider other less common but important conditions that require advanced imaging to diagnose. Abbreviations: CT, computerized tomography; CTA, computed tomographic angiography; CVST, cerebral venous sinus thrombosis; EDH, epidural hematoma; ICH, intracranial hemorrhage; IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage; LP, lumbar puncture; MRA, magnetic resonance angiography; PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; TCH, thunderclap headache. (*Adapted from* Ann Emerg Med, 2018 Nov;72(5):602 to 610.https://doi.org/10.1016/j.annemergmed.2018.06.009. Epub 2018 Jul 27.)

delayed cerebral ischemia is rare. Hyponatremia is not uncommon.[31] Patients who are on anticoagulants require decisions made about discontinuing and restarting them. For these reasons, diagnosing perimesencephalic SAH is still important.

Finally, although far less available in most EDs, because the accuracy of MRI is superior to CT in less acute bleeds, MRI can be used in place of CT,[32] especially in patients where LP is not feasible.

How to Proceed in Computed Tomography or MRI-negative Patients

Computed tomography followed by computed tomographic angiography

There has been a gradual shift away from the CT/LP diagnostic approach and toward a CT/computed tomographic angiography (CTA) approach. A fundamental difference

Table 3
Frequency of SAH in neurologically intact ED patients with non-traumatic acute-onset severe headache

Study & Year	Definition of Acute-Onset Severe HA	N (SAH)/N total in Study	Percent with SAH
Roberts et al,[12] 2022	Severe headache of immediate or almost immediate onset to peak intensity	23/644	3.5
Aaseth et al,[16] 2024	New sudden onset headache suspected to be SAH	170/3227	5.3
Perry et al,[14] 2013	Headache reaching maximal intensity <1 h	132/2131	6.2
TERN 2024	Headache reaching maximal intensity <1 h	237/3663	6.5
Perry 2008	Headache reaching maximal intensity in < 1 h	61/592	10.3
Total pooled		623/10,257	6.1

Abbreviations: ED, emergency department; SAH, subarachnoid hemorrhage.

in the two methods is that the LP diagnoses SAH whereas the CTA diagnoses aneurysms. Advantages of a CT/CTA approach include clinician convenience, reduction in ED length-of-stay, less pain and anxiety for the patient. Disadvantages include radiation and contrast nephropathy, and most importantly, diagnosing asymptomatic aneurysms.[33]

Approximately 3% of the adult population has cerebral aneurysms yet only 0.25% (1 in 400) will rupture.[34] If a CTA shows an aneurysm, there is no way to determine if it has bled without doing an LP. Most of these patients will undergo treatment by endovascular coiling or open surgical clipping, procedures that both have some intrinsic risks. For patients who do not receive definitive treatment, patient anxiety and possible insurance eligibility issues exist.

For these reasons, we prefer a CT/LP approach. The most recent American Heart Association/American Stroke Association guidelines also recommend this approach (Class 1, Level B).[35] However, the ACEP Clinical Policy has a weak recommendation

Box 2
The Ottawa SAH rule

Age ≥40 y

Neck pain or stiffness by history

Witnessed loss of consciousness

Onset during exertion

Thunderclap headache (instantly peaking pain)

Limited neck flexion on examination

If any of these 6 variables is present, the patient should be evaluated for subarachnoid hemorrhage.This clinical decision rule is only meant for SAH, not other serious secondary causes of headache. Some patients who do not have any of the 6 variables may also be evaluated for SAH. For example, a patient with a prior SAH or a first degree relative who had a SAH.*Abbreviation*: SAH, subarachnoid hemorrhage.

Table 4
Atypical presentations of subarachnoid hemorrhage

Presentation	Comments
Headache improves or resolves after analgesic administration	Pain relief is important and indicated; however, pain resolution should not be used to exclude a serious cause of headache, including SAH.
Viral syndrome presentation	Days after a minor bleed, meningeal irritation may cause HA, neck stiffness and low-grade fever, mimicking a viral syndrome or viral meningitis. This is one reason to do an LP on patients with question viral meningitis.
Prominent nausea and vomiting	Mimics a GI diagnosis. Avoid diagnosing gastroenteritis in the absence of diarrhea.
Prominent neck pain (and rarely, back pain)	Some patients describe severe, acute-onset neck (or back) pain that can mimic a musculoskeletal problem. The key is a sudden onset.
New quality HA in setting in patients with a migraine or tension-type HA syndrome	Always ask patients who have a prior HA diagnosis about how the current HA is the same as or different from prior episodes. The HA of a SAH is almost always qualitatively different.
Syncope and mild head injury	In the SAH patient who has syncope and hits their head, small amounts of SAH on a CT scan may be incorrectly attributed to the head injury.
Focus on cardiovascular effects of SAH	Some patients will have severe hypertension or ECG abnormalities that distract clinicians' attention from the HA.

Abbreviations: ECG, electrocardiogram; GI, gastrointestinal; HA, headache; LP, lumbar puncture; SAH, subarachnoid hemorrhage.

that either approach is reasonable, but a shared decision-making discussion with the patient is important in whichever approach is used.[23] The CT/CTA approach is preferable if LP is unsuccessful or refused by the patient, or if an LP contraindication (eg, coagulopathy) exists. If an aneurysm is found, neurosurgery should be consulted no matter how small the lesion. Although smaller aneurysms are less prone to rupture than larger ones, smaller ones are far more common.

CT followed by LP and CSF analysis

Performing an LP has other potential advantages. Measuring the opening pressure allows diagnosis of the occasional patient with idiopathic intracranial hypertension (IIH) or spontaneous intracranial hypotension (SIH). An elevated pressure may also help to distinguish traumatic LPs (opening pressure is normal) from true SAH (pressure is often elevated). Finally, other diagnoses may be made, especially viral meningitis which can mimic a mild SAH. Disadvantages of LP include patient discomfort, time required, diagnostic ambiguity from a traumatic tap, and complications such as post-LP headache.

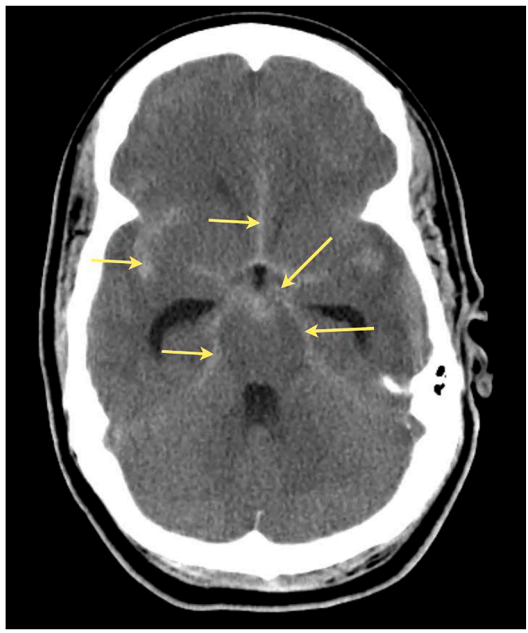

Fig. 2. Aneurysmal subarachnoid hemorrhage. Non-contrast CT scan of a patient with an obvious subarachnoid hemorrhage (*yellow arrows*) due to a ruptured cerebral aneurysm. Hyperdense blood is visible in the patient's interhemispheric fissure, right Sylvian fissure and around the midbrain. Mild hydrocephalus is also present. (Image Courtesy of Dr. Jonathan Edlow.)

Box 3
Caveats to the "six-hour" rule for computed tomography in subarachnoid hemorrhage

Patient-Related Factors
- The time from headache onset is clearly defined
- The CT is performed within 6 hours of headache onset
- The presentation is an isolated thunderclap headache (no primary neck pain, seizure or syncope at onset
- There is no meningismus and the neurologic examination is normal

Radiological factors
- The scanner is a third generation or newer machine
- The CT is technically adequate without significant motion artifact
- The CT takes thin cuts of $\leq$ 5mm that include the base of the brain
- The hematocrit is > 30%
- The physician interpreting the scan is an attending level radiologist (or has equivalent experience in reading brain CT scans)

Communication-related factors
- The clinicians should communicate the specific concern to the radiologist (eg, acute severe headache, rule out SAH), so that the radiologist can look for subtle finding such as mild hydrocephalus, and small amounts of isodense or hyperdense blood in the dependent portions of the ventricles and around the basal cisterns
- After a negative CT, the clinician should discuss with the patient that the post-test risk of SAH is extremely low ($\sim$1–2 per 1000)

Abbreviations: CT, computed tomography, SAH, subarachnoid hemorrhage.

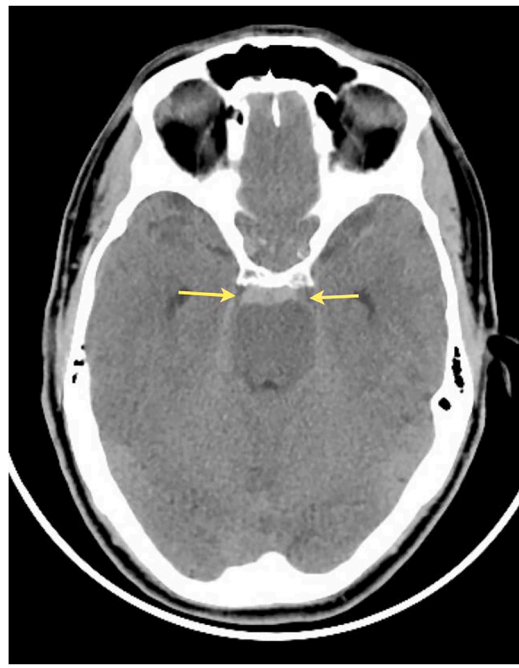

Fig. 3. Perimesencephalic subarachnoid hemorrhage (SAH). Perimesencephalic SAH represents 50% of non-aneurysmal SAH. The bleeding is thought be venous in nature and is localized to the region anterior to the pons (*yellow arrows*). These SAHs are sometimes called prepontine SAH. The outcomes in these patients are much better than in those with aneurysmal SAH. (Image Courtesy of Dr. Jonathan Edlow.)

Post-LP headache can be reduced by using atraumatic needles as opposed to cutting needles.[36] Smaller size needles decrease the incidence but also decrease the CSF flow rate. A 23G needle seems to be a happy medium. If a cutting needle is used, orienting the bevel toward the floor or ceiling when the patient is in the lateral decubitus position will help to "split" rather than transect the dural fibers, reduces the incidence of post-LP headache.[35]

Red blood cell (RBC) counts and xanthochromia, the yellowish discoloration of CSF resulting from in vivo bilirubin degradation are the two important findings, with RBCs being more sensitive early and xanthochromia being more sensitive later. Blood is present almost immediately after aneurysmal rupture.

Traumatic LPs in the ED occur in 10% to 15% of cases, depending on the threshold of RBCs used.[37] Although a reduction in RBC counts from the first to the last tube is an unreliable method to distinguish a traumatic tap from a true SAH,[38] if bloody CSF does occur, wasting 10 to 20 cc of CSF between the first and the last tubes to get the final tube to as close to zero RBC's as possible, is one practical method to reduce ambiguous CSF results. The presence of the combination of fewer than 2000 RBCs per cubic millimeter of CSF and absent xanthochromia reliably excludes SAH.[39]

Xanthochromia can be measured by visual inspection (**Fig. 4**) or by spectrophotometry. The former method is used in nearly all hospital laboratories in North America, whereas the latter is commonly used across Europe. While spectrophotometry is more sensitive than visual inspection, it lacks specificity, which for visual inspection is 97% and for spectrophotometry, 29%, a number that would lead to more

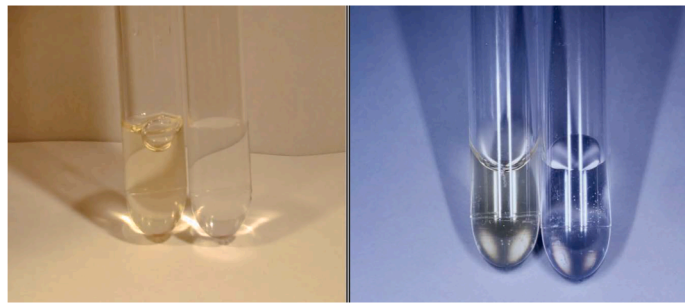

Fig. 4. Xanthochromia in a cerebrospinal fluid (CSF) sample. The same two tubes of CSF are pictured on the left side of each image, compared to a tube of distilled water on the right. The left pair of tubes is seen in incandescent light, which decreases the difference in the two tubes. The right pair of tubes is seen in fluorescent light, which better highlights the difference. Even when measuring using visual inspection, there is a process: rapid centrifuge of the sample, comparing to a second tube filled with an equal volume of distilled water, looking against a white background using neutral background light. (Image Courtesy of Dr. Jonathan Edlow.)

angiography.[40] No matter how it is measured, xanthochromia takes hours to develop. If there is still significant diagnostic ambiguity, vascular imaging and neurosurgical consultation is warranted.

Reversible Cerebral Vasoconstriction Syndrome

The other common cause of thunderclap headache is RCVS which accounts for approximately 8% of ED patients with thunderclap headache.[41]

Patients typically present with multiple thunderclap headaches that are shorter in duration than those associated with SAH. Three or more thunderclap headaches are probably pathognomonic of RCVS and one might consider going straight to CTA in this situation (**Fig. 1**).[42] A few patients with RCVS who do not present with a non-thunderclap headache usually present with wake-up headache, severe neck pain, seizure, or neurologic deficit,[43] findings which would usually precipitate an evaluation that would include at least a non-contrast CT.

Most patients with RCVS have associated triggers such as orgasm, pregnancy, physical exertion, acute stressful or emotional situations, Valsalva maneuver, extreme heat or cold, and exposure to various vasoactive medications.[42] Two diagnostic scoring systems have been described[43] but neither is ideal for emergency medicine practice. Some patients have associated conditions including posterior reversible encephalopathy syndrome (PRES), transient global amnesia, takotsubo cardiomyopathy, and coronary artery disease.[42,44]

Blood tests and CSF examination are generally normal. Non-contrast CT is usually normal but in 20% to 25% of patients, a convexal SAH will be present on the first CT (**Fig. 5**).[42] The combination of a convexal SAH in a patient with a thunderclap headache is highly likely to be RCVS.[44] The diagnosis is ultimately confirmed by CTA, which shows diffuse multifocal areas of vasoconstriction of medium to large cerebral arteries. Because smaller more peripheral arteries are affected first, CTA in the first week can be falsely negative.[42] Repeat CTA several days later usually shows the pathology, as larger more central vessels become involved.

Besides convexal SAH, intraparenchymal bleeds occur in 15% to 20% of cases, usually during the first week.[42] Ischemic strokes occur in 16% to 25% of cases, usually later in the course, although it can be a presenting symptom.[42] Despite this, the

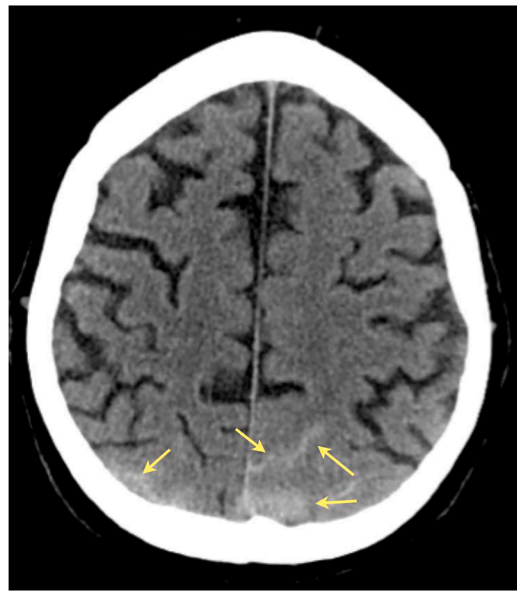

Fig. 5. Convexal subarachnoid hemorrhage (SAH). In this variety of SAH, the blood is found high up on the cerebral convexities (*yellow arrows*). The two most common causes are reversible cerebral vasoconstriction and cerebral amyloid angiopathy, but it can be seen less frequently in other conditions including hypertensive encephalopathy and cerebral venous sinus thrombosis. In patients who present with the combination of thunderclap headache and convexal SAH, reversible vasoconstriction is the most likely diagnosis.

vasoconstriction resolves over weeks to months and clinical outcomes for patients with RCVS tend to be quite good. Although over 90% of patients have a modified Rankin score of 0 to 2 at the time of hospital discharge, there is a 2% mortality rate.[42] Neurology should be consulted, and most patients should be admitted for pain control, trigger avoidance, and bedrest.[42]

Cervical Artery Dissection

Dissections of the carotid and vertebral arteries and their branches are uncommon.[45] Carotid dissections are twice as common as vertebral dissections.[45,46] Presentations are either due to local factors in the artery (headache and neck pain) or related to distal brain ischemia (neurologic deficit). In a series of nearly 1000 patients, thunderclap headache only occurred in 3.6% of 668 patients with carotid dissection and 9.2% of those with vertebral dissections.[46] Neck pain is more common in the latter group.[47]

The headaches from dissections are usually non-specific, progressive, and can be unilateral or bilateral, but almost always "different" from prior headaches.[48] The physical examination will show a Horner syndrome in roughly 50% (315 of 668) of carotid dissections.[46] When a stroke is present, deficits depend on the territory involved. The most common symptom from vertebral artery dissections is dizziness.[49]

Both CTA and MRA can establish the diagnosis; CTA is far more available in the ED. Two studies have shown that CTA is equal or superior to MRA.[50,51]

Cerebral Venous Sinus Thrombosis

CVST is another uncommon important cause of headache. Headache occurs in nearly all patients with CVST but there is no typical pattern. A thunderclap onset occurs in 5%

to 15% of cases.[52,53] Headache location, quality, and evolution over time are non-specific.[53] Determining hypercoagulability risks (including oral contraceptive use and the pregnant or post-partum state) may provide important clues to CVST.[54] Unless a complicating stroke has occurred, other symptoms such as visual obscurations, diplopia, and seizure occur in a minority of cases.[55]

Physical examination may show papilledema, especially in cases involving the sagittal sinus. Focal neurologic findings occur in those patients with a complicating stroke, which can be non-territorial venous infarcts or a brain hemorrhage. If an LP is done, CSF may show an elevated opening pressure and the presence of RBCs. While some have proposed use of D-dimer measurements the evidence is inconclusive and therefore we do not advocate for using a normal D-dimer level alone to exclude CVST.[56]

CVST is confirmed by imaging. With a sensitivity approaching 80%, a negative CT is insufficient to exclude CVST.[57] A meta-analysis showed that conventional MRI sequences (without magnetic resonance venography [MRV]) has a similar sensitivity (82%).[58] Venography confirms the diagnosis and CTV is equivalent to MRV for CVST.[53] The one exception is in the diagnosis of smaller cortical vein thromboses, for which MRV is more sensitive.[49] Standard CTA almost always images the cerebral venous sinuses,[59] but if CVST is the target diagnosis, communicating this to the radiologist may help with contrast bolus timing and the scrutiny paid to the venous sinuses.

Headaches Related to Hypertension

PRES is an uncommon condition that presents with various combinations of headache, hypertension, seizures, visual symptoms, and encephalopathy.[60] There is often some associated condition or trigger including various autoimmune disorders, immunosuppressive and cytotoxic drugs, various illicit drugs, pregnancy, and the post-partum state, natural toxins (eg, after a snake or scorpion bite) and possibly renal failure.[60,61]

The headache is usually non-descript, dull, and diffuse and rarely is it a thunderclap headache. Most have some degree of encephalopathy. When seizures occur, they usually follow headache onset. Visual symptoms such as visual field cuts or neglect occur in 20% to 40% of patients due to occipital lobe involvement.[60] Checking visual fields on physical examination will sometimes disclose a finding that the patient was either unaware of or had difficulty describing. Focal findings are otherwise uncommon.[61]

While facilitated by imaging, the diagnosis is clinical.[61] Non-contrast CT may show vasogenic edema but MRI sequences are more sensitive. While the classic location for these findings is the occipital lobes, they can occur anywhere in the brain or the spinal cord.[60,61] Although most treated patients recover without deficits within a few weeks, some patients have a fulminant course with a 2% mortality rate.[62]

Hypertensive emergency

A hypertensive emergency is defined as severe blood pressure elevation (usually > 180/110) associated with evidence of end-organ dysfunction, usually involving the brain, retina, heart, kidneys, or large arteries.[63] Headache is a common neurologic symptom in patients with severe hypertension, and determining which hypertensive headache patients have a true hypertensive emergency and which do not is based on finding evidence of end-organ involvement. There are no distinguishing features of the headache. Physical findings related to the retina (flame-shaped hemorrhages and papilledema), heart and lungs (a new S3 or S4 and rales) or a large artery (pulse deficit from an aortic dissection) can help make this distinction. Laboratories indicating

acute kidney injury or chest radiograph showing congestive heart failure can also help. CT can identify patients with a hypertensive ICH.

Headaches Related to Central Nervous System Infections

Meningitis

Headache is a common symptom in patients with meningitis but is almost always associated with altered mental status, fever, neck stiffness, nausea, vomiting, and/or rash.[64] Physical findings that are helpful if present include fever, meningismus, altered mental status, and Kernig's and Brudzinski's signs. Once the diagnosis is entertained, the priority is to administer intravenous antimicrobial agents as rapidly as possible, ideally after performing an LP. Non-contrast CT scanning should not delay antibiotic administration. The evidence supporting the use of CT prior to LP to reduce herniation is limited.[65]

Contraindications to an LP-first approach include severely altered mental status, signs of elevated ICP, focal neurologic deficit, coagulopathy, new dilated pupils, and a Cushing response. New-onset seizures and immunocompromised state are not absolute contraindications, although ongoing seizures are.[65] In patients whose LP will be delayed, two blood cultures should be obtained and dexamethasone and appropriate antimicrobials should be given as quickly as possible. Blood cultures drawn before antibiotic administration disclose the causative organism in 50% to 80% of cases.[66]

The risk of a complication of the LP must be balanced against the risk of delay in antibiotics. Diagnostic delays of bacterial meningitis still exist.[67] Although different investigators used different time intervals and definitions of poor outcomes, numerous studies confirm that delays in antibiotic administration are associated with worse clinical outcomes.[68,69] Unfavorable outcomes increase by 30% per hour of delay in the first 12 hours, corresponding with an absolute increase in mortality of 4% per hour.[65]

If LP is performed after antibiotics, identification of the offending organism is reduced by nearly half.[70] In such cases, polymerase chain reaction (PCR) and other molecular methods frequently identify the bacterium.[70] When an LP is done in patients for whom the clinician is concerned about the potential for herniation, removing a small volume of fluid sufficient for basic chemistries, cell counts, and culture through a small caliber needle theoretically reduces the likelihood of herniation.

In patients whose clinical presentation with headache, fever, and stiff neck that evolves over days to weeks, many will have viral meningitis but also other treatable causes meningitis such as Lyme, tuberculous, cryptococcal, syphilitic, or other types of meningitis. While these patients often present less acutely, it is still important to make the diagnosis through CSF analysis in order to target therapies and counsel patients on prognostic expectations.

Encephalitis

In general, patients with encephalitis present similarly to those with meningitis but have evidence of brain involvement evidenced by mental status changes and cognitive signs. Herpes encephalitis typically presents with acute onset of some combination of fever, headache, confusion, or altered mental status.[71] MRI often shows bilateral temporal lobe involvement. Those with varicella-zoster virus encephalitis may also have a diffuse vesicular rash. The CSF in these patients typically shows a mildly elevated protein, a lymphocytic pleocytosis with a normal glucose and CSF PCR will establish the diagnosis.

Patients with antibody-mediated encephalitis usually present with seizures, psychiatric and cognitive symptoms, abnormal movements, and decreased level of consciousness; headache is uncommon.[72]

Brain abscess

Even in the modern era, the mortality rate of brain abscess remains approximately 10%.[73] Headache is the most common symptom.[74] Other symptoms of brain dysfunction, including altered mentation and seizures, depend on the location and size of the abscess. Fever is present in only half of cases,[73,75] and the classic triad of fever, headache, and focal neurologic deficits is only found in 20%.[73] Both nuchal rigidity and papilledema are found in roughly a third of patients.[73] Because the majority of brain abscesses is in the frontal and the temporal lobes, focal deficits are often absent.[73,76]

White blood cell counts and inflammatory biomarkers are usually normal.[73] Blood cultures are positive in 28% of cases.[73] Performing an LP is *not* recommended. It has limited benefits and can be completely normal. The abnormal findings of pleocytosis and elevated protein are non-specific,[73] and CSF culture only identifies the causative organism in less than 25% of cases.[73] Furthermore, the opening pressure is frequently elevated,[75] and multiple studies document patients who deteriorate shortly after LP.[73,75] Thus, there is little benefit and clear harm.

Brain CT is usually positive but one meta-analysis reported that it was falsely negative in 44 of 728 (6%) of cases.[73] Suspicion of brain abscess is one indication where CT with and without contrast may be indicated. Early in the course, MRI is more sensitive than CT. MRI identifies nearly all brain abscesses (sensitivity is 96%),[74] often showing the classic peripheral "ring-enhancement."

Epidural empyema

Epidural empyema, usually caused by contiguous infection of the ear or paranasal sinuses, head trauma, or surgery, is rare.[77] Headache is usually accompanied by fever, nausea and vomiting, altered mental status, and seizures.[77] Both CT and MRI are usually positive.[77]

Headaches Related to Intracranial Masses

Brain tumors

Brain tumor is a common concern among ED patients with headache. The headache from brain tumors is often nondescript, although usually distinct from prior episodes. In one study of 111 patients with headache from brain tumor, the quality of the headache was similar to prior tension-type or migraine episodes in 86% of patients, but even in patients who described the tumor-related headache as typical of prior episodes, something was "different"—the severity, frequency or presence of other symptoms such as seizure or confusion.[78] This reinforces the importance of a detailed history.

Presentation with headache as the only symptom is unusual, most patients have headache "plus" some other symptom, usually seizure and/or focal findings or altered mentation.[79] A study of 183 patients with brain tumors reported that no patient had an isolated headache (with no additional symptoms) for longer than 10 weeks,[79] suggesting that the longer the duration of isolated headache, the lower the likelihood of a tumor as a cause.

Headaches that interfere with sleep at night or are worse upon awakening in the morning occur but its absence does not exclude the diagnosis. This phenomenon may be caused by cerebral vasodilation from mild hypercarbia during sleep or increases in ICP due to the recumbent position. Some patients also complain that their headache worsens with coughing, straining, or activities that are associated with the Valsalva maneuver.[79] This phenotype may be more common in patients with elevated ICP.

Pituitary apoplexy

Pituitary apoplexy results from bleeding into or infarction of a pre-existing adenoma.[80] Headache associated with the adenoma without apoplexy are similarly non-descript as for other brain tumors. However, headaches from pituitary apoplexy are often a thunderclap onset.[80] Varying degrees of ophthalmoplegia, decreased visual acuity, and/or field cuts are common and some patients will have altered mental status.[80] This is one instance where non-contrast CT in a patient with a thunderclap headache may be normal and MRI with dedicated views of the sella turcica are diagnostic.

Colloid cyst of the third ventricle

Colloid cyst of the third ventricle is very rare condition but is a cause of headache that can be associated with severe rapid decompensation and sudden death.[81] Headache is the initial symptom in the majority of cases.[82] The headache is usually severe and almost always intermittent.[83] Attacks last seconds to minutes, and occasionally a few hours and can occur over months to years.[83] There is often a postural component—worse on standing up and relieved by lying down.[83] Non-contrast CT in symptomatic patients will nearly always show a hyperdense lesion and hydrocephalus in about half.[82]

In a series of patients with colloid cysts, more than half were discovered incidentally. In this group, acute deterioration is rare,[82,84] and these patients can be electively referred to a neurosurgeon.

Headaches Related to Abnormal Cerebrospinal Fluid Pressure

Idiopathic intracranial hypertension

Patients with IIH are typically young (mean age 29 years), females (>90% of patients) who are obese (average body mass index $\geq$ 40).[85] There are many associated conditions.[86] Roughly 85% present with headaches,[85] which phenotypically resemble primary headache disorders.[86] The headache often worsens with Valsalva maneuvers and can be worse on awakening.[87] Transient visual obscurations, which are very brief (<60 seconds) episodes of decreased vision occur in 70% of patients.[85–87] Pulsatile tinnitus is described in over half of cases.[85,87] Diagnostic criteria include (a) symptoms of elevated ICP, (b) normal physical examination (except for papilledema and sixth nerve palsy), (c) normal CSF except for opening pressure greater than 250 cm of water, and (d) normal brain imaging sufficient to exclude CVST.[86]

Other than the above exceptions, physical examination is normal. Roughly 5% of patients do not have papilledema.[88] This is one reason why measuring the opening pressure, which helps to establish the diagnosis, is so important. When the diagnosis is suspected at the time of LP, removal of sufficient CSF to lower the closing pressure to less than 20 cm H_2O will help reduce or eliminate the headache.[89] Although brain imaging is "normal," MRI may show an empty sella, flattening of the posterior aspects of the globe, distention of the perioptic subarachnoid space and transverse sinus stenosis.[86] Diagnosis is important because treatments decrease the likelihood of permanent visual loss.

Spontaneous intracranial hypotension

SIH is an uncommon disorder that is usually caused by spontaneous leaks of CSF in the spine.[90] Nearly 100% of patients have headache, which is almost always positional—worse on standing up and better when lying down.[54,90] There is often a time lag of several minutes between the postural change and development or improvement of headache.[90] Other common symptoms include nausea and vomiting, neck pain or stiffness, dizziness, and disturbances of hearing.[54] Physical examination is usually normal.

Table 5
Selected causes of headache in pregnant and postpartum women

Reversible Cerebral Vasoconstriction Syndrome	Multiple short-duration (several hours) thunderclap headaches occurring over days to weeks. Physical examination may be normal. CTA is useful in establishing the diagnosis but may be falsely normal early in course
Arterial dissection	Occurs in ~ 3–5% of carotid dissections and ~ 10% of vertebral dissections. Physical examination may be normal. Epidemiologic data are mixed as to whether dissections are more common in this population
Cerebral venous sinus thrombosis	Occurs in ~ 10% of venous sinus thromboses. Physical examination may be normal. This is most common in late pregnancy and the postpartum period. Headache usually precedes seizure.
Posterior reversible encephalopathy syndrome	Usually not thunderclap. A seizure precedes the headache. Visual symptoms are common. Most cases have hypertension. Seizures usually precede headache.
Pre-eclampsia/eclampsia	Can occur up to 6 wk post-partum
Pituitary apoplexy	Often in setting of a preexisting pituitary adenoma, often with ophthalmoplegia and bitemporal hemianopsia. Physical examination may be normal
Post-dural puncture headache	Seen in patients who have had inadvertent dural puncture from axial anesthesia, or occasionally due to spinal dural tears from labor-related pushing
Acute subdural hematoma	Subdural hematoma can be seen in patients who have had inadvertent dural puncture from axial anesthesia

Abbreviation: CTA, computed tomographic angiography.

Interestingly, the opening pressure, while low in 67% of patients, can be normal in 32% and rarely even elevated.[54] MRI often shows diffuse meningeal enhancement, subdural hygromas and/or brain sagging.[54] Patients with this diagnosis should be admitted for neurology evaluation and large volume blood patch if a leak is found on spine imaging.

MISCELLANEOUS CAUSES OF "CANNOT MISS" HEADACHE

Giant Cell Arteritis

GCA is an important cause of headache in patients over 50 years of age.[91] There are no typical headache characteristics. Patients may have low-grade fever, malaise, jaw claudication, scalp tenderness, and symptoms of polymyalgia rheumatica.[92] Physical examination may disclose temporal artery swelling and inflammation.[93] Erythrocyte sedimentation rate and C-reactive protein are nearly always abnormal, but because there may be discordance between the two, we recommend sending both if available.[91]

Table 6
Treatments steps that should be considered or initiated in the emergency department

Cervical artery dissection	In consultation with a neurologist, consider starting either an anticoagulant or an anti-platelet agent
Cerebral venous sinus thrombosis	In consultation with a neurologist, consider starting an anticoagulant, even in patients who have an ICH from the venous sinus thrombosis
Posterior reversible encephalopathy syndrome	If the blood pressure is severely elevated, begin to pharmacologically reduce it
Hypertensive emergency	Pharmacologically reduce blood pressure about 20% from the peak pressure
Bacterial meningitis	Immediately after obtaining 2 blood cultures and CSF, administer IV steroids and antibiotics. If CT is done first, give the steroids and antibiotics immediately after drawing 2 blood cultures but before the patients goes for CT.
Herpes encephalitis	Once the diagnosis is likely, administer IV acyclovir
Brain tumor	In very select cases, and usually after consultation with a neurologist or neurosurgeon, give IV steroids if there is significant vasogenic edema and clinical findings of elevated ICP. Note that in some cases of lymphoma, even a single dose of steroids can significantly alter the pathology
Idiopathic intracranial hypertension	If the diagnosis is likely after measuring the opening pressure on an LP, remove sufficient CSF to bring the closing pressure down to 20 cm of water
Giant cell arteritis	Administer oral steroids to be sure patient gets firs dose and for patients who already have visual symptoms, in consultation with an ophthalmologist or neurologist, give IV steroids
Carbon monoxide poisoning	Give 100% oxygen by mask and consider transferring to a center that offers hyperbaric oxygen
Acute narrow angle closure glaucoma	Consult ophthalmology and discuss administering ocular and IV medications to reduce intra-ocular pressure prior to definitive surgery
Eclampsia	Consult obstetrics and administer parenteral magnesium

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; ICH, intracranial hemorrhage; ICP, intracranial pressure; IV, intravenous; LP, lumbar puncture.

The most common cause of morbidity is permanent visual loss, and in patients who have one eye affected, the second eye becomes affected within 24 hours in a third of cases and within a week in another third.[94] Initiation of steroids does not affect temporal artery biopsy results for at least 2 weeks.[95] Thus, steroids should be started in the ED. In patients who present with visual symptoms, in consultation with a neurologist or ophthalmologist, strongly consider using intravenous methylprednisolone rather than oral steroids.[96]

Carbon Monoxide Poisoning

Carbon monoxide (CO) poisoning is common, the usual sources being related to engine exhaust or a faulty heating apparatus.[97] Headache occurs at carboxyhemoglobin levels of 10% to 20%. Levels should be measured by co-oximetry as standard pulse oximeter devices do not measure carboxyhemoglobin levels. There are no typical headache characteristics. Clues to the diagnosis include multiple persons involved from a single site and winter season.

Acute Narrow Angle Glaucoma

Rarely, patients with acute narrow angle closure glaucoma present primarily with headache.[98] Frequent episodes of unilateral retro orbital headaches lasting minutes to a few hours occur, often without any visual symptoms occur, and sometimes over years misdiagnosed as migraine.[92] In patients with retro orbital headaches, measurement of intraocular pressure should be performed.

HEADACHE IN PREGNANT AND POST-PARTUM PATIENTS

Headaches are common in pregnant and postpartum patients and primary headache disorders are by far the most common cause.[99,100] However, many other causes occur in this patient population, including preeclampsia, eclampsia, CVST, PRES, RCVS, and post-dural puncture headache (**Table 5**).

TREATMENT OF PATIENTS WITH SECONDARY HEADACHES

Although the focus of this article is diagnosis, some treatment steps should be considered and/or initiated in the ED (**Table 6**).

SUMMARY

Even though the large majority of ED patients with headache do not have serious secondary causes requiring acute treatment, a thorough evaluation for red flags in the history and physical examination will help to identify those who do. All patients with thunderclap headache require a brain CT, which, if done after 6 hours from symptom onset, requires some additional testing. Due to the brisk circulation of CSF, the sensitivity of all tests for SAH change with time. RCVS is the second most common cause of thunderclap headache. Most patients with other serious secondary causes of headache have clues in the clinical evaluation that help to determine which need additional testing.

CLINICS CARE POINTS

- A small proportion of ED patients with headache have a "cannot miss" secondary cause that if misdiagnosed or have a delay in diagnosis, can result in significant morbidity and mortality.

- Emergency physicians should be able to identify "red flags" through the history and physical examination that indicate a serious cause of headache and require further testing.
- Bedside examination findings such as papilledema and ONSD measurements on point-of-care ocular ultrasound can indicate elevated ICP and underlying serious pathology.
- The most serious cause of a thunderclap headache is SAH, although other secondary causes should be considered as well.
- In patients for whom there is concern for SAH, a negative head CT beyond 6 hours does not rule out the diagnosis; further workup with LP and possible vascular imaging is required.
- Xanthrochomia can be measured through visual inspection or spectrophotometry.
- Noncontrast head CTs have poor sensitivity for CVST; a CT venogram or MR venogram is the appropriate test to diagnose this condition.
- In patients with bacterial meningitis, non-contrast CT scanning should not delay antibiotic administration.
- "Cannot miss" non-neurologic causes of headache include acute angle closure glaucoma, CO poisoning, and GCA.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Gottlieb M, Moyer E, Bernard K. Epidemiology of headache presentations to United States emergency departments from 2016 to 2023. Am J Emerg Med 2024;85:1–6.
2. Edlow JA. Misdiagnosis of acute headache: mitigating medico-legal risks. Emerg Med Clin North Am 2025;43(1):67–80.
3. Chu KH, Howell TE, Keijzers G, et al. Acute headache presentations to the emergency department: a state-wide cross-sectional study. Acad Emerg Med 2017; 24(1):53–62.
4. Ramirez-Lassepas M, Espinosa CE, Cicero JJ, et al. Predictors of intracranial pathologic findings in patients who seek emergency care because of headache. Arch Neurol 1997;54(12):1506–9.
5. Ravishankar K. WHICH headache to investigate, WHEN, and HOW? Headache 2016;56(10):1685–97.
6. Mackay DD, Garza PS, Bruce BB, et al. The demise of direct ophthalmoscopy: a modern clinical challenge. Neurol Clin Pract 2015;5(2):150–7.
7. Biousse V, Bruce BB, Newman NJ. Ophthalmoscopy in the 21st century: the 2017 H. Houston Merritt lecture. Neurology 2018;90(4):167–75.
8. Sachdeva V, Vasseneix C, Hage R, et al. Optic nerve head edema among patients presenting to the emergency department. Neurology 2018;90(5):e373–9.
9. Fernando SM, Tran A, Cheng W, et al. Diagnosis of elevated intracranial pressure in critically ill adults: systematic review and meta-analysis. Br Med J 2019;366:l4225.
10. Edlow JA, Panagos PD, Godwin SA, et al, American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. Ann Emerg Med 2008;52(4):407–36, doi:S0196-0644(08)01463-7 [pii].

11. Pope JV, Edlow JA. Favorable response to analgesics does not predict a benign etiology of headache. Headache 2008;48(6):944–50.
12. Roberts T, Horner DE, Chu K, et al. Thunderclap headache syndrome presenting to the emergency department: an international multicentre observational cohort study. Emerg Med J 2022;39(11):803–9.
13. Headache Classification Committee of the International Headache Society (IHS) The international classification of headache disorders, 3rd edition. Cephalalgia 2018;38(1):1–211.
14. Perry JJ, Stiell IG, Sivilotti ML, et al. Clinical decision rules to rule out subarachnoid hemorrhage for acute headache. JAMA 2013;310(12):1248–55.
15. Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med 2000;342(1):29–36.
16. Aaseth K, Dhami SKG, Kravdal G, et al. Diagnostic workup of acute headache and subarachnoid hemorrhage in a Norwegian population: an observational study. Eur J Neurol 2024;31(9):e16385.
17. Trainee Emergency Research N. Subarachnoid haemorrhage in the emergency department (SHED): a prospective, observational, multicentre cohort study. Emerg Med J 2024;41(12):719–27.
18. Edlow JA, Malek AM, Ogilvy CS. Aneurysmal subarachnoid hemorrhage: update for emergency physicians. J Emerg Med 2008;34(3):237–51, doi: S0736-4679(07)00729-9 [pii].
19. Vermeulen MJ, Schull MJ. Missed diagnosis of subarachnoid hemorrhage in the emergency department. Stroke 2007;38(4):1216–21.
20. Waxman DA, Kanzaria HK, Schriger DL. Unrecognized Cardiovascular Emergencies Among Medicare Patients. JAMA Intern Med 2018;178(4):477–84.
21. Bellolio MF, Hess EP, Gilani WI, et al. External validation of the Ottawa subarachnoid hemorrhage clinical decision rule in patients with acute headache. Am J Emerg Med 2015;33(2):244–9.
22. Hoh BL, Ko NU, Amin-Hanjani S, et al. Guideline for the management of patients with aneurysmal subarachnoid hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke 2023;54(7):e314–70.
23. American College of Emergency Physicians Clinical Policies Subcommittee on Acute H, Godwin SA, Cherkas DS, et al. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Acute Headache. Ann Emerg Med 2019;74(4):e41–74.
24. Dubosh NM, Bellolio MF, Rabinstein AA, et al. Sensitivity of Early Brain Computed Tomography to Exclude Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-Analysis. Stroke 2016;47(3):750–5.
25. Edlow JA. Rules About Rules - The 6-h CT Rule For Subarachnoid Hemorrhage. J Stroke Cerebrovasc Dis 2020;29(12):105311.
26. Savitz SI, Edlow J. Thunderclap headache with normal CT and lumbar puncture: further investigations are unnecessary: for. Stroke 2008;39(4):1392–3.
27. Perry JJ, Stiell IG, Sivilotti ML, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. Bmj 2011;343:d4277.
28. Mark DG, Sonne DC, Jun P, et al. False-negative Interpretations of Cranial Computed Tomography in Aneurysmal Subarachnoid Hemorrhage. Acad Emerg Med 2016;23(5):591–8.
29. Perry JJ, Sivilotti MLA, Emond M, et al. Prospective Implementation of the Ottawa Subarachnoid Hemorrhage Rule and 6-Hour Computed Tomography

Rule. Stroke 2020;51(2):424–30. https://doi.org/10.1161/STROKEAHA.119.026969.
30. Mensing LA, Vergouwen MDI, Laban KG, et al. Perimesencephalic Hemorrhage: A Review of Epidemiology, Risk Factors, Presumed Cause, Clinical Course, and Outcome. Stroke 2018;49(6):1363–70.
31. Rinkel GJ, van Gijn J, Wijdicks EF. Subarachnoid hemorrhage without detectable aneurysm. A review of the causes. Stroke 1993;24(9):1403–9.
32. Nelson SE, Sair HI, Stevens RD. Magnetic Resonance Imaging in Aneurysmal Subarachnoid Hemorrhage: Current Evidence and Future Directions. Neurocritical care 2018;29(2):241–52.
33. Edlow JA. What are the unintended consequences of changing the diagnostic paradigm for subarachnoid hemorrhage after brain computed tomography to computed tomographic angiography in place of lumbar puncture? Acad Emerg Med 2010;17(9):991–5 [discussion 996-7].
34. Thompson BG, Brown RD Jr, Amin-Hanjani S, et al. Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015;46(8):2368–400.
35. Amorim JA, Gomes de Barros MV, Valenca MM. Post-dural (post-lumbar) puncture headache: risk factors and clinical features. Cephalalgia 2012;32(12):916–23.
36. Nath S, Koziarz A, Badhiwala JH, et al. Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis. Lancet 2018;391-(10126):1197–204.
37. Shah KH, Richard KM, Nicholas S, et al. Incidence of traumatic lumbar puncture. Acad Emerg Med 2003;10(2):151–4.
38. Heasley DC, Mohamed MA, Yousem DM. Clearing of red blood cells in lumbar puncture does not rule out ruptured aneurysm in patients with suspected subarachnoid hemorrhage but negative head CT findings. AJNR Am J Neuroradiol 2005;26(4):820–4.
39. Perry JJ, Alyahya B, Sivilotti ML, et al. Differentiation between traumatic tap and aneurysmal subarachnoid hemorrhage: prospective cohort study. Bmj 2015;350:h568.
40. Perry JJ, Sivilotti ML, Stiell IG, et al. Should spectrophotometry be used to identify xanthochromia in the cerebrospinal fluid of alert patients suspected of having subarachnoid hemorrhage? Stroke 2006;37(10):2467–72.
41. Grooters GS, Sluzewski M, Tijssen CC. How often is thunderclap headache caused by the reversible cerebral vasoconstriction syndrome? Headache 2014;54(4):732–5.
42. Edlow JA, Baggett M, Singhal A. Reversible Cerebral Vasoconstriction Syndrome for the Internist-A Narrative Review. Am J Med 2024. https://doi.org/10.1016/j.amjmed.2024.10.034.
43. Ducros A, Bousser MG. Thunderclap headache. Bmj 2013;346:e8557.
44. Edlow JA, Singhal AB, Romero JM. Case 18-2024: A 64-Year-Old Woman with the Worst Headache of Her Life. N Engl J Med 2024;390(22):2108–18.
45. Lee VH, Brown RD Jr, Mandrekar JN, et al. Incidence and outcome of cervical artery dissection: a population-based study. Neurology 2006;67(10):1809–12.
46. von Babo M, De Marchis GM, Sarikaya H, et al. Differences and similarities between spontaneous dissections of the internal carotid artery and the vertebral artery. Stroke 2013;44(6):1537–42.

47. Debette S, Grond-Ginsbach C, Bodenant M, et al. Differential features of carotid and vertebral artery dissections: the CADISP study. Neurology 2011;77(12):1174–81.
48. Arnold M, Cumurciuc R, Stapf C, et al. Pain as the only symptom of cervical artery dissection. J Neurol Neurosurg Psychiatry 2006;77(9):1021–4.
49. Gottesman RF, Sharma P, Robinson KA, et al. Clinical characteristics of symptomatic vertebral artery dissection: a systematic review. Neurologist 2012;18(5):245–54.
50. Hanning U, Sporns PB, Schmiedel M, et al. CT versus MR Techniques in the Detection of Cervical Artery Dissection. J Neuroimaging 2017;27(6):607–12.
51. Vertinsky AT, Schwartz NE, Fischbein NJ, et al. Comparison of multidetector CT angiography and MR imaging of cervical artery dissection. AJNR Am J Neuroradiol 2008;29(9):1753–60.
52. de Bruijn SF, Stam J, Kappelle LJ. Thunderclap headache as first symptom of cerebral venous sinus thrombosis. CVST Study Group. Lancet 1996;348-(9042):1623–5.
53. Wasay M, Kojan S, Dai AI, et al. Headache in Cerebral Venous Thrombosis: incidence, pattern and location in 200 consecutive patients. J Headache Pain 2010;11(2):137–9.
54. D'Antona L, Jaime Merchan MA, Vassiliou A, et al. Clinical Presentation, Investigation Findings, and Treatment Outcomes of Spontaneous Intracranial Hypotension Syndrome: A Systematic Review and Meta-analysis. JAMA Neurol 2021;78(3):329–37.
55. Saposnik G, Bushnell C, Coutinho JM, et al. Diagnosis and Management of Cerebral Venous Thrombosis: A Scientific Statement From the American Heart Association. Stroke 2024;55(3):e77–90.
56. Alons IM, Jellema K, Wermer MJ, Algra A. D-dimer for the exclusion of cerebral venous thrombosis: a meta-analysis of low risk patients with isolated headache. BMC Neurol 2015;15:118.
57. Xu W, Gao L, Li T, et al. The Performance of CT versus MRI in the Differential Diagnosis of Cerebral Venous Thrombosis. Thromb Haemost 2018;118(6):1067–77.
58. Khandelwal N, Agarwal A, Kochhar R, et al. Comparison of CT venography with MR venography in cerebral sinovenous thrombosis. AJR Am J Roentgenol 2006;187(6):1637–43.
59. Linn J, Ertl-Wagner B, Seelos KC, et al. Diagnostic value of multidetector-row CT angiography in the evaluation of thrombosis of the cerebral venous sinuses. AJNR Am J Neuroradiol 2007;28(5):946–52.
60. Geocadin RG. Posterior Reversible Encephalopathy Syndrome. N Engl J Med 2023;388(23):2171–8.
61. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol 2015;14(9):914–25.
62. Alshami A, Al-Bayati A, Douedi S, et al. Clinical characteristics and outcomes of patients admitted to hospitals for posterior reversible encephalopathy syndrome: a retrospective cohort study. BMC Neurol 2021;21(1):107.
63. Peixoto AJ. Acute Severe Hypertension. N Engl J Med 2019;381(19):1843–52.
64. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016;22(Suppl 3):S37–62. https://doi.org/10.1016/j.cmi.2016.01.00764.

65. Glimaker M, Johansson B, Bell M, et al. Early lumbar puncture in adult bacterial meningitis–rationale for revised guidelines. Scand J Infect Dis 2013;45(9):657–63.
66. Brouwer MC, Thwaites GE, Tunkel AR, et al. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. Lancet 2012;380(9854):1684–92.
67. Torres SD, Kim CY, Das M, et al. Delays in Diagnosis and Treatment of Bacterial Meningitis in NYC: Retrospective Cohort Analysis. Neurohospitalist 2022;12(2):268–72.
68. Bodilsen J, Dalager-Pedersen M, Schonheyder HC, et al. Time to antibiotic therapy and outcome in bacterial meningitis: a Danish population-based cohort study. BMC Infect Dis 2016;16:392.
69. Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM 2005;98(4):291–8.
70. McGill F, Heyderman RS, Panagiotou S, et al. Acute bacterial meningitis in adults. Lancet 2016;388(10063):3036–47.
71. Bharucha T, Houlihan CF, Breuer J. Herpesvirus Infections of the Central Nervous System. Semin Neurol 2019;39(3):369–82.
72. Dalmau J, Graus F. Antibody-Mediated Encephalitis. N Engl J Med 2018;378(9):840–51.
73. Brouwer MC, Coutinho JM, van de Beek D. Clinical characteristics and outcome of brain abscess: systematic review and meta-analysis. Neurology 2014;82(9):806–13.
74. Brouwer MC, Tunkel AR, McKhann GM 2nd, et al. Brain abscess. N Engl J Med 2014;371(5):447–56.
75. Morgan H, Wood MW, Murphey F. Experience with 88 consecutive cases of brain abscess. J Neurosurg 1973;38(6):698–704.
76. Sonneville R, Ruimy R, Benzonana N, et al. An update on bacterial brain abscess in immunocompetent patients. Clin Microbiol Infect 2017;23(9):614–20.
77. Pradilla G, Ardila GP, Hsu W, Rigamonti D. Epidural abscesses of the CNS. Lancet Neurol 2009;8(3):292–300.
78. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. Neurology 1993;43(9):1678–83.
79. Vazquez-Barquero A, Ibanez FJ, Herrera S, et al. Isolated headache as the presenting clinical manifestation of intracranial tumors: a prospective study. Cephalalgia 1994;14(4):270–2.
80. Johnston PC, Hamrahian AH, Weil RJ, et al. Pituitary tumor apoplexy. J Clin Neurosci 2015;22(6):939–44.
81. Musa G, Simfukwe K, Gots A, et al. Clinical and radiological characteristics in fatal third ventricle colloid cyst. Literature review. J Clin Neurosci 2020;82(Pt A):52–5.
82. Beaumont TL, Limbrick DD Jr, Rich KM, et al. Natural history of colloid cysts of the third ventricle. J Neurosurg 2016;125(6):1420–30.
83. Kelly R. Colloid cysts of the third ventricle; analysis of twenty-nine cases. Brain 1951;74(1):23–65.
84. Velicu MA, Rossmann K, Vahedi A, et al. On Natural History and Management of Colloid Cysts: Time to Rethink? World Neurosurg 2023;170:e188–99.
85. Wall M, Kupersmith MJ, Kieburtz KD, et al. The idiopathic intracranial hypertension treatment trial: clinical profile at baseline. JAMA Neurol 2014;71(6):693–701.

86. Mollan SP, Davies B, Silver NC, et al. Idiopathic intracranial hypertension: consensus guidelines on management. J Neurol Neurosurg Psychiatry 2018;89-(10):1088–100.
87. Markey KA, Mollan SP, Jensen RH, et al. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. Lancet Neurol 2016;15(1):78–91.
88. Digre KB, Nakamoto BK, Warner JE, et al. A comparison of idiopathic intracranial hypertension with and without papilledema. Headache 2009;49(2):185–93.
89. Ducros A, Biousse V. Headache arising from idiopathic changes in CSF pressure. Lancet Neurol 2015;14(6):655–68. https://doi.org/10.1016/S1474-4422(15)00015-0.
90. Schievink WI. Spontaneous Intracranial Hypotension. N Engl J Med 2021;385-(23):2173–8.
91. Edlow JA, Hoffmann B. Managing Patients With Acute Visual Loss. Ann Emerg Med 2022;79(5):474–84. https://doi.org/10.1016/j.annemergmed.2021.10.019.
92. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. Lancet 2008;372(9634):234–45.
93. van der Geest KSM, Sandovici M, Brouwer E, et al. Diagnostic accuracy of symptoms, physical signs, and laboratory tests for giant cell arteritis: a systematic review and meta-analysis. JAMA Intern Med 2020;180(10):1295–304.
94. Jonasson F, Cullen JF, Elton RA. Temporal arteritis. A 14-year epidemiological, clinical and prognostic study. Scott Med J 1979;24(2):111–7. https://doi.org/10.1177/003693307902400203.
95. Narvaez J, Bernad B, Roig-Vilaseca D, et al. Influence of previous corticosteroid therapy on temporal artery biopsy yield in giant cell arteritis. Semin Arthritis Rheum 2007;37(1):13–9.
96. Fein AS, Ko MW. Neuro-ophthalmologic complications of giant cell arteritis: diagnosis and treatment. Semin Neurol 2019;39(6):673–81. https://doi.org/10.1055/s-0039-1698761.
97. Weaver LK. Clinical practice. Carbon monoxide poisoning. N Engl J Med 2009;360(12):1217–25.
98. Shindler KS, Sankar PS, Volpe NJ, et al. Intermittent headaches as the presenting sign of subacute angle-closure glaucoma. Neurology 2005;65(5):757–8.
99. Edlow JA, Caplan LR, O'Brien K, et al. Diagnosis of acute neurological emergencies in pregnant and post-partum women. Lancet Neurol 2013;12(2):175–85.
100. Bilello LA, Greige T, Singleton JM, et al. Retrospective Review of Pregnant Patients Presenting for Evaluation of Acute Neurologic Complaints. Ann Emerg Med 2021;77(2):210–20.
101. Garcia-Azorin D, Abelaira-Freire J, Gonzalez-Garcia N, et al. Sensitivity of the SNNOOP10 list in the high-risk secondary headache detection. Cephalagia 2022;42(14):1521–31.