# Managing Patients With Nontraumatic, Severe, Rapid-Onset Headache

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***Editor's Note:*** *The Expert Clinical Management series consists of shorter, practical review articles focused on the optimal approach to a specific sign, symptom, disease, procedure, technology, or other emergency department challenge. These articles—typically solicited from recognized experts in the subject area—will summarize the best available evidence relating to the topic while including practical recommendations where the evidence is incomplete or conflicting.*

## INTRODUCTION

Severe rapid-onset headache, sometimes called thunderclap headache, is a relatively common emergency department (ED) chief complaint. Although these headaches have been defined as "peaking within one minute,"[1,2] some have questioned this rigid time criterion.[3] In one study of subarachnoid hemorrhage diagnosis, the interobserver agreement in the ED for "thunderclap" onset was only moderate ($\kappa$=0.49), and 6 (of 132) subarachnoid hemorrhage patients reported time to peak intensity of 1 hour.[4] For these reasons, I do not strictly use "sudden onset" in practice, but these patients generally recall exactly what they were doing at headache onset.

All headache patients with new neurologic deficits require sufficient evaluation to explain those findings. This article focuses on the diagnosis of neurologically intact patients with nontraumatic, rapid-onset, severe and unusual headaches.

## DIFFERENTIAL DIAGNOSIS

The most serious cause of severe rapid-onset headache is subarachnoid hemorrhage, accounting for approximately 7% to 8% of such patients.[5,6] The converse is that nearly all awake patients with subarachnoid hemorrhage will complain of such a headache. Most subarachnoid hemorrhage patients have cerebral aneurysms, although other causes exist (Table 1). History of neck pain (positive likelihood ratio [LR+] 4.1) or stiffness on examination (LR+ 6.6) suggests subarachnoid hemorrhage.[5] Forty percent of patents with subarachnoid hemorrhage appear well and have isolated severe headache.[6]

Less commonly considered in the ED, the second most common potentially serious cause is reversible cerebral vasoconstriction syndrome, accounting for approximately 8% to 9% of cases in 2 ED-based series (personal communication, W. Y. Kim, 2017).[7] Patients with cerebral vasoconstriction were treated by nearly 5 physicians before receiving a correct diagnosis.[8] Vasoconstriction typically presents with multiple thunderclap headaches (mean of 4) during days to weeks. This presentation is probably pathognomonic.[9,10] Although the onset of these headaches is identical to those in subarachnoid hemorrhage, their duration is usually much shorter, typically several hours.[9,10] Triggers (including exposure to marijuana, vasoactive and immunosuppressive drugs, autoimmune diseases, postpartum state, conditions that abruptly raise sympathetic output, sexual activity, and exposure to cold or heat, especially showering and bathing) are common.[8-10] Diagnostic criteria exist (Figure 1).

By definition, the vasoconstriction is "reversible," and most patients have benign outcomes. However, some patients have seizures (1% to 17%) or ischemic or hemorrhagic stroke with persistent deficit (3% to 20%), making this entity an important condition for emergency physicians to recognize.[9-11] Hemorrhagic events occur early and ischemic events occur later.[9] Death is rare.[9]

Uncommon but serious causes include cervical arterial dissection, cerebral venous sinus thrombosis, and pituitary apoplexy (Table 1).[1]

A study of 970 patients with arterial dissections showed that 5% presented with thunderclap headache (3.6% carotid and 9.2% vertebral).[12] Nearly half of the 668 patients with carotid dissections had Horner's syndrome.[12] Examine these patients for mild ptosis and

**Table 1.** Differential diagnosis of thunderclap headache and clinical clues to the diagnosis in neurologically intact patients.

| Diagnosis | Clinical Clues to Diagnosis | Best Diagnostic Test |
|---|---|---|
| Subarachnoid hemorrhage | Neck pain by history or meningismus on physical examination, transient loss of consciousness<br>Acute hypertension | CT followed by LP (depending on timing of the CT)<br>CTA to show the offending vascular lesion* |
| Unruptured cerebral aneurysm | Third nerve palsy, usually with pupillary dilatation | CTA |
| Reversible cerebral vasoconstriction syndrome | Multiple thunderclap headaches during days or weeks is pathognomic<br>There is usually a "trigger" to the headache (see text)<br>Acute hypertension | CTA or MRA (may be falsely negative during the first week) |
| Hemorrhagic stroke | Focal neurologic deficit or altered mental status is usually present | CT |
| Cerebral venous sinus thrombosis | Any hypercoagulable risk factor, including pregnancy, postpartum state, and oral contraceptive use<br>Papilledema | CTV or MRV<br>LP will often show elevated opening pressure |
| Cervical artery dissection | Headache or neck pain, recent (even minor) head or neck trauma, subtle physical examination findings (see text) of posterior ischemia<br>Horner's syndrome (carotid dissection) | CTA or MRA (need both head and neck) |
| Posterior reversible encephalopathy syndrome/hypertensive encephalopathy | Acute hypertension (compared with patient's baseline), pregnancy or postpartum state (blood pressure elevation in these patients may be modest)<br>Seizure and visual symptoms | MRI |
| Spontaneous intracranial hypotension | Positional headache (worse on standing up, resolves with lying down)<br>Recent spine surgery or vaginal delivery<br>Tinnitus, sound distortion, and dizziness | LP with opening pressure<br>MRI with gadolinium |
| Pituitary apoplexy | Prominent visual symptoms: ptosis, various degrees of ophthalmoplegia, and decreased vision or field cut(s) | MRI with dedicated cuts of the sella turcica |
| Colloid cyst of third ventricle | Associated vomiting, dizziness, and visual symptoms; transient loss of consciousness<br>Headache is often paroxysmal and positional | CT and MRI |
| Sphenoid sinusitis | Preceding URI symptoms, fever | CT |
| Meningitis/encephalitis | Fever, neck pain, or stiffness | LP |
| Isolated acute-onset headache would be a rare presentation | Altered mental status (encephalitis) | |

*LP*, Lumbar puncture; *CTA*, CT angiography; *CTV*, computed tomographic venography; *MRV*, magnetic resonance venography; *MRA*, magnetic resonance angiography.
This table does not list various rare conditions that have been reported to cause severe rapid-onset headache as case reports. These include myocardial infarction, aortic dissection, temporal arteritis, retroclival hematoma, and rare acute ischemic stroke (although these patients should by definition have some measurable neurologic deficit). Some of the listed conditions such as meningitis rarely present with severe acute-onset headache, but are important considerations.
*Aneurysms cause approximately 80% of nontraumatic subarachnoid hemorrhages. Approximately 10%, called perimesencephalic hemorrhages, are nonaneurysmal and probably due to venous bleeding. The other 10% are caused by a wide range of vascular abnormalities, including arteriovenous malformations, blood vessel abnormalities such as moyamoya, and vasculitis or coagulapathies.[6]

anisocoria (easier to appreciate in a dark room so that the unaffected pupil dilates, accentuating the difference in size). Patients with vertebral dissections may have subtle vestibular findings, including limb ataxia, nystagmus, or abnormal gait.[13] Intracranial dissections not involving the cervical portions of the relevant artery can occur.[14]

Of patients with cerebral venous sinus thrombosis, 5% to 15% present with severe rapid-onset headache.[15,16] Some patients have papilledema. In a recent meta-analysis, the negative likelihood ratio (LR–) of a sinus thrombosis after a negative D-dimer result for patients presenting with isolated headache was 0.03 (95% confidence interval 0.0 to 0.18), suggesting that venography is unnecessary in this population.[17] For patients with risk factors, including those receiving oral contraceptives, there are currently insufficient data to use D-dimer as a rule-out test.

Pituitary apoplexy occurs from bleeding into a previously undiagnosed pituitary adenoma and can be fatal without treatment. Nearly all individuals with pituitary apoplexy have thunderclap headache, often with vomiting. Ptosis, diplopia, or decreased vision is commonly present.[18]

Table 1 summarizes clinical clues and suggested testing for these conditions. Pregnant and postpartum

1. Acute-onset severe headache (often thunderclap) with or without focal deficits or seizures
2. Monophasic course without new clinical symptoms more than 1 mo after clinical onset
3. Segmental constriction of cerebral arteries on MRA, CTA, or direct catheter angiography
4. No evidence of aneurysmal SAH (may have convexal SAH)
5. Normal or near normal CSF results (protein <1 g/L, WBC counts <15/mL, and normal glucose)
6. Complete or marked normalization of arteries on follow-up indirect or direct angiography performed within 12 wk of clinical onset

*SAH*, Subarachnoid hemorrhage; *CSF*, cerebrospinal fluid.

**Figure 1.** Diagnostic criteria for reversible cerebral vasoconstrictive syndrome.

patients with severe rapid-onset headache are at particular risk for conditions that require magnetic resonance imaging (MRI) and magnetic resonance angiography, even if noncontrast computed tomography (CT) and cerebrospinal fluid results are normal.[19] Of patients with severe rapid-onset headache, 80% ultimately receive a diagnosis of benign primary headache syndromes.

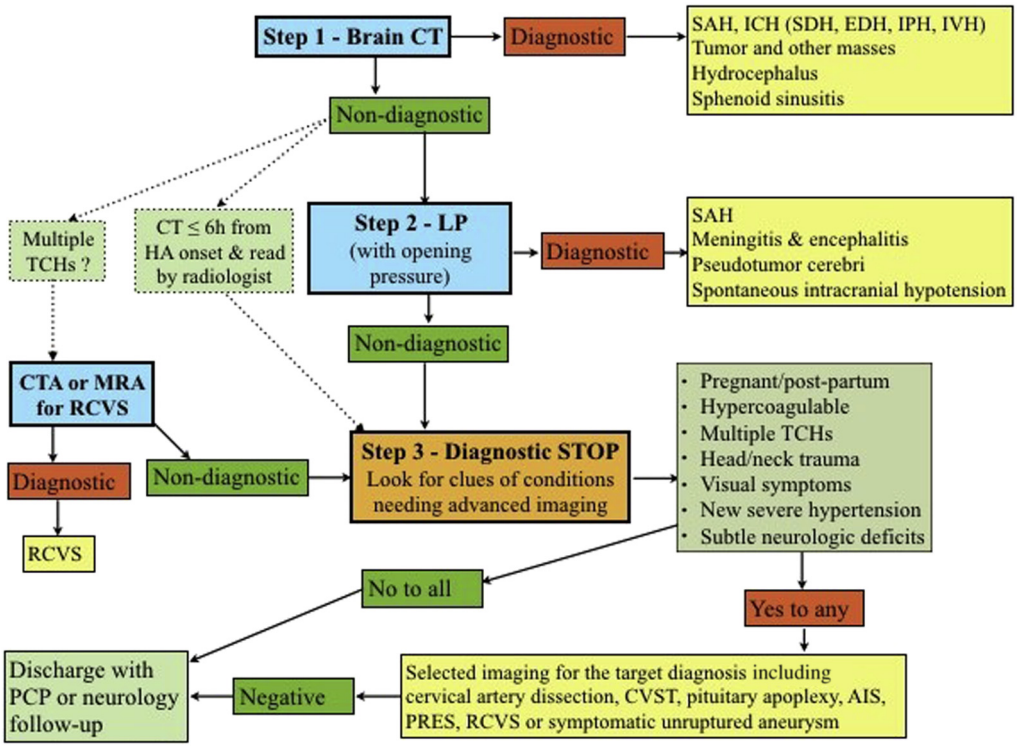


**Figure 2.** Diagnostic algorithm for patients with nontraumatic severe rapid-onset headache. Step 1: The first diagnostic step is noncontrast brain CT. Although ischemic stroke is often listed in the differential diagnosis of TCH, this would be associated with neurologic deficits. Sphenoid sinusitis 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 2 exceptions. The first group is patients whose CT result is negative within 6 hours of headache onset (in which CT result is nearly perfect). In this group, one can directly go to step 3. The other exception is patients who present with multiple TCHs, in which case, use 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 deliberately consider other less common but important vascular conditions that require advanced imaging to diagnose. *ICH*, Intracranial hemorrhage; *SDH*, subdural hematoma; *EDH*, epidural hematoma; *IPH*, intraparenchymal hemorrhage; *IVH*, intraventricular hemorrhage; *TCH*, thunderclap headache; *HA*, headache; *RCVS*, reversible cerebral vasoconstriction syndrome; *PCP*, primary care physician; *CVST*, cerebral venous sinus thrombosis; *AIS*, acute ischemic stroke; *PRES*, posterior reversible encephalopathy syndrome.

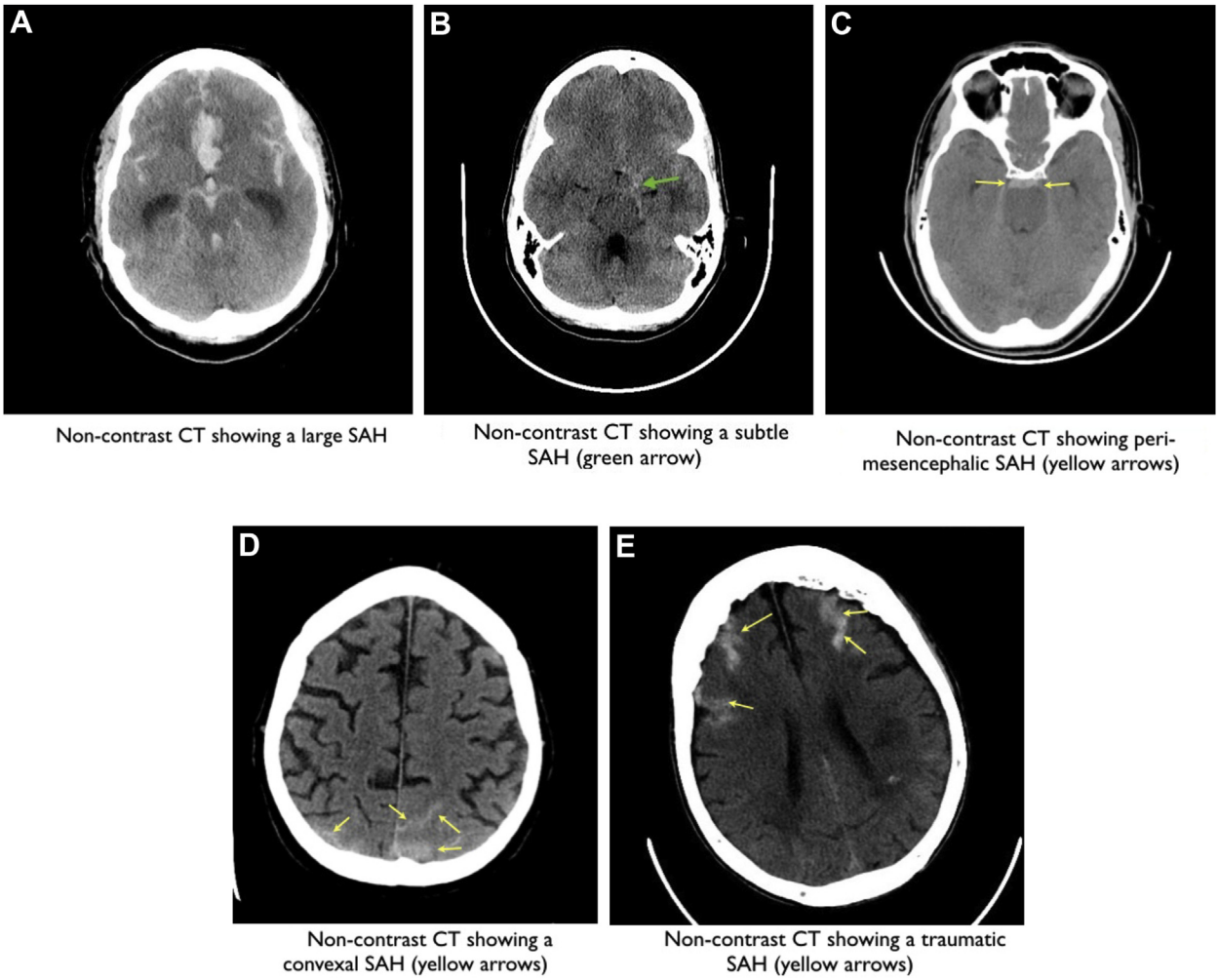


**Figure 3.** Various radiologic patterns of subarachnoid hemorrhages. *A*, Obvious large SAH: hyperdense blood in all the basal cisterns, with some dilatation of the temporal horns of the lateral ventricles, suggesting early hydrocephalus. *B*, More subtle, smaller SAH: small hyperdense collection of blood in the basal cistern adjacent to the left pons and suprasellar cistern (green arrow). *C*, Perimesencephalic SAH: the yellow arrows indicate a perimesencephalic (sometimes called a pretruncal) SAH. These hemorrhages represent approximately 10% of nontraumatic SAHs. They are thought to be caused by venous bleeding, will have a negative CTA result, and usually have an excellent outcome. However, the radiographic pattern is also observed with posterior circulation aneurysms, so all of these patients require neurosurgical consultation and vascular imaging. *D*, Convexal SAH: the yellow arrows indicate a high convexal SAH. This pattern is observed in 2 groups of patients. In younger patients, it is usually due to RCVS, but in older ones, it often indicates amyloid angiopathy. In a patient presenting with a severe rapid-onset headache, RCVS would be the likely diagnosis. *E,* Traumatic SAH: the history usually suggests a traumatic SAH (the most common cause). However, if this pattern (small amounts of SAH abutting bone, often in the anterior frontal and temporal bones) is observed in a patient without a clear history of trauma, the likely cause is a traumatic SAH.

## TRADITIONAL EVALUATION

Because history and physical examination cannot distinguish serious from benign causes, all patients with severe rapid-onset headache should undergo further evaluation, starting with CT.[4,6,20,21] The CT may be diagnostic (Figure 2), which would prompt diagnosis-specific management steps.[6,22] Not all subarachnoid hemorrhage is aneurysmal, and the blood's location portends its cause (Table 1 and Figure 3). The common radiologic finding of paranasal sinus mucosal thickening does not equate with clinical sinusitis and should not stop the evaluation for more serious diagnoses.[23]

In patients whose CT result is nondiagnostic, lumbar puncture is the next diagnostic step. A key concept, that the sensitivity for every diagnostic test for subarachnoid hemorrhage is time dependent, is due to the brisk flow of

Patient Factors
- The time of onset of the headache is clearly defined.
- The CT is performed within 6 h of headache onset.
- The presentation is an isolated severe rapid-onset headache (no primary neck pain, seizure, or syncope at onset, or other atypical presentations).
- There is no meningismus and the neurologic examination result is normal.

Radiologic Factors
- The CT scanner is a modern, third-generation or newer machine with thin cuts through the brain.
- The CT is technically adequate, without significant motion artifact.
- The hematocrit level is >30%.
- The physician interpreting the scan is an attending-level radiologist (or has equivalent experience in reading brain CT scans).
- Radiologists should specifically examine the brain CTs for subtle hydrocephalus, small amounts of blood in the dependent portions of the ventricles, and small amounts of isodense or hyperdense material in the basal cisterns.

Communication Factors
- The clinician should communicate the specific concern to the radiologist (eg, "severe acute headache; rule out SAH").
- After a negative CT result, the clinician should communicate the posttest risk of subarachnoid hemorrhage that persists (1–2 per 1,000).

**Figure 4.** Considerations in omitting the lumbar puncture in patients whose CT result is negative within 6 hours of headache onset.

cerebrospinal fluid. Manufactured in the choroid plexuses at a rate of 25 mL per hour, cerebrospinal fluid circulates and is reabsorbed in the arachnoid granulations.[24] CT and RBC counts are more sensitive early. Xanthochromia (from catabolism of hemoglobin in vivo) is more sensitive later.

Mounting evidence shows that a CT conducted within 6 hours of headache onset and whose results are read by an attending radiologist as negative has an LR– of 0.01, essentially ruling out the diagnosis.[5,25] For these early-presenting patients, I no longer recommend lumbar puncture, but attention to details is important. I discuss the data and the options with the patient and document that conversation (Figure 4).

In patients with negative results for CT conducted beyond 6 hours from headache onset, the CT's LR– is 0.14 (95% confidence interval 0.14 to 0.17).[26] However, the sensitivity of CT is not a dichotomous variable with a cut point at 6 hours, and in fact, it decays rapidly with time from headache onset. The LR– of a negative CT result for a patient scanned at 4 days from headache onset is much higher than for a CT conducted at 12 hours after headache onset. This is a critical limitation of the extant subarachnoid hemorrhage diagnosis literature; the LR– is applied to a temporally heterogeneous group of patients.

Current guidelines recommend performing a lumbar puncture,[21,27] which gives unique diagnostic information (cell counts, xanthochromia, and opening pressure). If a lumbar puncture is performed, measure the opening pressure (normally 6 to 25 cm of water).[24] Low pressure (<6 cm of water) suggests spontaneous intracranial hypotension, and elevated pressure (>25 cm of water) suggests subarachnoid hemorrhage,[28] or the occasional case of idiopathic intracranial hypertension and venous sinus thrombosis.[6] In the classic study by Walton[28] of nearly 300 patients from the pre-CT era, opening pressure was high (>25 cm of water) in 96 of 213 patients (45%) who had the pressure recorded. Elevated pressure is not consistent with a traumatic tap.

When a traumatic lumbar puncture is immediately recognized, after measuring the opening pressure, waste 5 to 10 mL of cerebrospinal fluid between the first and last tubes collected, which greatly increases the likelihood that the final tube will contain no (or very few) RBCs. The body will replace 10 mL of cerebrospinal fluid in 20 to 30 minutes.

One study found that no patient with an RBC count in the final tube of less than 100 had a subarachnoid hemorrhage, that counts greater than 10,000 greatly increased the likelihood of subarachnoid hemorrhage, and that the percentage decrease from the first to last tubes also suggested subarachnoid hemorrhage.[29] However, this study enrolled only small numbers of patients who mostly had positive CT results (and presumably higher RBC counts).[29] Another study found that the combination of no xanthochromia and RBCs at fewer than 2,000/mL of cerebrospinal fluid for subarachnoid hemorrhage diagnosis had a LR– of zero.[30] All 89 of the patients in the study by Walton[28] who received lumbar puncture within the first 12 hours had bloody cerebrospinal fluid, but after 12 hours, a few patients' cerebrospinal fluid had no RBCs.[28] This proportion increased with passage of time after the hemorrhage.

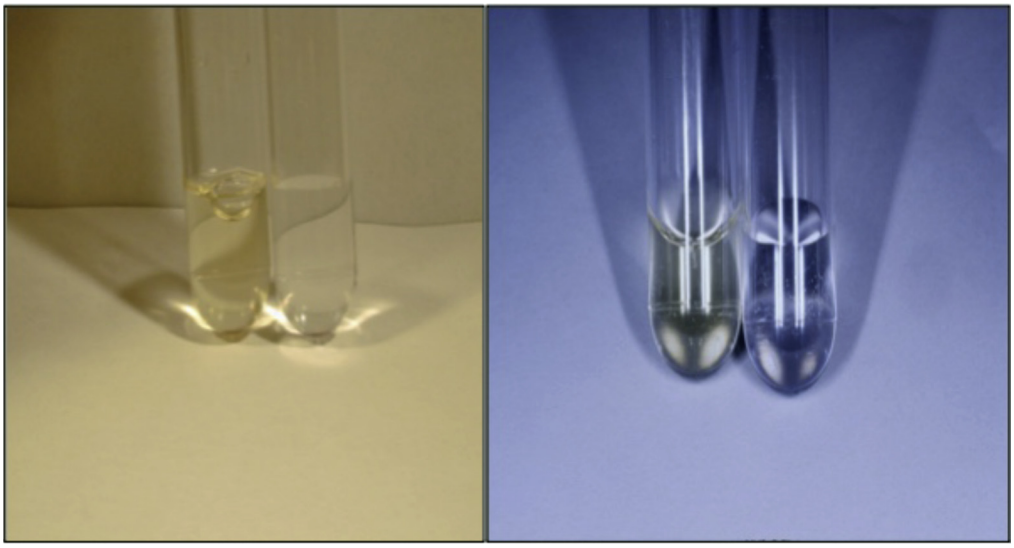

**Figure 5.** Xanthochromia. These 2 images are of the same tubes (the left tube containing CSF that is xanthochromic and the right tube containing distilled water). The photo on the left was taken with incandescent light (which makes the difference between the CSF and the water less apparent), and the photo on the right was taken in fluorescent light (which makes the difference easier to see). Xanthochromia results from the in vivo degradation of hemoglobin and requires time. By 12 hours from the SAH, all patients will have this finding, even when the visual inspection method is used. Xanthochromia can also be identified by spectrophotometry, which is more sensitive but less specific.

Xanthochromia is measured either by visual inspection or spectrophotometry (Figure 5).[31] Spectrophotometry is more sensitive but less specific than visual inspection.[32,33] Visual inspection has good performance characteristics,[34,35] and nearly all US hospital laboratories use visual inspection.[36] Whichever technique is used, xanthochromia requires 6 to 12 hours to develop. All 180 patients who received lumbar puncture between 12 hours and 14 days (for whom the presence of visually apparent xanthochromia was recorded) had the finding.[28]

A positive lumbar puncture result for subarachnoid hemorrhage should prompt immediate neurosurgical consultation and CT angiography[37] or other steps if another diagnosis is found, depending on the diagnosis. Normal CT and cerebrospinal fluid results (no RBCs or xanthochromia) within 2 weeks of the bleeding event effectively exclude subarachnoid hemorrhage.[28,38,39]

## IF CT AND LUMBAR PUNCTURE RESULTS ARE NORMAL, IS ADDITIONAL TESTING NECESSARY?

Neurologists often recommend performing advanced imaging on all thunderclap headache patients[1]; however, they see a referral population rather than "all comers." My approach is a selective one. The 2008 American College of Emergency Physicians guidelines state that patients with severe, rapid-onset headache with negative CT and cerebrospinal fluid results can be safely discharged.[21] A pooled analysis of 813 such patients supports this conclusion.[39] At this stage of the evaluation, I recommend a "diagnostic STOP" to deliberately consider other uncommon diagnoses (Figure 2). Patients with bloody cerebrospinal fluid and negative CT angiography results are probably safe to discharge.[40]

## ALTERNATIVE DIAGNOSTIC STRATEGIES FOR SUBARACHNOID HEMORRHAGE

Driven by factors such as ease of CT angiography, increasing availability of MRI and magnetic resonance angiography, radiation concerns, and increasing reluctance to perform lumbar puncture and its low yield in CT-negative patients, alternative diagnostic strategies have been proposed. To my knowledge, no clinical trials compare new algorithms with the traditional one.

A CT–CT angiography strategy has gained particular traction. Issues arise in that this approach focuses on subarachnoid hemorrhage rather than the full differential diagnosis. For example, which body part should be imaged? This depends on the indication (head only for most diagnoses, but head and neck for dissection). How should the bolus be timed? Arterial is indicated for most diagnoses, but the venous phase is necessary for sinus thrombosis. What about the timing from headache onset? In the first week of reversible cerebral vasoconstriction syndrome, the

**Table 2.** Advantages and disadvantages of various diagnostic testing strategies in patients presenting with thunderclap headache.

| Diagnostic Algorithm | Advantages | Disadvantages | Comments |
|---|---|---|---|
| LP first | Ensures that an LP is conducted<br>Diagnoses conditions that require CSF analysis<br>No radiation<br>Widely available | No information derived from CT<br>Pain and anxiety from LP<br>Ambiguity from traumatic tap<br>Time spent performing the LP<br>Post-LP headache | May be useful in a resource-poor environment<br>Important to conduct a careful neurologic examination before LP<br>Has not been studied clinically |
| CT only | Rapid<br>Widely available<br>Avoids pain/anxiety and other complications of LP | Misses occasional CT-negative SAH and other diagnoses made by CSF analysis | Will miss the occasional patient with SAH who is CT negative but LP positive<br>Likely the best strategy in patients with negative CT results in <6 h from onset of headache |
| CT/LP | Widely available, no IV contrast, excellent sensitivity for SAH, will diagnose conditions that require CSF analysis | Will miss some patients with the less common vascular causes (see text)<br>Pain and anxiety from LP<br>Time spent performing the LP<br>Ambiguity from traumatic tap<br>Post-LP headache | This is the traditional, guideline-recommended approach |
| CT/CTA | Accurately diagnoses aneurysms and arteriovenous malformations<br>Fast and widely available | May miss an SAH<br>Will diagnose incidental aneurysms in 3.2% of patients<br>Radiation and IV contrast effects | Unintended consequences of diagnosing incidental aneurysms include complications of treatments (if treated) and anxiety, cost of cumulative surveillance imaging studies, and potential difficulty obtaining health insurance (if untreated)<br>Must consider limitations (in regard to sensitivity for reversible cerebrovascular vasoconstriction syndrome, cerebral venous sinus thrombosis, and dissections) per text |
| MRI only | No radiation<br>Better for diagnosing subacute SAH<br>Diagnoses many uncommon conditions | Not often readily available<br>Issues with MRI contraindications | MRI has the same issue as CT with respect to spectrum bias, so that ideally, LP should be performed after a negative MRI result |
| MRI/MRA | No radiation<br>Better for diagnosing subacute SAH (than CT)<br>Diagnoses many uncommon conditions | Not often readily available<br>Issues with MRI contraindications | Unintended consequences of diagnosing incidental aneurysms (see above) |
| MRI/LP | No radiation<br>Better for diagnosing subacute SAH (than CT)<br>Diagnoses many uncommon conditions | Not often readily available<br>Issues with MRI contraindications<br>Pain and anxiety from LP<br>Ambiguity from traumatic tap<br>Post-LP headache | If available, this is a rational approach because MRI will pick up subacute blood, as well as unusual conditions, much better than CT |

*IV*, Intravenous.
These advantages and disadvantages can be considered "biases" on the part of both the physician and the patient. If a physician uses one of the nontraditional approaches, he or she should discuss these with the patient. The text does not discuss the LP-only approach (which has been suggested only according to mathematical modeling) or MRI-based approaches (which are logical but not readily available approaches).

CT angiography result is often negative.[9] And finally, what is the significance of finding an aneurysm, which occurs incidentally in 3.2% of individuals?[41]

The negative consequences of routine CT angiography beyond incremental radiation exposure have been reviewed (Table 2).[42] Chief among them is diagnosing incidental aneurysms. Short of cerebrospinal fluid examination, there is no way to distinguish a ruptured from an incidental aneurysm. That said, if an aneurysm is diagnosed, no matter the size, a neurosurgeon should be consulted because, contrary to conventional wisdom, small aneurysms account for nearly half of all subarachnoid hemorrhages. In 2 studies of patients with subarachnoid hemorrhage (total N=991), 47% to 48% were less than 5 mm.[43,44]

In one study of 70 patients with acute severe headache, normal CT results, and normal cerebrospinal fluid analysis results, CT angiography showed vascular lesions in 13 (19%).[45] However, the patient population was a highly

selected cohort from a larger group (225 patients) for whom the physicians decided not to perform CT angiography; they had been treated at a referral center, and 5 of the 13 had previous known subarachnoid hemorrhage or venous sinus thrombosis. All 8 aneurysms identified were considered unruptured but treated anyway.

Two cost-effectiveness analyses concluded that CT followed by lumbar puncture was equivalent to or better than CT and CT angiography.[46,47] However, the utility of lumbar puncture after negative CT result beyond 6 hours has been questioned.[5,48,49] In an observational retrospective review, only 9 of 1,898 patients with possible subarachnoid hemorrhage and negative CT result with a positive lumbar puncture result had a causative vascular lesion (0.5%) but did not report time from symptom onset.[48] On the other hand, in a large prospective study (2,179 patients who presented beyond 6 hours from headache onset, of whom 119 had subarachnoid hemorrhage), the CT result was falsely negative for 17 patients.[26] Because these data are somewhat contradictory and not as clear as some articles would suggest, and because of the aforementioned lack of study of CT accuracy by time intervals, my own practice is to perform a lumbar puncture in these later-presenting patients. Current national guidelines (American College of Emergency Physicians 2008 and American Heart Association 2012) still recommend CT followed by lumbar puncture.[21,27]

Each strategy has clear advantages and disadvantages that incorporate physician and patient biases (Table 2), which, in the spirit of shared decisionmaking, the physician should discuss with patients; some may wish to avoid radiation exposure, whereas others may adamantly refuse lumbar puncture. Regardless of the strategy chosen, it is important to consider the full range of potentially serious causes of severe rapid-onset headache, not just subarachnoid hemorrhage.

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