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Evidence-Based Medicine

IS A LUMBAR PUNCTURE REQUIRED TO RULE OUT ATRAUMATIC SUBARACHNOID HEMORRHAGE IN EMERGENCY DEPARTMENT PATIENTS WITH HEADACHE AND NORMAL BRAIN COMPUTED TOMOGRAPHY MORE THAN SIX HOURS AFTER SYMPTOM ONSET?

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☐ **Abstract—Background: Atraumatic subarachnoid hemorrhage (SAH) is a deadly condition that most commonly presents as acute, severe headache. Controversy exists concerning evaluation of SAH based on the time from onset of symptoms, specifically if the headache occurred > 6 h prior to patient presentation. Clinical Question: Do patients undergoing evaluation for atraumatic SAH who have a negative computed tomography (CT) scan of the head obtained more than 6 h after symptom onset require a subsequent lumbar puncture to rule out the diagnosis? Evidence Review: Studies retrieved included a retrospective cohort study, two prospective cohort studies, and a case-control study. These studies provide estimates of the diagnostic accuracy of head CT imaging obtained > 6 h from symptom onset and diagnostic test characteristics of subsequent lumbar puncture. Conclusion: The probability of SAH above which emergency clinicians should perform a lumbar puncture is 1.0%. This threshold is essentially the same as the estimated probability of SAH in patients with a negative head CT obtained more than 6 h from symptom onset. Emergency physicians might reasonably decide to either perform or forego this procedure. Consequently, we contend that the decision whether to perform lumbar puncture in these instances is an excellent candidate for shared decision-making.**

☐ **Keywords—subarachnoid hemorrhage; decision tool; computed tomography; lumbar puncture**

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CASE REPORT

A 43-year-old woman presents via ambulance to the Emergency Department (ED) with a headache. She reports the initial onset of symptoms while walking 12 h prior to presentation. She endorses diffuse head pain and associated nausea with one episode of emesis. On physical examination, the patient is morbidly obese and resting on a stretcher. Her only reported past medical history is a lumbar spine fusion. She is alert and oriented to person, place, time, and location. Her vital signs are notable for a systolic blood pressure of 170 mm Hg and a diastolic blood pressure of 110 mm Hg. The neurologic

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examination is without focal abnormality, though she expresses some discomfort in her neck during range-of-motion testing. Given the presence of multiple signs and symptoms concerning for potential subarachnoid hemorrhage, you order computed tomography (CT) of the head, which shows no evidence of intracranial bleed. You ponder whether you must now perform a lumbar puncture diagnostic procedure to rule out subarachnoid hemorrhage.

CLINICAL QUESTION

Do patients undergoing evaluation for atraumatic subarachnoid hemorrhage (SAH) who have negative CT of the head more than 6 h after symptom onset require a subsequent lumbar puncture to rule out the diagnosis?

CONTEXT

SAH is a deadly disease that emergency physicians must maintain in their differential of patients presenting to the ED with atraumatic headache. Headaches due to SAH classically are severe and sudden in onset (1,2). Other characteristic symptoms include nausea and vomiting and meningismus (3,4). It is not uncommon for emergency physicians to miss the diagnosis given its relative rarity among the many headache patients presenting to ED settings (5).

Two broad categories of SAH exist. First is rupture of an aneurysm of the cerebral arterial vasculature, accounting for 75–80% of SAH (6,7). The prevalence of cerebral aneurysms in the adult population without specific risk factors approximates 2.3% (8). The risk of aneurysm rupture is strongly associated with aneurysm size, with aneurysms 7 mm or smaller at near negligible risk of rupture (9). When SAH does occur due to an aneurysm, those SAH bleeds carry the highest risk of mortality and require surgical intervention (10–12). Surgical treatment options include surgical clipping or coiling (13). Expedient diagnosis is critical to optimize outcomes in these patients, with one cohort study reporting 14% absolute difference in mortality between aneurysmal SAH patients initially misdiagnosed vs. patients correctly diagnosed (14).

The second broad category of SAH is a bleed without any identified aneurysm, termed a peri-mesencephalic SAH. In contrast to aneurysmal bleeds, the prognosis for these patients is generally excellent (15–17). Furthermore, given that there is no discrete anatomic correlate for the patient's bleed, there are no corresponding neurosurgical interventions to stem the bleeding itself. Interventions instead focus upon supportive measures to alleviate the complications of the disease process, such as symptomatic management or, more rarely, ventricular drains for secondary hydrocephalus (18). Hence, early identification of these bleeds is less imperative than for aneurysmal SAH given that indicated interventions focus less upon the SAH cause per se and more upon the sequelae resulting from that bleed that would often be apparent without knowing the underlying diagnosis.

Of central importance for the emergency clinician, then, is rapid and accurate diagnosis or rule-out of aneurysmal SAH. The recently validated Ottawa SAH Rule offers clinicians a highly sensitive (100%), albeit poorly specific (12.7%), tool for ruling out SAH without the need for any neuroimaging (19). For patients such as the woman in this clinical case vignette, with high-risk features for whom rule-out is not possible using this rule, CT of the head without contrast is the mainstay for the initial evaluation. Historical data indicate that this imaging modality is highly accurate within the first 6 h after initial onset of symptoms (>95% sensitivity), though sensitivity declines as more time from initial onset of symptoms elapses (20–22). The Ottawa SAH Rule prospective validation study confirmed 95.5% sensitivity of a negative head CT obtained within 6 h of symptom onset (19). Accordingly, the American College of Emergency Physicians (ACEP) Clinical Policy on headaches recommends no further diagnostic work-up for SAH among neurologically intact patients with a negative head CT obtained within this time horizon (23).

The appropriate diagnostic strategy for patients with a negative CT scan of the head obtained > 6 h from initial symptom onset is less clear. The aforementioned ACEP clinical policy recommends that these patients undergo either lumbar puncture or CT angiography for further evaluation (23). These studies are not without risk. In the case of lumbar puncture, complications may include post lumbar puncture headache (25%), radicular pain (1.5%), rarely, in the case of anticoagulated patients bleeding with paraparesis (1.5%), or a traumatic tap (24–26). In the case of CT angiography, radiation and contrast exposure can be problematic, though more contemporary data suggest a minimal risk of nephrotoxicity from contrast (27–29). Additionally, clinicians must consider the risk of unnecessary coiling and clipping procedures, which carry an associated mortality of approximately 0.7% (30). This is a particular concern for patients with aneurysms 7 mm or less in size, which, given an incredibly low risk of rupture, may well represent incidental findings during an evaluation for SAH.

EVIDENCE SEARCH

To address the clinical question, you search for studies reporting diagnostic test characteristics for CT imaging after 6 h to inform pretest probability. You also seek studies

reporting yield for lumbar puncture as part of the subsequent workup for SAH. The patient population in whom you are interested is, specifically, ED patients with a negative head CT more than 6 h after symptom onset. You restrict your search results to primary literature. Utilizing the search terms "subarachnoid hemorrhage," "CT," and "emergency department" yields 140 citations. Adding the term "lumbar puncture" narrows the results to 48 citations. From these citations, you pull the following four resources from the literature.

EVIDENCE REVIEW

Title: Is the Combination of Negative Computed Tomography Result and Negative Lumbar Puncture Result Sufficient to Rule Out Subarachnoid Hemorrhage? (31).

Population: ED patients > 15 years of age with a nontraumatic acute headache.

Study design: Prospective cohort study.

Primary outcome: SAH was defined by any one of the following criteria. The first was subarachnoid blood on CT, as reported in the final radiology report. The second was xanthochromia in the cerebrospinal fluid by visual inspection of the supernatant post centrifugation. The third was red blood cells (RBCs) in the final tube of cerebrospinal fluid exceeding 5×10^6 RBCs/L; this criterion requires confirmation of an aneurysm demonstrated on cerebral angiography whether traditional, CT, or magnetic resonance imaging (MRI). The final criterion included autopsy results confirming subarachnoid hemorrhage. The investigators contacted all subjects by phone at least 6 months from the initial ED visit to ascertain any previously unmeasured outcomes.

Inclusion criteria: Patients with a normal neurologic examination who underwent a noncontrast head CT and lumbar puncture. All patients had headaches reaching maximal intensity within 1 h and presenting within 14 days of onset of symptoms.

Main results: Of 592 enrolled patients, 61 had subarachnoid hemorrhage. There were 61 true positives, 55 diagnosed by CT and 6 diagnosed by lumbar puncture. There were 175 false positives, all of which were attributed to traumatic taps (RBCs exceeding 5×10^6 RBCs/L with no subsequent identification of an aneurysm). There were no false negatives and 356 true negatives. These data correspond to a sensitivity of 100% and a specificity of 67%. In additional analyses, assuming some patients lost to follow-up had a SAH, the sensitivity was 98%, and specificity remained 67%. The authors do not report the duration of headache symptoms for individual patients in the study.

Title: Time-Dependent Test Characteristics of Head Computed Tomography in Patients Suspected of Nontraumatic Subarachnoid Hemorrhage (32).

Population: All patients > 15 years of age presenting to the investigators' ED clinical suspicion for nontraumatic SAH.

Study design: Retrospective cohort study.

Primary outcome: SAH was defined by a noncontrast head CT demonstrating blood in the subarachnoid space. Alternatively, the authors considered cerebrospinal fluid positive for bilirubin as consistent with the diagnosis of SAH.

Inclusion criteria: Inclusion criteria comprised patients known to have a time of onset of symptoms within 14 days. Patients further had a normal level of consciousness (Glasgow Coma Scale score of 15), did not undergo transfer from an outside hospital, and did not have any focal neurologic deficits. Finally, patients had not undergone a lumbar puncture procedure in the month preceding presentation.

Main results: The authors included 250 patients in their analysis. Of these, 137 (54.8%) underwent head CT within 6 h of symptom onset, whereas the remaining 113 (45.2%) underwent CT imaging after 6 h of symptom onset. In both groups, the specificity of head CT was 100%. Sensitivity dropped from 98.5% when obtained within 6 h of symptom onset to 90.0% after 6 h of symptom onset (negative likelihood ratio 0.10).

Title: Sensitivity of Computed Tomography Performed Within Six Hours of Onset of Headache for Diagnosis of Subarachnoid Haemorrhage: Prospective Cohort Study (33).

Population: Consecutive ED adult patients aged over 15 years presenting with nontraumatic acute headache or syncope associated with headache.

Study Design: Prospective multicenter cohort study.

Primary Outcome: SAH was determined by any of the following criteria. The first was subarachnoid blood on noncontrast head CT. The second included visible xanthochromia in the cerebrospinal fluid. The final criterion was $> 5 \times 10^6$ RBCs/L in the final tube of cerebrospinal fluid collection together with an aneurysm identified on cerebral angiography (including digital subtraction, CT, or MRI).

Inclusion Criteria: Patients were alert (Glasgow Coma Scale score of 15), had headache symptoms that started within 14 days of presentation, and did not undergo transfer from another facility with confirmed SAH. Patients did not have a history of recurrent headaches of similar character to their current symptoms. Patients, further, did not have focal neurologic deficits or papilledema. Finally, patients did not have a history of known cerebral aneurysm, SAH, ventricular shunt, or brain neoplasm.

Main Results: The study enrolled 3132 patients, of whom 240 (7.7%) had confirmed SAH. Of these, 953 (30.4%) underwent CT within 6 h of symptom onset, and the remaining 2179 (69.6%) patients underwent CT

Bayesian analysis - A method of statistical inference (named for English mathematician Thomas Bayes) that allows one to combine prior information about a population parameter with evidence from information contained in a sample to guide the statistical inference process.

Gold Standard - A reference standard for evaluating the performance of a diagnostic test. The gold-standard test is assumed to be correct in identifying the presence or absence of disease 100% of the time.

Pretest Probability - The probability of disease for a given patient before the physician knows the results of a specific diagnostic test. Generally thought to equal the prevalence of the disease in the population of patients that most resemble the patient before the test is conducted.

Post-test Probability - The probability of disease for a given patient after the physician knows the results of a specific diagnostic test. The post-test probability is different from the pretest probability as a function of the magnitude of the likelihood ratio characteristic of the diagnostic test.

Testing Threshold – The indifference point for the choice between therapy and performing a diagnostic test to further reduce uncertainty.

Sensitivity - The ability of a test to identify patients who have a specific disease or outcome. The true-positive rate. The probability of a positive test result in patients with the disease.

Specificity - The ability of a test to identify patients without the disease or outcome when it is not present. The true-negative rate. The probability of a negative test result in patients without the disease.

Negative Predictive Value – The probability of no disease in patients with a negative test result.

Positive Predictive Value – The probability of disease in patients with a positive test result.

Figure 1. Evidence-based medicine teaching points.

after 6 h of symptoms onset. Only 1546 (49.4%) of included patients underwent lumbar puncture. In both groups, the specificity of the head CT was 100%. Head CT sensitivity for SAH dropped from 100% when obtained within 6 h of symptom onset to 85.7%, 95% confidence interval (CI) 78.3–90.9%, after 6 h of symptom onset (negative likelihood ratio of 0.14, 95% CI 0.09–0.22).

Title: Nontraumatic Subarachnoid Hemorrhage in the Setting of Negative Cranial Computed Tomography Results: External Validation of a Clinical and Imaging Prediction Rule (34).

Population: ED patients > 18 years of age with a related International Statistical Classification of Diseases and Related Health Problems, Ninth Edition (ICD-9) diagnosis code of SAH (430) along with both a noncontrast head CT and cerebrospinal fluid analysis during their ED visit.

Study design: Case-control chart review study.

Primary outcome: SAH was defined by meeting at least one of the following criteria. The first was presence of xanthochromia on visual inspection of cerebrospinal fluid. The second was angiographic evidence of cerebral aneurysm or arteriovenous malformation. The third was subsequent cranial imaging demonstrating SAH within 48 h of index lumbar puncture procedure.

Inclusion criteria: Case inclusion criteria included head CT without evidence of SAH by final radiology interpretation, normal neurological examination (aside from isolated single cranial nerve deficits), and > 5 RBCs/μL of cerebrospinal fluid. Cases also required at least one of the criteria noted above under "primary outcome" as evidence of SAH. Matched controls were patients with ED-related ICD-9 diagnosis codes of headache (784 and 339) who also underwent both noncontrast CT and cerebrospinal fluid analysis with documented concern by SAH by the treating physician during the ED visit. The investigators matched controls to cases by year and ED facility in a ratio of three controls for every case to control for variations in ED practice and CT technology over time.

Main results: The investigators identified 55 patients with SAH during the 11-year study period presenting to 21 EDs across the Kaiser Permanente health system. Of these, 34 (62%) were aneurysmal. The authors do not report the sensitivity and specificity of CT imaging across all patients but note that 11 of the 55 patients with SAH (20%) had a negative head CT within 6 h of symptom

onset. Of these cases, one had an arteriovenous malformation and 6 had aneurysms on subsequent angiography, all of which were 7 mm or less in size.

CONCLUSIONS

Perry et al. provide evidence that the combination of head CT and lumbar puncture can effectively rule out SAH with near 100% sensitivity with symptom duration up to 14 days (31). Unfortunately, this sensitivity comes at the expense of specificity (67%), likely due to traumatic taps (26). The remaining three studies highlight the dangers of omitting lumbar puncture among patients with a negative head CT scan. Backes et al. (32) and Perry et al. (33) report a sensitivity of head CT obtained > 6 h from symptom onset of 90.0% and 85.7%, respectively. Furthermore, Mark et al.'s case-control study, admittedly susceptible to bias due to retrospective design, finds that 20% of their patients with SAH reportedly had negative CT imaging *within* 6 hours of symptom onset (34,35). Taken together, these results support a conservative approach of incorporating lumbar puncture in the evaluation of these patients.

How best to determine whether to trade specificity for sensitivity through the addition of lumbar puncture to head CT imaging? You decide to use the concept of a testing threshold (Figure 1). As formulated by Pauker and Kassirer, the testing threshold represents the "indifference point for the choice between withholding therapy and performing a diagnostic test" (36). The threshold represents the pretest probability of disease, above which the combined consideration of test accuracy, test harm, and treatment benefits and harm warrants proceeding with a diagnostic test. The formula for the testing threshold is:

$$\frac{(1-\text{Specificity})*(\textit{Risk of Treatment})+\textit{Risk of Testing}}{(1-\text{Specificity})*(\textit{Risk of Treatment})+(\text{Specificity})*\textit{Benefit of Treatment}}$$

Accounting for all potential risks and benefits would require use of a utility-based outcome measure (37). An approximate calculation is possible by considering a single terminal outcome measure of interest, namely mortality. Assuming a sensitivity of 100% and specificity of 67% for lumbar puncture, 0.45% mortality with surgical treatment, no testing risk, and a 14% absolute reduction in mortality with treatment yields a testing threshold of 1.0%, above which you should pursue lumbar puncture testing (14,30,31,34). The prospective consecutive patient cohort data from Perry et al. reported a 7.7% prevalence of SAH and a negative likelihood ratio of disease after CT imaging more than 6 h from symptom onset of 0.14 (33). These values translate to a probability of disease after head CT but prior to lumbar puncture of approximately 1.1%, exceeding the testing threshold.

Your calculation of pre-lumbar puncture probability of SAH and testing threshold are close in value. Given this proximity, subtle shifts in numbers can have a significant impact on decision-making. Indeed, the confidence interval of the negative likelihood ratio for negative CT imaging obtained more than 6 h from symptoms onset spans 0.09 to 0.22. Accordingly, this means the range of probability of disease for SAH after a negative CT scan in this time window ranges from 0.7% to 1.7%. In fact, the true range of potential values is undoubtedly greater, as could be demonstrated by techniques beyond the scope of this exercise, such as probabilistic sensitivity analyses simultaneously capturing uncertainty in all variables, not just CT sensitivity (37).

Further decision-making complexity arises from acknowledgement that uncertainty similarly exists in the calculation of the testing threshold. For example, Carpenter et al. calculated a 2% test threshold for post-CT lumbar puncture (38). Although not dramatically different from our 1.0% value, this estimate would change management, assuming a 1.1% probability of disease after a negative head CT obtained more than 6 h after onset of symptoms. The discrepancy arises from differences in their calculation inputs to include assuming a higher risk of lumbar puncture testing and different diagnostic test characteristics. These calculations highlight that Bayesian analyses are highly dependent upon the values used to calculate estimated probability of disease and testing thresholds.

Ultimately then, emergency physicians might reasonably decide to either perform or forego this procedure. Consequently, we contend that the decision whether to perform lumbar puncture in these instances is an excellent candidate for shared decision-making. In this instance, given the imperative to not miss deadly pathology, you and the patient collectively decide that you will perform a lumbar puncture to rule out SAH.

Commentary–Dr. Florian Schmitzberger, Dr. William Meurer

Sudden onset of a severe headache should prompt diagnostic consideration of subarachnoid hemorrhage. Current consensus in emergency medicine is that CT of the

head performed within 6 h of symptom onset is sufficient to make this critical diagnosis. Beyond this timeframe, controversy exists. It is less clear whether modern CT is sufficiently sensitive or if a lumbar puncture is required to assess for xanthochromia or RBCs. Lumbar punctures are not without risk. They can cause acute localized pain and have delayed problems such as post-dural puncture headaches, infection, or bleeding. This procedure can be unpopular with clinicians and patients. Reasons for this, in addition to potential for discomfort, include the additional time required to perform the procedure, the risk of an unsuccessful attempt, and the small number of SAH identified after a negative head CT.

Given these barriers, it is important to accurately assess pretest risk, which is a difficult undertaking. The classic presentation of the "worst headache of my life" is not truly pathognomonic for SAH, and accurately assessing who truly requires imaging and possible further investigation is largely subjective. One can achieve some calibration with pretest risk by looking at nationally representative data. Consider that EDs see roughly 4 million visits for headaches a year; only 1–2% (about 30,000 per year) of these visits are due to an underlying aneurysmal SAH (39). Or put another way, nearly one in five U.S. adults have a serious headache in a given 3-month period, yet only 1 in roughly 26,000 will experience hospitalization for SAH (40). Finally, as CT scanning for headache inexorably increases (while the number of cases of spontaneous SAH remains relatively constant), the number of studies evaluating the false negative rate observed in practice will go down. Put another way, as our collective threshold for CT scanning in headache has gotten lower over the years, fewer studies are positive—thus inflating the observed negative predictive value (as prevalence among those scanned has actually decreased owing to the larger number of scans.) If we estimate that 25% of the 4 million ED headache visits in the United States have CT scanning, this would mean our collective pre-CT probability of SAH is only 3%.

Contemporary guidelines such as the ACEP Clinical Policy on headaches have evolved to give guidance for patients presenting with such symptoms. Clinical decision rules, such as the Ottawa SAH rule, can be helpful, and shared decision-making can be utilized. A remaining consideration, however, is which testing to perform and how to deal with potentially nondiagnostic tests or incidental findings. In one study, 61 of 592 headache patients ultimately had SAH, 55 diagnosed by CT and 6 by LP; however, there were 175 LP false positives, all due to traumatic punctures (31). Is a specificity of 67% adequate and are you facing a situation such as using a D-dimer where a positive result often essentially forces your hand in ordering a CT angiogram in this case? Some practitioners may elect to perform a CT angiogram after a nondiagnostic CT without contrast, given these limitations.

Looking ahead, there are calls for MRI/magnetic resonance angiography (MRA) to be studied as an ionizing radiation-free option that avoids iodinated contrast agents. This is particularly pertinent in times where more EDs have access to rapid MRI. CT imaging has been the standard in evaluating for hemorrhage in stroke and trauma, but recent research strongly suggests that MRI/MRA has good sensitivity and may be a future desired alternative. Future research in this area is needed (41). The studies referenced in this review can help with answering these questions, but have limitations and do not give a perfectly clear picture and, depending on choice of statistical analysis, demonstrate a range of risk–benefit estimates. There is a powerful urge for the practitioner to avoid causing pain to the patient and forgo a lumbar puncture, however, given available data, it may be prudent to go one step further beyond a CT scan to truly rule out devastating and intervenable pathology. Lumbar puncture remains a useful tool and we need to remain highly proficient at it to maximize the chance it provides us with diagnostically useful information.

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ARTICLE SUMMARY

1. Why is this topic important?

The utility of lumbar puncture after normal head computed tomography (CT) in patients presenting after 6 h from headache onset is controversial in the evaluation of subarachnoid hemorrhage (SAH).

2. What is the clinical question?

Do patients undergoing evaluation for atraumatic SAH who have a negative head CT obtained more than 6 h after symptom onset require a subsequent lumbar puncture to exclude SAH?

3. Search strategy.

PubMed search using combined keywords of "subarachnoid hemorrhage," "CT," and "emergency department."

4. Citations appraised.

Is the Combination of Negative Computed Tomography Result and Negative Lumbar Puncture Result Sufficient to Rule Out Subarachnoid Hemorrhage? (31).

Time-Dependent Test Characteristics of Head Computed Tomography in Patients Suspected of Nontraumatic Subarachnoid Hemorrhage (32).

Sensitivity of Computed Tomography Performed Within Six Hours of Onset of Headache for Diagnosis of Subarachnoid Haemorrhage: Prospective Cohort Study (33).

Nontraumatic Subarachnoid Hemorrhage in the Setting of Negative Cranial Computed Tomography Results: External Validation of a Clinical and Imaging Prediction Rule (34).

5. Are the results valid?

Yes–for patients with suspected SAH.

6. What are the results?

The probability of SAH above which emergency clinicians should perform a lumbar puncture is 1.0%, which is lower than the estimated probability of SAH in patients with a negative head CT scan obtained more than 6 h from symptom onset.

7. Can I apply the results to my practice?

Yes.