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

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Study objective: Current clinical practice assumes a negative computed tomography (CT) head scan result and a negative lumbar puncture result together are adequate to rule out subarachnoid hemorrhage in patients with acute headache. Our objective is to determine the sensitivity of a negative CT result combined with a negative lumbar puncture result to exclude subarachnoid hemorrhage.

Methods: This prospective cohort study was conducted at 2 tertiary care emergency departments (EDs) during 3 years. We enrolled all patients who were older than 15 years, had a nontraumatic acute headache and normal neurologic examination result, and who had a CT head scan and a lumbar puncture if the CT result was negative (ie, no blood in the subarachnoid space). Patients were followed up with a structured telephone questionnaire 6 to 36 months after their ED visit and electronic hospital records review to ensure no missed subarachnoid hemorrhage. We calculated sensitivity, specificity, and likelihood ratios of the strategy of CT and then lumbar puncture for subarachnoid hemorrhage.

Results: Five hundred ninety-two patients were enrolled, including 61 with subarachnoid hemorrhage. The mean patient age was 43.6 years, with 59.1% female patients. All cases of subarachnoid hemorrhage were identified on initial CT or lumbar puncture. One patient without subarachnoid hemorrhage was subsequently diagnosed with cerebral aneurysm, requiring surgery. The strategy classified patients with subarachnoid hemorrhage with sensitivity, specificity, and positive and negative likelihood ratios (with 95% confidence intervals [CIs]) of 100% (95% CI 94% to 100%), 67% (95% CI 63% to 71%), 3.03 (95% CI 2.69 to 3.53), and 0. For diagnosis of subarachnoid hemorrhage or aneurysm, these were 98% (95% CI 91% to 100%), 67% (95% CI 63% to 71%), 2.98 (95% CI 2.63 to 3.38), and 0.02 (95% CI 0.00 to 0.17), respectively.

Conclusion: To our knowledge, this is the largest prospective study evaluating the accuracy of a strategy of CT and lumbar puncture to rule out subarachnoid hemorrhage in alert ED patients with an acute headache. This study validates clinical practice that a negative CT with a negative lumbar puncture is sufficient to rule out subarachnoid hemorrhage. [Ann Emerg Med. 2007;xx:xxx.]

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Editor’s Capsule Summary

What is already known on this topic
Physicians typically use normal brain computed tomography (CT) in combination with blood-free spinal fluid to exclude the diagnosis of acute subarachnoid hemorrhage. The sensitivity of this strategy is not well established.

What question this study addressed
How many patients who had a negative CT and lumbar puncture result on initial evaluation were diagnosed with subarachnoid hemorrhage in the subsequent 3 years?

What this study adds to our knowledge
Sixty-one of 592 patients experienced subarachnoid hemorrhage. All were identified on initial presentation, 55 by CT and 6 by lumbar puncture.

How this might change clinical practice
This article supports the current practice of using the combination of a negative CT and lumbar puncture result to exclude the diagnosis of subarachnoid hemorrhage.

INTRODUCTION
Subarachnoid hemorrhage is a serious but rare cause of headache in the emergency department (ED). Subarachnoid hemorrhage has an annual incidence of 1 per 10,000 of the general population in the United States and accounts for 1% of ED visits for acute headache.1-3 Up to 40% of patients with subarachnoid hemorrhage have been reported to have had a small warning bleed (or “sentinel leak”) a short time before a larger bleed. These patients often look well, which sometimes leads them to be misdiagnosed on initial presentation to a health care provider.4 Misdiagnosis is the main reason for a delay in referral to specialist care.4,18 Patients with misdiagnosis or undiagnosed warning bleeds that subsequently rebled have a poorer prognosis.15 Early definitive aneurysm management (ie, surgical clipping or endovascular management) has been shown to significantly decrease the mortality of subarachnoid hemorrhage patients.19 Hence, physicians are concerned about misdiagnosing subarachnoid hemorrhage as a benign headache and try to completely rule out subarachnoid hemorrhage for all patients with headache when subarachnoid hemorrhage is considered a possibility.20-22

The current standard of care for patients suspected of having a subarachnoid hemorrhage is usually to obtain head computed tomography (CT) without contrast. If the CT result is negative and the diagnosis of subarachnoid hemorrhage is still considered, a lumbar puncture is done if there are no contraindications (ie, bleeding disorders, increased intracranial pressure, patient refuses to consent to procedure). If the lumbar puncture or the CT is suggestive of subarachnoid hemorrhage, then a cerebral angiogram is usually performed, which is the criterion standard for locating a cerebral aneurysm (not for diagnosis of subarachnoid hemorrhage).

Some have proposed that patients have an angiogram as a standard part of their investigation.23 Others have advocated that spectrophotometry be used to analyze the cerebral spinal fluid for xanthochromia.24-26 Both of these suggestions are contrary to current North American practice, and there is no evidence either for or against the need for this procedure as part of the standard investigations for patients. No study has clearly defined the specificity of a negative CT and lumbar puncture result (by spectrophotometry or visual inspection techniques for xanthochromia).

The objective of this study was to determine the sensitivity and specificity of the strategy of a negative CT scan result of the head and negative result in the final tube of cerebrospinal fluid and the resulting likelihood ratios for ruling out the presence of a subarachnoid hemorrhage in ED headache patients suspected of having a subarachnoid hemorrhage.

MATERIALS AND METHODS

Study Design
This study was a prospective multicenter cohort study for alert patients with a sudden severe headache to prospectively identify and conduct long-term follow-up of patients.

Setting
We conducted the study in 2 tertiary care Canadian academic EDs with a combined annual census of 120,000 patients.

Selection of Participants
We enrolled consecutive alert patients 15 years of age or older, presenting to EDs with a chief complaint of a nontraumatic acute headache or syncope associated with a headache. This study was conducted from November 2000 to November 2003. Inclusion criteria were headache patients who had the following characteristics: alert, defined by a Glasgow Coma Scale score of 15 (ie, awake and fully oriented); nontraumatic, defined as no falls or direct trauma to the head in the previous 7 days; and acute, defined as reaching maximal intensity in less than 1 hour and the patient presenting to the ED within 14 days of the headache’s onset.

Patients were excluded if they fell into one of the following categories: (1) recurrent headaches, ie, 3 or more headaches of the same character and severity during a period of greater than 6 months (ie, likely diagnosis of migraine headaches); (2) confirmed subarachnoid hemorrhage, ie, by CT or lumbar puncture before presentation at study ED; (3) reassessment of the same headache, ie, previously investigated with both CT and lumbar puncture for the same headache; (4) papilledema on examination; (5) new focal neurologic deficit on physical examination; (6) previous diagnosis of subarachnoid hemorrhage; (7) previous diagnosis of a brain neoplasm; (8)
neurologic shunt; and (9) post-lumbar puncture headache, ie, headache within 72 hours after a lumbar puncture.

Our study protocol was approved by the research ethics board at the study hospitals, without the need for informed patient consent at the initial ED visit. There were no specific ethical concerns because patients were investigated and treated according to current practice. Participants were informed that they may be contacted in the future for an update on their status. Verbal consent was obtained at the time of each follow-up telephone call.

All eligible patients who presented during the study period had a follow-up telephone call with a short structured follow-up questionnaire to determine whether they had had a subsequent subarachnoid hemorrhage. In addition, the electronic computer system was searched at the study hospital to determine whether they had a subsequent admission or surgery for a subarachnoid hemorrhage/intracranial aneurysm. The study centers were the only neurosurgical sites in the geographic region of the study. All follow-up assessments were conducted at least 6 months from the time of their ED visit.

Outcome Measures

The primary outcome, subarachnoid hemorrhage, was defined by any one of the following: (1) subarachnoid blood on CT, as reported in the final neuroradiology report; (2) xanthochromia in the cerebrospinal fluid by visual inspection of the centrifuged supernatant; (3) RBCs in the final tube of cerebrospinal fluid (>5 x 10^6 RBCs/L), with an aneurysm demonstrated on cerebral angiography (traditional, CT, or magnetic resonance imaging [MRI]); or (4) autopsy results confirming subarachnoid hemorrhage.27 This was assessed for all patients who had recorded information from the computer records at one of the participating hospitals, or from the autopsy report.28,29

Eligible patients were contacted by telephone to verify that they had not had any subsequent adverse events. The questions listed in Figure 1 were asked with yes or no answers unless otherwise stated. If the patients had difficulty comprehending the questions, a research nurse helped the patient to understand the meaning of the questions. Patients were classified as not having a subarachnoid hemorrhage if they did not have a subsequent diagnosis of subarachnoid hemorrhage.

Primary Data Analysis

Descriptive analysis for the patient characteristics was calculated. The sensitivity and specificity of a negative testing result (CT and cerebrospinal fluid) for subarachnoid hemorrhage, with their corresponding 95% confidence intervals (CIs), were determined. Likelihood ratios (negative and positive) were also calculated for subarachnoid hemorrhage.

RESULTS

We enrolled 592 patients, with 61 who had subarachnoid hemorrhage during the 3-year study period. Figure 2 displays the flow of this study. Follow-up was achieved in 89.6% of patients, 80.4% by telephone and an additional 9.2% with repeated visits to one of the hospital sites after the study, without visit for subarachnoid hemorrhage. Four patients were contacted but declined to participate. Two patients were dead on follow-up. Both of these patients died after an ischemic stroke, both with new infarcts documented on CT imaging. One patient was identified as having had 2 aneurysms 1 year after her index ED visit. This patient had MRI angiography to screen her for aneurysms because of a strong family history of cerebral aneurysms.

The Table demonstrates the characteristics of the entire cohort. The majority of patients were women, with a mean age of 43.6 years. The most common diagnosis was benign headache, including tension headache, cluster migraine, and nonspecific headache without a serious cause attributed to it during initial visit or on our follow-up. Migraine was also common. Serious headache accounted for 11.7%, which included subarachnoid hemorrhage, bacterial meningitis, intracerebral hemorrhage, neoplastic lesions, or ischemic stroke.

Figure 3 shows the classification performance of the study strategy for identifying subarachnoid hemorrhage. The strategy had 100% sensitivity for subarachnoid hemorrhage (95% CI 94% to 100%). There were many false positives, all due to the result of the lumbar puncture of greater than 5 x 10^6 RBCs/L. There were no false-positive CT scan results. Thus, according to our data, the posttest negative likelihood ratio was found to be less than 0.0001, subject to the CIs surrounding sensitivity and specificity. Hence, our results indicate that in an ED headache patient at risk of subarachnoid hemorrhage, similar to those in our study with a 10% subarachnoid hemorrhage prevalence, a patient with a normal CT result and a normal lumbar puncture
result has a posttest probability of subarachnoid hemorrhage of less than 0.0001%. If the patient were a very high-risk patient with a pretest probability of 50%, the posttest probability would be less than 0.0005%.

We performed a sensitivity analysis of our results for identifying subarachnoid hemorrhage or cerebral aneurysm and assuming that some patients who were lost to follow-up did in fact have a missed subarachnoid hemorrhage. The first sensitivity analysis found that the sensitivity for subarachnoid hemorrhage or cerebral aneurysm was 98% (95% CI 91% to 100%), specificity for subarachnoid hemorrhage or cerebral aneurysm was 67% (95% CI 63% to 71%), and negative likelihood ratio was 0.024 (95% CI 0.00 to 0.17). The second sensitivity analysis assumed that one of the patients lost to follow-up had a subarachnoid hemorrhage; this analysis found that the sensitivity for subarachnoid hemorrhage or cerebral aneurysm was 97% (95% CI 89% to 99%), with a negative likelihood ratio of 0.047 (95% CI 0.01 to 0.17).

LIMITATIONS

As with all clinical research, this study has some limitations. One limitation is that one patient had the subsequent discovery of aneurysms. This 51-year-old woman with no past medical problems experienced a severe rapidly peaking headache, reaching maximal pain within seconds. The headache was rated by the patient as 9 of 10, with 10 representing the worst pain imaginable. She had a negative CT result and a completely normal lumbar puncture result (no RBCs and no xanthochromia by visual inspection of supernatant). She then remained asymptomatic for more than 1 year. She subsequently had an MRI angiogram because of a strong family history for aneurismal subarachnoid hemorrhage, on which she was found to harbor 2 aneurysms. One was 6 mm at the left posterior communicating artery; the other, 4 mm at the left middle cerebral artery. She had surgical clipping and did well postoperatively. The preceding headache 1 year earlier was thought to not be related by her treating neurosurgeon because there was no sign of adjacent brain injury at surgery. However, if this patient was considered to have actually been a missed small subarachnoid hemorrhage by the testing strategy, this would still be an excellent testing strategy to exclude subarachnoid hemorrhage.

Another limitation was that we did not reach 19.6% of the patients by telephone. We were able to determine that none of these patients had a subsequent subarachnoid hemorrhage or aneurysm within our region (our study sites were the only neurosurgical sites in the region). Further, we were able to determine that 9.2% of the patients were alive and subsequently treated at one of the 2 study sites after their ED visit for headache. In the unlikely event that the patient described above and one of the patients who were lost to follow-up subsequently had a subarachnoid hemorrhage (ie, presented to a community hospital with sudden death or was admitted there for palliative management), this strategy would still result in a high sensitivity for subarachnoid hemorrhage, and an extremely small negative likelihood ratio of 0.047.

In addition, many of the lumbar punctures resulted in traumatic tap and are considered a positive result. Although there have been many suggestions on how to determine whether

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Table. Characteristics of the 592 study subjects.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of Patients (N=592)</th>
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<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>43.6 (15.2)</td>
</tr>
<tr>
<td>Range</td>
<td>15-87</td>
</tr>
<tr>
<td>Female (%)</td>
<td>350 (59.1)</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>181 (30.6)</td>
</tr>
<tr>
<td>Mean pulse rate (SD)</td>
<td>79 (15)</td>
</tr>
<tr>
<td>Mean systolic blood pressure (SD)</td>
<td>146 (29)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (SD)</td>
<td>82 (14)</td>
</tr>
<tr>
<td>Median number of days until telephone follow-up IQR</td>
<td>477</td>
</tr>
<tr>
<td></td>
<td>191.737</td>
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<tr>
<td><strong>Investigations (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal CT result</td>
<td>68 (11.5)</td>
</tr>
<tr>
<td>Abnormal lumbar puncture result, N=539</td>
<td>183 (34.0)</td>
</tr>
<tr>
<td>Xanthochromia present</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td>Angiography</td>
<td>77 (13.0)</td>
</tr>
<tr>
<td><strong>Final diagnosis (%)</strong></td>
<td></td>
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<tr>
<td>Benign headache</td>
<td>275 (46.5)</td>
</tr>
<tr>
<td>Migraine headache</td>
<td>156 (26.4)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>61 (10.3)</td>
</tr>
<tr>
<td>Viral illness</td>
<td>41 (6.9)</td>
</tr>
<tr>
<td>Postcoital headache</td>
<td>15 (2.5)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Syncope</td>
<td>7 (1.2)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>CNS tumor</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (3.0)</td>
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</table>

CNS, central nervous system.
A lumbar puncture result is due to traumatic tap, there is no certain way to do so. We defined any lumbar puncture result with blood in the final tube (>5×10⁶ RBCs/L) as a positive test, but only patients with a positive angiography result or subsequent positive CT result (immediate or delayed) or death were considered to have had a subarachnoid hemorrhage. This could result in some patients with subarachnoid hemorrhage being misclassified as having a benign headache if they had either a false-negative angiography study result or another cause of subarachnoid hemorrhage (ie, non-aneurysmal subarachnoid hemorrhage). However, this potential misclassification would affect only the specificity (decreasing the reported specificity from the true specificity). The sensitivity would not be affected because the strategy already has classified these patients as positive. Most patients with positive lumbar puncture results with small amounts of RBCs will be considered to have had a traumatic tap and will not receive further investigations. This study does not assist physicians in determining which patients with blood in the cerebrospinal fluid have this blood because of traumatic tap versus subarachnoid hemorrhage.

**DISCUSSION**

Our study found that the strategy of conducting head CT followed by a lumbar puncture to look for RBCs or visual xanthochromia virtually excludes the chance of subarachnoid hemorrhage. Hence, this study’s findings support the current practice of accepting the strategy of a normal CT result with a normal lumbar puncture result as sufficient to rule out subarachnoid hemorrhage.

The use of CT scan of the head and lumbar puncture to rule out a subarachnoid hemorrhage is a common and widely accepted practice. However, the evidence in literature confirming the reliability of this practice is limited. Some small previous studies followed individuals who had a negative CT scan result, as well as a negative lumbar puncture result. Studies by Wijdicks et al and Harling et al followed 71 and 14 patients, respectively. There were no patients identified with a subarachnoid hemorrhage during the follow-up period, which ranged from 18 months to 3.3 years. This corresponds to a specificity of negative testing to rule out subarachnoid hemorrhage of 100%, with a 95% CI of 95% to 100% for the larger study. Results of other small studies by Linn et al (N=93), Landblom et al (N=137), and Marcus (N=18) were also consistent with our study’s result.

Until now, the practice of assuming that a negative CT scan result of the head and negative lumbar puncture result are adequate to rule out subarachnoid hemorrhage has never been rigorously tested. To our knowledge, this study was the largest prospective study conducted to date to determine whether a negative CT head scan result and a negative lumbar puncture result are sufficient to adequately exclude the possibility of subarachnoid hemorrhage. This study was prospectively conducted on all patients who presented to the 2 study sites, thereby minimizing any selection bias.

The results of this study will reassure physicians that a negative CT scan result with a negative cerebrospinal fluid analysis is sufficient to exclude subarachnoid hemorrhage without the need for additional testing. These results do not assist physicians in adjudicating equivocal cerebrospinal fluid results with the presence of RBCs greater than 5×10⁶ cells/L. These patients will still require physician judgment to determine who is at significant enough risk for subarachnoid hemorrhage to justify cerebral angiography.

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Future efforts need to establish which ED patients with severe headache need to be evaluated for subarachnoid hemorrhage. A clinical decision rule would greatly assist physicians in determining which patients require any investigations. Further study is also required to determine ways of distinguishing traumatic tap versus true subarachnoid hemorrhage in patients with small amounts of RBCs present in the cerebrospinal fluid without the presence of xanthochromia.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Subarachnoid hemorrhage</th>
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<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>61</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>356</td>
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<tr>
<th>Sensitivity (95% CI)</th>
<th>100% (94-100)</th>
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<tbody>
<tr>
<td>Specificity (95% CI)</td>
<td>67% (63-71)</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>100% (98-100)</td>
</tr>
<tr>
<td>LR+</td>
<td>3.03 (2.69-3.53)</td>
</tr>
<tr>
<td>LR-</td>
<td>&lt;0.00001 (*)</td>
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Figure 3. A, Primary analysis: Classification performance of strategy for 61 subarachnoid hemorrhage cases among 592 patients. B, Sensitivity analysis: Classification performance of strategy for 62 subarachnoid hemorrhage or cerebral aneurysm cases among 592 patients.
This prospective study validates current clinical practice that a negative CT result with a negative lumbar puncture result is sufficient to rule out subarachnoid hemorrhage in patients presenting to the ED with an acute headache. Future study should determine which headache patients are at risk and require this strategy of CT and then lumbar puncture to safely exclude subarachnoid hemorrhage.

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Author contributions: JJP conceived the study, designed the trial, and obtained research funding. JJP and AS supervised the conduct of the trial and data collection. JJP, AS, MF, MM, CS, and NF undertook recruitment of participating centers and patients and managed the data, including quality control. IGS assisted with the design of the study and in preparing the manuscript. GAW and JJP provided statistical advice on study design and analyzed the data. JJP drafted the article, and all authors contributed substantially to its revision. JJP takes responsibility for the paper as a whole.

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Editor’s Capsule Summary: What is already known on this topic: Physicians typically use normal brain computed tomography (CT) in combination with blood-free spinal fluid to exclude the diagnosis of acute subarachnoid hemorrhage. The sensitivity of this strategy is not well established. What question this study addressed: How many patients who had a negative CT and lumbar puncture result on initial evaluation were diagnosed with subarachnoid hemorrhage in the subsequent 3 years? What this study adds to our knowledge: Sixty-one of 592 patients experienced subarachnoid hemorrhage. All were identified on initial presentation, 55 by CT and 6 by lumbar puncture. How this might change clinical practice: This article supports the current practice of using the combination of a negative CT and lumbar puncture result to exclude the diagnosis of subarachnoid hemorrhage.


