

ORIGINAL CONTRIBUTION

An Observational Study of 2,248 Patients Presenting With Headache, Suggestive of Subarachnoid Hemorrhage, Who Received Lumbar Punctures Following Normal Computed Tomography of the Head

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Abstract

Objectives: The objective was to determine the incidence of subarachnoid hemorrhage (SAH) diagnosed by lumbar puncture (LP) when the head computed tomography (CT) was reported as demonstrating no subarachnoid blood.

Methods: Data were obtained on patients who received LP to diagnose or exclude SAH attending six hospitals over 5 years. Subsequent investigations and outcomes were reviewed in all patients with LPs that did not exclude SAH.

Results: A total of 2,248 patients were included. A total of 1,898 LPs were suitable for biochemical analysis, of which 92 (4.8%) were positive for blood, suggesting SAH; 1,507 (79.4%) were negative; and 299 (15.6%) were inconclusive. Of the 92 patients with positive cerebrospinal fluid analysis, eight patients (0.4%) had aneurysms on further imaging, and one had a carotid cavernous fistula.

Conclusions: In patients presenting to the emergency department with acute severe headache, LP to diagnose or exclude SAH after negative head CT has a very low diagnostic yield, due to low prevalence of the disease and uninterpretable or inconclusive samples. A clinical decision rule may improve diagnostic yield by selecting patients requiring further evaluation with LP following nondiagnostic or normal noncontrast CT brain imaging.

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Acute headache is a common presentation to the emergency department (ED), accounting for around 1% to 2% of all encounters.^{1,2} The differential diagnosis is wide and includes potentially life-threatening conditions, such as aneurysmal subarachnoid hemorrhage (SAH). Aneurysmal SAH has an incidence of approximately six to eight per 100,000 per

person-years, and prevalence of 0.4% to 6%, estimated overall to be around 2%.^{3,4} There is an overall risk of rupture of 1.9%.⁴ SAH has a 1-month mortality of around 40% to 45%, and of those surviving the hemorrhage, around 30% will have severe disabilities.^{5,6} Following the initial presentation, the risk of rebleeding is approximately 1.5% per day and 15% to 20% in the first

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2 weeks.^{7,8} This is the largest cause of death from SAH. Early diagnosis and aneurysm repair using endovascular or surgical treatment improves outcomes.^{9,10} Patients with no focal signs and Glasgow Coma Scale scores of 15 have the potential for curative treatment if detected prior to rebleeding; even a patient with an obtunded presentation and high-grade SAH has a 10% to 15% chance of making a good recovery.^{10,11} These factors induce physicians to have a low threshold for investigation of headache suspicious for SAH.

There is a wide differential diagnosis for severe pathologies causing acute headache, which includes aneurysmal SAH, intracranial arterial dissection, angitis, meningitis, tumor, vascular malformations, reversible cerebral vasoconstriction syndrome, and central sinus thrombosis. A uniform approach to diagnostic imaging modalities cannot be achieved because different imaging techniques have different sensitivities and specificities.¹² This issue is compounded by the spectrum of imaging available in different hospitals and the varying skill sets of those interpreting the images. These factors result in a wide variety in diagnostic protocols.

Noncontrast computed tomography (CT) of the head has a sensitivity for SAH of around 98% if performed within 12 hours of maximum pain, but falls to 50% by the end of the first week.^{13–15} Magnetic resonance imaging may offer a higher rate of late diagnosis, but sensitivity is not 100%.² Red cells in the cerebrospinal fluid (CSF) undergo lysis and phagocytosis, and this releases oxyhemoglobin, which is converted over time into bilirubin and sometimes methemoglobin. Bilirubin is the only pigment that is produced solely *in vivo*, while oxyhemoglobin and methemoglobin can be produced *in vivo* or *in vitro*, for example, during CSF analysis. These pigments are tested for using spectrophotometry. Therefore, when the CT is negative and the clinical suspicion remains high, the diagnosis is made based on CSF analysis for red blood cells, xanthochromia, and bilirubin.^{2,16,17} Early testing has the risk of producing false-negative results due to inadequate time for *in vivo* bilirubin formation;^{16,17} hence, the U.K. guidelines for CSF analysis in suspected SAH state that a lumbar puncture (LP) be carried out 12 hours after maximal headache pain and CSF obtained for spectrophotometry analysis.^{12,18} However, the timing of LP and methods used to assess CSF vary between and within countries, and the use of spectrophotometry remains limited worldwide, with most North American and some European centers assessing samples for visual xanthochromia and red cell counts, but not using spectrophotometry.^{12,18,19}

There are risks associated with LP, and the low threshold for investigation means that a high number of procedures are performed for each positive diagnosis. LP is a potentially painful test and carries risks including low-pressure headache, meningitis, epidural hematoma, nerve root damage, and local site infection.²⁰ The requirement for LP at least 12 hours after maximum headache means that a proportion of patients require a period of observation following CT while awaiting LP. LP can sometimes be nondiagnostic due to procedural failure or inadequate, spoiled, or lost samples.

The primary objective of this study was to determine the rate of diagnosis of SAH by LP after negative CT.

The secondary objective was to identify the rate of aneurysmal SAH following positive LP.

METHODS

Study Design

This was a retrospective chart review. Institutional ethics approval was sought but since there were no study interventions or deviations from routine practice, the study was designated as a service evaluation and was registered along local guidelines. All data were stored on a dedicated password-protected computer.

Study Setting and Population

Patients presenting to six urban EDs with acute headache, had CT scans with no cause for the headache (negative CT), and LP performed for CSF analysis were included. All participating centers were U.K. Department of Health Type 1 EDs, which means that the emergency service was led by consultant-grade (staff specialist, attending) emergency physicians, assisted by trainees in emergency medicine and other specialties.²¹ All centers had the capacity to perform LPs and analyze CSF by spectrophotometry. Data were collected over a 5-year period (December 2006 to December 2011).

Adult patients (>17 years) presenting with acute non-traumatic headache suspicious for SAH were included. All patients had nondiagnostic noncontrast CT head and LP for CSF analysis. Patients who did not receive LP or who had LP as part of the work-up for meningitis were excluded from analysis.

Study Protocol

In the hospitals involved in this study, patients presenting with acute headache and the main diagnostic concern of SAH were investigated along a standard protocol of noncontrast CT followed, if nondiagnostic, by LP. The diagnosis of an aneurysm is then made on CT angiography or, if contraindicated, magnetic resonance angiography (MRA).

The CT protocols for each site were different but all had multislice scanners (16 to 64); five sites used slice thickness of 2.5 mm or less, and one site used 3 mm. In participating hospitals CTs were interpreted initially by on-call radiologists in training or radiologists who have completed training. The images are then reviewed by board-certified neuroradiologists (four centers) or a board-certified general radiologist, and a final report was produced. We used this final report as the reference standard in this study.

Chart abstraction was performed in accordance with previously published guidelines.²² Patients were identified by electronic searches of the local pathology databases for requests for CSF analysis for bilirubin. Patients who had LP requested by the treating medical team were included. Those who had not had CT prior to LP and those who had CT that gave diagnoses were excluded. Results of the CSF analysis were reported according to current guidelines (Table 1).¹⁷ The records of all patients with positive CSF results were reviewed to determine the diagnoses and outcomes. The initial noncontrast CT was reviewed with the provisional and final reports. All imaging and medical records were

Table 1
Possible Outcomes of Lumbar Puncture

Outcome	NBA, AU	NOA
Positive for blood in CSF	>0.007	0
	>0.007	≤0.1
	>0.007	>0.1
Negative for blood in CSF	≤0.007	0
	≤0.007	<0.1
	≤0.007	≥0.1
Inconclusive	≤0.007	≥0.1

CSF sample uninterpretable; unsuitable for analysis, e.g. insufficient sample, exposed to light, blood contamination. Methemoglobin to be treated as oxyhemoglobin.
 AU = absorbance units; CSF = cerebrospinal fluid; NBA = net bilirubin absorbance; NOA = net oxyhemoglobin absorbance.

identified by the study team. Demographic data were not available for three hospitals.

Outcome Measures

The primary outcome was the result of the CSF biochemical analysis. Positive LP is defined by the Association for Clinical Biochemistry guideline 2008.^{16,17} There are four potential results obtained from a LP: negative for blood, positive for blood, inconclusive, or uninterpretable. Specific biochemical determinants of these are given in Table 1. Reasons for a sample to be uninterpretable include being unsuitable for analysis, e.g., insufficient sample, exposed to light, blood contamination, incorrect storage, incorrect transport, or sample loss. The term xanthochromia is often used to describe CSF analysis results. However, xanthochromia is defined as a yellowish discoloration of the CSF on visual inspection and has no specific biochemical or diagnostic definition, and the term therefore is not used in this article.

Data Analysis

Gaussian distributed variables are expressed as mean (standard deviation [SD]) and nonnormally distributed variables as median (interquartile range [IQR]). All analysis was done using Microsoft Excel 97-2004.

RESULTS

We found 2,248 patients as meeting inclusion criteria. The results are presented in Figure 1 and Table 2. There were 92 positive samples, 1,507 negative samples, 299 inconclusive samples, and 350 uninterpretable samples. All patients with positive LP had subsequent neuroimaging, with CTA or MRA, as determined by local protocols. Of the 92 patients with SAH, nine (9.3%) patients had vascular abnormalities confirmed on subsequent neuroimaging (eight aneurysms and one carotid cavernous fistula). Of the 299 patients with inconclusive LP results, no vascular abnormalities were found. In the 350 patients with uninterpretable samples, two aneurysms were found on further investigation. Table 3 gives a brief clinical outline of the patients who had further intracranial vascular pathology.

The handling of uninterpretable LPs was analyzed at two sites only. At one site 28 patients had uninterpretable results; five were investigated with further

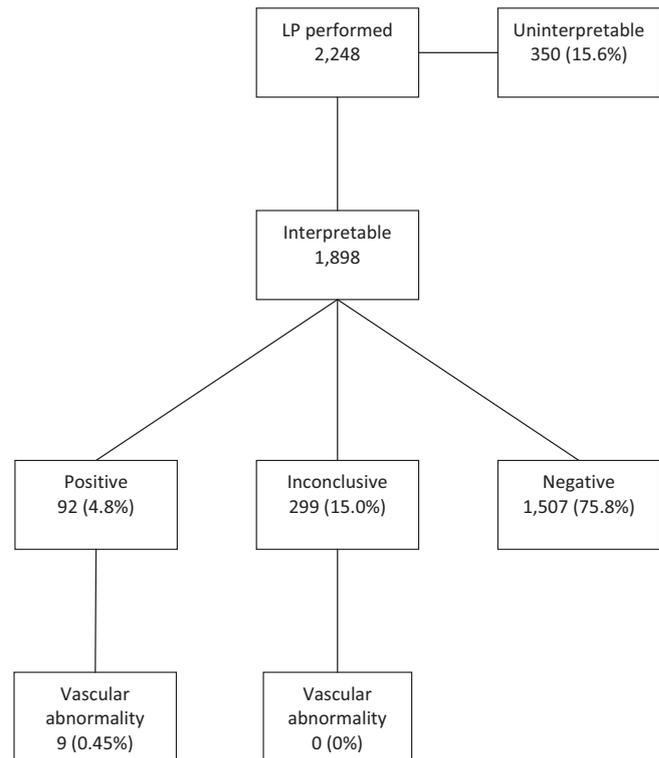


Figure 1. Flow diagram of LP results. LP = lumbar puncture.

Table 2
CSF Outcome Results

Result	n (%)
Total number interpretable samples	1,898
LP negative	1,507 (67.0)
LP positive	92 (4.8)
Positive bilirubin alone	45 (2.3)
Positive bilirubin and oxyhemoglobin	47 (2.4)
LP inconclusive	299 (13.0)
Positive oxyhemoglobin	297 (14.9)
Positive methemoglobin	2 (0.1)

Percentages given as percentage of analyzable samples.
 CSF = cerebrospinal fluid; LP = lumbar puncture.

imaging based on clinical suspicion. None of these patients were found to have aneurysms. The other 25 were not imaged. At the second site, 56 patients had uninterpretable LP results. Seventeen of these patients had further imaging; of these, two had aneurysms and 15 had normal imaging. Of the remaining 39 patients, 37 were discharged without further imaging, one discharged him- or herself, and one was subsequently diagnosed with meningitis.

Demographic data were available for three of the hospitals that took part in the study (n = 760). There were 340 males (44.8%) with a mean (±SD) age of 41.1 (±14.7) years.

DISCUSSION

To the best of our knowledge this is the largest retrospective study to date that focuses on patients present-

Table 3
Clinical Summary of Patients With Identified Intracranial Pathology

Clinical Characteristics	Pathology
Patients with positive LP	
Presented via a headache clinic greater than 1 week after peak headache severity.	Aneurysm
Presented after 1 week of headache, originally treated as lymphocytic meningitis before xanthochromia results had come back.	Anterior communicating aneurysm
Presented to ED around 1 week after headache peak severity.	Posterior communicating aneurysm
Presented to ED following 1 week of continuous headache.	Aneurysm
Presented to ED after 1 week of continuous headache.	Aneurysm
Patient had original CT > 6 hours following acute headache. Subsequent angiography performed.	Carotid cavernous fistula
Patient presented to ED > 6 hours post headache peak; had had a previous aneurysm coiled. This made initial CT difficult to interpret.	Aneurysm
Patient had worse ever headache 1 week prior to CT scan.	Aneurysm
Patient attended with acute, severe headache at 11:20; a negative CT was performed at 15:11.	Aneurysm
Patients with uninterpretable LP	
Presented 5 to 6 days after headache. Previously had had negative CTA (separate attendance); diagnosed due to high clinical suspicion prompting further imaging.	Aneurysm
Presented 18 hours after worst ever headache. Further imaging performed due to high clinical suspicion found aneurysm.	Aneurysm

CT = computed tomography; CTA = computed tomographic angiography; LP = lumbar puncture.

ing to the ED with acute severe headache who receive LP following normal CT imaging of the brain. We identified a positive LP rate of 4.1% of all LPs undertaken. Within the group of patients with positive LP, there were nine patients with vascular abnormalities, which equates to a rate of 9.8% of SAH or a rate of 0.47% of all LPs undertaken with analyzable CSF. This represents a rate of 204 LPs per identified vascular abnormality. In 13.2% of our samples, the results were inconclusive. This was due to raised oxyhemoglobin, which completely obscures the bilirubin peak on spectrophotometry when sufficiently elevated.

Subarachnoid hemorrhage diagnosis rates on LP with negative CT scans are low, varying from 1% to 7.7%.^{23,24} There is one study in which the SAH diagnosis rate is substantially higher, at 28%,²⁵ but the selection criteria for this study was those patients referred to a regional neurosurgery center, and as such the diagnosis rate may be subject to selection bias. Considering the prevalence of aneurysms in the general population has been reported to be approximately 2%, with a range of 0.9% to 9%,⁴ we report a seemingly low incidence of lesions in this article. This may reflect a falling incidence of ruptured aneurysms, which may be a consequence of lower smoking prevalence and improved hypertensive control. A reduced incidence could potentially affect the diagnostic utility of LP, with decreasing true and increasing false-positive CSF samples a consequence of the falling prevalence of the disease. The risk of finding asymptomatic aneurysms may thus be smaller than suggested by older studies. Coupled with the high rate of false-positive findings of SAH (for aneurysms) reported here, the high rate of nondiagnostic LPs, and the morbidity associated with LP, the use of CT angiography may prove a more efficient screening tool than the current paradigm of plain CT head followed by LP.

We identified eight aneurysms and one cavernous sinus fistula in the group of 92 (4.1%) patients with posi-

tive LPs, which is similar to the expected number of 5%.³ We identified no aneurysms in the group of 299 patients with inconclusive LP results (we would expect around 15 incidental aneurysms to be detected) and two aneurysms in the group of 350 patients with uninterpretable CSF (we would expect around 17 incidental aneurysms). This is likely to be because a high proportion of patients did not receive imaging. Imaging in this group is at the discretion of the reviewing clinicians and local audit suggests around 50% of patients do not have subsequent imaging. On reviewing the characteristics of the 11 patients who had SAH “missed” on the initial CT (Table 3), only one had a CT scan within 6 hours.

The proportion of patients with normal brain CT but CSF evidence of subarachnoid blood in which underlying vascular pathology (most commonly an aneurysm) is identified varies greatly between series, with figures ranging from 1% to 69%.²⁶⁻³¹ In a cohort of 3,132 patients presenting to the ED with acute headache that peaked in intensity within 1 hour, there was an overall SAH rate of 7.7%; however, the CT-negative LP-positive rate was not reported.²⁴ The wide variation in the proportion of patients with SAH on LP in whom an aneurysm is identified may be due to differing definitions of blood on CSF analysis, whether or not spectrophotometry is used, and/or patient selection for LP.

A 2014 U.K. retrospective chart review of 179 patients with negative CT followed by LP reported 158 (88.3%) were LP negative, which is similar to the 67.0% that we report.²³ Two LP CSF samples were positive for blood (1.1%), compared to 4.1% in our study, with the final diagnosis not reported. The authors report a rate of inconclusive LPs of 5%, which is less than the 13.2% that we report, and a procedural failure rate of 5.6%, compared to the rate we report of 15.0%. The authors defined procedural failure as due to technical difficulty, insufficient sample, or patient refusal, whereas our definition was wider.

In a cohort of 1,448 patients there was a 6.5% SAH rate on LP with negative CT, which is similar to our findings. However, there was a rate of vascular abnormality of 43%, which is a much higher figure than our finding of 9.7%. There may be a selection bias in this study, as the patients were all admitted to a neurosurgical center.³² In a recent U.K. study of 163 patients with LP following negative CT for headache, there was a SAH rate of 22.1%.²⁵ Of those, there was a vascular abnormality rate of 37%, an inconclusive LP rate of 18.4%, and an inadequate for analysis rate of 13.5%. The higher vascular abnormality rate compared to our study may again be attributable to the population sample being taken from a neurosurgical center. In a cohort of 453 patients who had LP after negative CT for headache, there was a 1% SAH rate, and most of those had no vascular abnormality. This low incidence (of aneurysm rupture) is similar to our results, and this may be accounted for by the setting of this study being an ED.³⁰

We found vascular pathology in nine (9.7%) of the 92 patients with positive CSF for blood (eight aneurysms and one carotid cavernous fistula), and conversely no cause for SAH was found in more than 90% of positive LPs. Patients with positive LP and normal subsequent imaging have an excellent prognosis.³³ Causes of spontaneous SAH in these cases include perimesencephalic hemorrhage, brain or spinal arteriovenous malformation, cerebral arterial dissection, vasculitis, stroke, venous sinus thrombosis, sickle cell disease, pituitary apoplexy, and substance abuse. Nonaneurysmal SAH typically presents with headache and no focal neurology and thus may be overrepresented in the study group. Some of these cases may be due to the recently described reversible cerebral vasoconstriction syndrome, but the relationship of this disease and LP biochemical xanthochromia is poorly understood.³⁴ This disease is characterized by diffuse, segmental cerebral arterial vasoconstriction and has been hypothesized to be a cause of the majority of thunderclap headaches presenting to the ED.¹²

In our study, of the nine patients with vascular abnormalities diagnosed on imaging following positive LP, one had had a noncontrast CT performed within 6 hours of onset of headache. This is in contrast to a study by Perry et al.,²⁴ who reported 100% sensitivity, specificity, positive predictive value, and negative predictive value for identifying patients with SAH. CT performance and reporting protocols were similar in ours and the study by Perry et al. An important difference was definition of "positive CSF," which in the study by Perry et al. was microscopic red cell count and xanthochromia assessed by visual inspection, not biochemical analysis.

LIMITATIONS

A complete demographic data set was not collected at all sites. Consequently we are unable to completely describe the population we have analyzed. We did not collect data on the patients with uninterpretable or inconclusive LPs. We are therefore unable to report the proportions that proceeded to further imaging. We obtained specific data focusing on this issue at one site,

where 23 of 28 (82%) of patients were not evaluated with further imaging following clinical review. We did not collect data on the factors that led clinicians to further evaluate these patients or discharge them.

The high morbidity and mortality associated with this low-prevalence disease necessitates a very low tolerance for a missed diagnosis. The diagnostic pathway is therefore necessarily complex, employing at least one radiologic investigation following positive LP. Because this study obtained data from multiple sites, and was retrospective in nature, there is variability in diagnostic procedure. The study hospitals had differing radiology capabilities and differing local protocols. All study centers used multislice CT scanners but there was variation in slice thickness and subspecialty training of reporting radiologists. Radiologic investigations following positive LP with normal head CT were CTA or MRA, depending either on local protocol or on diagnostic plans made in neurosurgical multidisciplinary case conferences. There was therefore no standard evaluation procedure for patients with acute headache employed in this study once the initial noncontrast CT and LP had been performed. The variability in use of various second-line radiologic investigations is a source of selection bias for which we could not control. These factors suggest we could have missed presentations of SAH. However, since the clinicians performed 204 LPs for each significant finding, a low threshold for initial investigation is probable.

There were 297 (13.2%) inconclusive samples due to large amounts of oxyhemoglobin, potentially masking a bilirubin rise. In addition, there were 350 (15.6%) uninterpretable samples taken, due to procedure failure. A subset of these patients, representing one site for local audit purposes, were exhaustively followed up for outcomes. This was not done for all sites owing to logistic difficulties.

We did not follow up patients or review coroners' records and so may have missed subsequent fatal presentations of SAH in those patients discharged without LP or with nondiagnostic LP and no subsequent imaging. This group may have had undiagnosed SAH. However we did search radiologic databases for all hospitals in our region so were able to obtain information as regards to the requirement for any subsequent imaging diagnostic of SAH in our cohort, and none were identified. We also identified all CSF samples sent to our laboratories for analysis, and therefore subsequent LPs were identified. It is possible that some patients may have attended other EDs outside our study area for further evaluation.

Although attempts were made to follow quality standards in chart abstraction,²² there were difficulties in maintaining standardization in abstraction and there was no consistent abstraction form used throughout the study. The consequence of this was a high variability in data concerning imaging modalities data completeness between study centers. Abstractors had no formal training in this specific study and were not blinded to the study hypotheses. Inter-rater reliability was not quantified.

We report only nine vascular abnormalities in 2,248 LPs in total. Our data suggest that a more targeted

approach to identifying SAH should be sought to reduce the number of LPs performed. This in turn could reduce resources required for diagnosis.

CONCLUSIONS

In patients presenting to the ED with acute severe headache, lumbar puncture to rule in or out subarachnoid hemorrhage after negative head computed tomography has a very low diagnostic yield due to low prevalence of the disease and uninterpretable or inconclusive samples. A clinical decision rule may improve diagnostic yield by selecting patients requiring further evaluation with a lumbar puncture following a nondiagnostic or normal noncontrast computed tomography brain imaging.

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