

Worst Headache and Subarachnoid Hemorrhage: Prospective, Modern Computed Tomography and Spinal Fluid Analysis

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Study objective: This study investigated the hypothesis that modern computed tomographic (CT) imaging is sufficient to exclude subarachnoid hemorrhage (SAH) in patients with severe headache.

Methods: All 38,730 adult patients who presented to Hermann Hospital in Houston, Texas, during a 16-month period were prospectively screened to detect those with "the worst headache of my life." Two neuroradiologists blinded to the study hypothesis interpreted the CT scans. Patients with negative scans underwent comprehensive cerebrospinal fluid (CSF) analysis including cell count in first and last tubes, visual and spectrophotometric detection of xanthochromia, and CSF D-dimer assay.

Results: A chief complaint of headache was elicited in 455 patients, and 107 of these had "worst headache" and were enrolled in the study. CT-confirmed SAH was found in 18 of the 107 (17%). Only 2 patients (2.5%, 95% confidence interval, .3% to 8.8%) had SAH detected by CSF analysis among those with negative CT imaging result. CSF spectrophotometric detection was the most sensitive test for blood. Three patients with less than 6 red blood cells in tube 1 had positive spectrophotometric results, but in all 3, tube 4 was negative on spectrophotometric analysis, suggesting a high false-positive rate.

Conclusion: Modern CT imaging is sufficient to exclude 97.5% of SAH in patients presenting to the ED with "worst headache" symptoms.

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INTRODUCTION

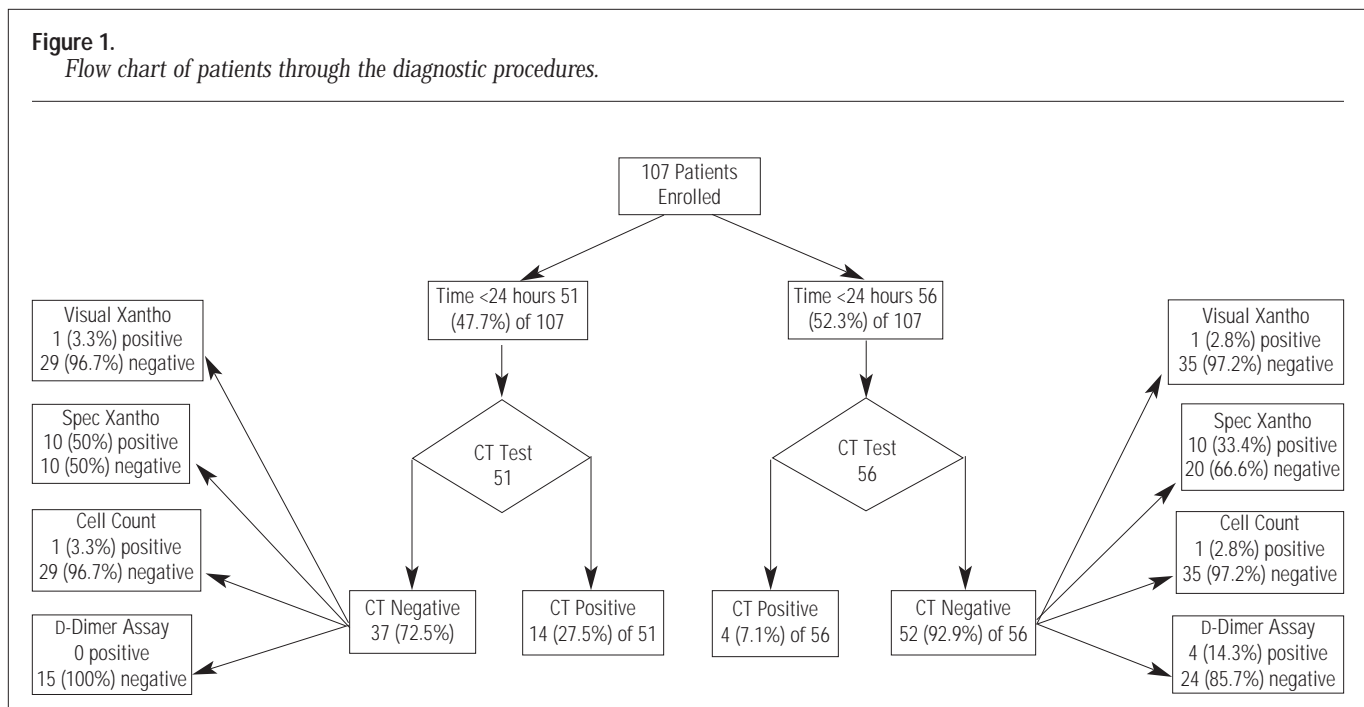
Early studies on the diagnosis of subarachnoid hemorrhage (SAH) suggested that approximately 10% of SAHs are missed by noncontrast head computed tomography (CT).^{1,2} The stroke council of the American Heart Association strongly recommends that lumbar puncture (LP) follow a negative head CT scan in patients with suspected SAH.³ SAH from aneurysm rupture affects 28,000 people each year in the United States, often in previously healthy individuals in the prime of life, ages 35 to 65 years.⁴ The early mortality rate approaches 50%.⁵ Between 15% and 40% of patients with SAH have a warning leak or sentinel hemorrhage.^{4,6} Detecting a sentinel hemorrhage in a neurologically normal patient may be a golden opportunity to intervene early before complete aneurysm rupture leads to death or disability.

Although LP may be the best test for SAH, the discomfort, time, and expense of this procedure may preclude its routine use in some emergency departments. In an informal survey we found that fewer than 50% of patients with severe headache and negative head CT scan results had LPs in our university ED. We undertook the current study to determine whether modern head CT imaging was sufficient to exclude SAH. We also studied the various spinal fluid tests to determine which had the best diagnostic value to detect SAH.

MATERIALS AND METHODS

This was a prospective study conducted at the Hermann Hospital Emergency Department from March 1995 through June 1996. Hermann Hospital is a large, urban institution that serves as the primary academic hospital for the University of Texas, Houston. Adult patients were asked by the triage physician and nurse for their chief complaint. If a chief complaint of headache was elicited, then patients were asked "Is this the worst headache of your life?" and "On a scale of 1 to 10, with 10 being most severe, rate the severity of this headache." If patients said that it was the worst headache of their life, or 10 out of 10, they were eligible for the study. Prespecified exclusion criteria were (1) head trauma within the past 3 months, (2) LP within the previous 2 weeks, (3) coagulopathy or current anticoagulant use yielding a prothrombin time or partial thromboplastin time greater than 1.2 times control, (4) platelet count less than 50,000, (5) temperature greater than 38.5°C, (6) head CT evidence of mass lesion, cerebral edema, or intracerebral hemorrhage, (7) systemic or central nervous system cancer, and (8) focal neurologic signs other than nuchal rigidity and photophobia. Focal neurologic symptoms without objective signs were permissible for entry into the study. To monitor the reliability of case ascertainment the records of all patients treated in the ED were reviewed continu-

Figure 1. Flow chart of patients through the diagnostic procedures.



ously throughout the study period to detect any eligible patients missed by the prospective screening process.

Patients who met the inclusion criteria and none of the exclusion criteria were asked a series of demographic, risk factor, and symptoms questions. A standard noncontrast head CT was performed using a GE model 9800 Hi-Lite Advantage scanner. The standard protocol involves 5-mm cuts through the posterior fossa and 10-mm cuts above. The head CT scan was interpreted independently by 2 neuroradiologists blinded to the experimental question. If the scan did not show intracranial hemorrhage an LP was performed.

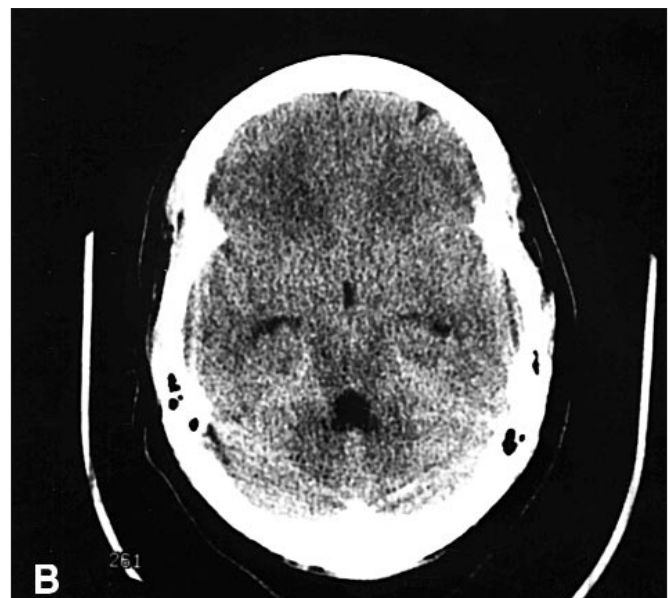
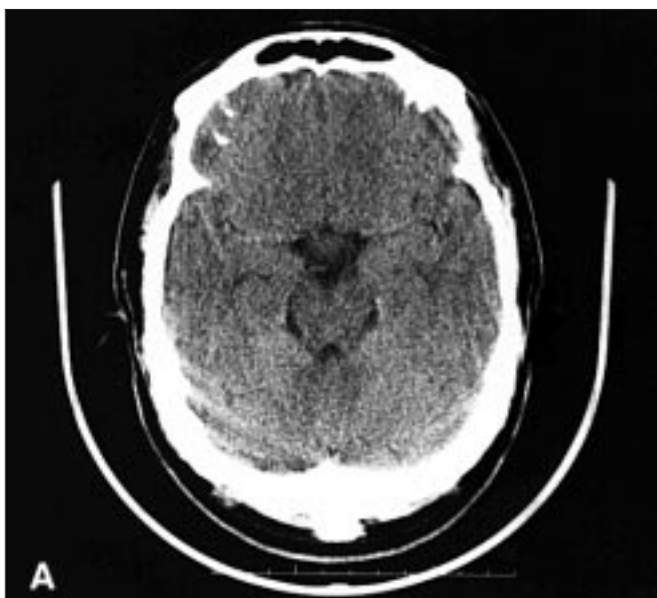
Cerebrospinal fluid (CSF) was sent for cell count and differential in first and fourth tubes. The second tube was sent for analysis of glucose and protein. The third tube was sent for microbiologic studies. The first and last tubes were also centrifuged at 2100 rpm for 5 minutes (Dynac II centrifuge, Clay Adams Co.), and the supernatant was examined for visual xanthochromia using a white-paper background. Supernatant from the first and last tubes were also examined by spectrophotometry using a Varian Cary 1 Uv-Vis spectrophotometer. Specimens were scanned to record the absorption spectrum between 350 and 650 nm. A spectrophotometric test result was considered positive for SAH when values above .023 absorbance units at 415 nm,

a peak in the 450 to 460 nm range, or both, were noted.^{7,8} Supernatant from first and last tubes for D-dimer studies were frozen at -70°C . After thawing at 37°C , samples, along with controls, were brought to room temperature. Dimertest II (American Diagnostica, Greenwich, CT) was used to analyze the CSF samples and positive and negative controls provided with the kits for the presence of cross-linked fibrin degradation products by the latex agglutination method. Agglutination of the specimen or the control 3 minutes after mixing indicated a positive reaction. Patients were considered to have SAH by LP results if the CSF RBC count was greater than 1,000 and no decrement of more than 25% was noted from first to last tubes, and 1 of the following criteria were met: (1) visual xanthochromia detected, (2) spectrophotometric xanthochromia detected, or (3) positive D-dimer assay result.

The data were accumulated in Microsoft Access and descriptive statistics were used to describe patients with (1) CT results positive for SAH (CT⁺), (2) CT results negative for SAH and LP negative for SAH (CT⁻/LP⁻), and (3) CT results negative for SAH, but LP results positive for SAH (CT⁻/LP⁺). The κ statistic⁹ for multiple diagnostic tests and 2 diagnostic categories were used to assess the agreement between the 4 LP tests (spectrophotometry, serial tube red blood cell counts, visual xanthochromia after centrifuga-

Figure 2.

Noncontrast head CT of the 2 patients with negative results after brain imaging, but positive CSF findings for subarachnoid hemorrhage. A, A 35-year-old man with a 5-day history of headache. B, A 37-year-old woman with a 1-hour history of headache. The CT reveals hydrocephalus.



tion, and D-dimer assay). Relative risks were used to compare the CT+ and CT-/LP- group with regard to demographic, symptom, medical history, and admission characteristics. The relative risk was calculated as the probability of SAH given the presence of the variable in question divided by the probability of SAH given the absence of that variable. Comparison of group means was done with *t* tests for independent samples with unequal variances. Exact confidence intervals (CIs) for all proportions were calculated using Intercooled STATA. This study was approved by the University of Texas, Houston, Committee for the Protection of Human Subjects.

RESULTS

During the 16-month study period, 38,730 patients were prospectively screened. Their charts were also reviewed again at a subsequent time. A chief complaint of headache was noted in 455 patients. Of these, 170 (37%) had the

worst headache of their life and were eligible and 107 were enrolled. A head CT scan was performed in all 107 of these patients and SAH was noted in 18 (17%, 95% CI 10% to 25%). Subarachnoid blood was detected in 2 of 79 (2.5%, 95% CI .3% to 8.8%) patients undergoing LP. No LP was performed in 10 patients because of patient refusal. Of the 107 patients enrolled, 53% presented more than 24 hours after symptom onset. Figure 1 is a flow chart of results by time of presentation after symptom onset and diagnostic test. Complete CSF analysis including all 4 diagnostic tests was accomplished in 43 of 79 cases. Of those receiving LP, 24% had an LP within 12 hours of symptom onset. Table 1 shows the demographic and clinical characteristics of the CT+, CT-/LP+, and CT-/LP- groups. The mean age (36 years) of the CT-/LP- patients was significantly lower than the mean age of the CT+ patients (53 years; *t*=-4.97, *P*<.00001). CT-/LP- patients had lower systolic blood pressure than CT+ patients (132 and 160, respectively; *t*=3.3, *P*=0.004).

Table 1.
*Demographic and clinical information on patients receiving CT and LP**

Variables	CT-/LP- (n=77)	CT+ (n=18)	CT-/LP+ (n=2)
Demographic			
Mean age (y, [SD])	36.3 (12.5)	53.1 (13.0)	36 (1.4)
Mean temperature (SD)	36.9°C (98.4°F)(1.6)	36.2°C (97.0°F) (1.7)	37.8°C (100°F)
Mean systolic blood pressure (mm Hg, [SD])	132.4 (23.7)	159.6 (29.7)	130
Male (%)	72.0	50.0	50.0
Female (%)	28.0	50.0	50.0
Non-Hispanic white (%)	20.8	22.2	50.0
Black (%)	42.9	50.0	50.0
Hispanic American (%)	35.1	27.7	0.0
Symptoms			
Photophobia (%)	45.1	28.5	50.0
Stiff neck (%)	26.4	37.5	100.0
Nausea (%)	64.8	36.4	100.0
Lethargy (%)	17.4	40.0	50.0
Focal neurologic deficit (%)	9.9	50.0	0.0
Medical history			
SAH (%)	0.0	0.0	0.0
Hypertension (%)	25.7	75.0	50.0
Stroke (%)	4.3	20.0	0.0
MI/Angina (%)	1.4	36.3	0.0
Migraine (%)	19.4	11.1	0.0
Headache (%)	47.8	27.3	0.0
Diabetes (%)	10.1	41.7	0.0
Previous LP (%)	14.9	20.0	0.0
Admission data			
Stiff neck (%)	8.5	20.0	100.0
Photophobia (%)	36.6	20.0	100.0
Time <24 h (%)	58.4	75.0	50.0

BP, Blood pressure; MI, myocardial infarction.
*Cell values reflect percents within a given column.

Table 2 provides relative risk data of patients with CT+ results for SAH compared with those whose results were CT-/LP- for SAH. Presentation with a focal neurologic symptom and a history of hypertension, stroke, myocardial infarction/angina, or diabetes, all were significantly associated with a CT+ diagnosis of SAH. Presentation less than 24 hours after symptom onset was associated with a significantly less chance of a CT+ SAH. Of the 107 enrolled patients, 10 refused LP so that a final diagnosis could not be established and these patients are excluded from Table 1.

Table 3 provides spinal fluid results for the CT-/LP- and CT-/LP+ groups. RBC counts and protein were considerably higher in the CT-/LP+ group. There were 22 patients with any positive spinal fluid test results (Table 4). Of these, 2 met prespecified criteria for SAH by RBC count greater than 1,000 and lack of 25% decrement between first and last tubes combined with either positive spectrophotometry, D-dimer assay, or visual xanthochromia. These 2 patients formed the CT-/LP+ group. The remain-

ing 20 patients with any positive spinal fluid test results were classified as CT-/LP-. Follow-up telephone contact was made with this group of 20 patients at a mean 24.4 months from hospital presentation. All of the 18 patients available for contact were alive and well and had not had a recurrence of symptoms or any evidence of cerebral bleeding. The remaining 2 were not available for contact.

Spectrophotometry detected blood components in tube 1 in 3 patients with RBC counts less than 6. In all 3 patients, tube 4 was negative by spectrophotometry. The κ statistic for multiple diagnostic tests was used to examine the agreement among visual xanthochromia, spectrophotometric xanthochromia, serial tube RBC count, and D-dimer assay. The results indicate that the observed agreement was not greater than that expected by chance alone ($\kappa=.027$, $P=.358$).

Of the 63 eligible but nonenrolled patients, the explanation for exclusions were as follows: patient uncertain if this was worst headache of their life ($n=27$), recent history of viral meningitis ($n=1$), no obvious reason for exclusion ($n=35$). The 63 patients who were eligible but not enrolled did not differ from the enrolled group in age; presenting systolic blood pressure; presenting temperature; time of presentation after symptom onset; history of stroke, myocardial infarction, migraine, diabetes; and presence of focal neurologic symptoms. A significantly ($P<.05$) higher percentage of women were in the eligible, not enrolled group relative to the eligible and enrolled group (60% and 40%, respectively). Compared with the eligible, nonenrolled group, those enrolled had significantly ($P<.01$) higher serum WBC count, were more likely to have photophobia, nuchal rigidity, nausea and lethargy, and have a history of hypertension. Of the 63 eligible, nonenrolled patients, 52 had a head CT scan; all results were negative for hemorrhage.

Neither of the 2 CT-/LP+ patients had a detectable aneurysm after an exhaustive search. The first patient was a 35-year-old man with no significant medical history who

Table 2.
Association of demographic and clinical variables with CT+ SAH relative to CT-/LP-.

	Relative Risk	95% Confidence Interval
Demographic		
Male/Female	.48	.21-1.08
Non-Hispanic white/All others	1.07	.40-2.90
Black/All others	1.26	.55-2.90
Hispanic American/All others	.76	.30-1.94
Symptoms*		
Photophobia	.52	.11-2.50
Stiff neck	1.58	.41-6.07
Nausea	.37	.12-1.15
Lethargy	2.63	.83-8.21
Focal neurologic deficit	5.75	1.96-16.89
Medical history		
SAH	—	—
Hypertension	6.11	1.80-20.76
Stroke	3.75	1.07-13.19
MI/Angina	8.69	3.78-19.94
Migraine	.55	.07-4.07
Headache	.46	.13-1.61
Diabetes	4.11	1.56-10.84
Previous LP	1.35	.33-5.61
Admission data		
Stiff neck	2.28	.58-8.95
Photophobia	.47	.11-2.08
Time <24 h	.27	.10-.76

MI, Myocardial infarction.
*Present/Absent.

Table 3.
Summary of lumbar puncture results by diagnostic category.

LP Results	CT-/LP- (n=77) Median (IQR)	CT-/LP+ (n=2) Median
Median RBCs tube 1 (IQR)	19 (291)	162,775
Median RBCs tube 4 (IQR)	0 (5)	221,400
Median glucose (mg/dL; IQR)	62 (16)	52.5
Median protein (mg/dL; IQR)	28 (12)	457
Median WBC (IQR)	9 (3)	15.3

presented with a 5-day history of the worst headache of his life with nausea, emesis, and nuchal rigidity. Results of the neurologic examination were normal. His temperature was 37.8°C (100.0°F), and blood pressure was 130/90 mm Hg. The head CT scan did not show blood (Figure 2, A). LP tube 1 contained 80 WBCs and 19,750 RBCs. Tube 4 contained 50 WBCs and 22,000 RBCs. The CSF glucose was 51 mg/dL and protein was 44 mg/dL. Spectrophotometry and D-dimer CSF test results were positive. He was admitted and had 3 normal cerebral angiograms over 1 month. The second patient was a 37-year-old woman who presented after acute onset of the worst headache of her life 1 hour before presentation. She had nausea and nuchal rigidity and a history of hypertension. Results of the neurologic examination were normal. She was afebrile with blood pressure of 130/65 mm Hg. The head CT scan did not show blood, but did reveal mild hydrocephalus (Figure 2, B). LP tube 1 contained 200 WBCs and 305,800 RBCs. Tube 4 contained 400 WBCs and 420,800 RBCs. The CSF glucose was 54 mg/dL and protein 870 mg/dL. The CSF was positive for visual and spectrophotometric xanthochromia; the D-dimer assay result was negative. Angiography showed a small posterior fossa arteriovenous malformation that was not amenable to treatment.

DISCUSSION

The decision of whether to use a diagnostic test involves weighing the diagnostic yield of the test, the importance of diagnosing the disease in question, and the discomfort and expense of the test for the patient. Detecting a sentinel SAH in a patient is very important because the consequences of full aneurysmal rupture are often catastrophic. LP is minimally uncomfortable and a relatively inexpensive ED procedure. Although these facts argue in favor of LP as a diagnostic test, the current study calls into question the diagnostic yield of CSF analysis in patients with normal CT imaging results. In more than 38,000 patient encounters at a busy urban ED, only 2 patients were found to have a CT-/LP+ SAH. In both cases blood was not readily apparent on CT imaging, but the patients were admitted for further evaluation because of the CT findings and clinical presentation in addition to the CSF results.

These results can be compared with data from the Netherlands. Van der Wee et al¹⁰ investigated a consecutive series of 175 neurologically normal patients with sudden and severe headache. CT within 12 hours of onset detected SAH in 117 (67%) of these. In 2 of the remaining 58 patients, CSF spectrophotometry showed SAH, and in

Table 4.
LP results for patients whose results were positive for any LP test.

Patient	Time	Xanthochromia	Spectrophotometric	Cell Count	RBC Tube 1	RBC Tube 4	D-Dimer	Diagnosis
1	1	-	+	+	19750	22000	+	+
2	1	-	+	-	133000	55500	+	-
3	1	+	+	-	990	20	-	-
4	1	-	+	-	136	0	-	-
5	0	-	+	-	230	0	-	-
6	1	-	+	-	440	5	-	-
7	0	-	+	-	407	4	-	-
8	1	-	+	-	560	40	-	-
9	0	-	+	-	650	1	-	-
10	1	-	+	-	1080	20	-	-
11	0	-	+	-	750	0	-	-
12	0	-	+	-	30	410	-	-
13	0	-	+	-	0	0	-	-
14	1	-	+	-	125	1	-	-
15	1	-	+	-	2		-	-
16	0	-	+	-	6		-	-
17	1	-	+	-	27		-	-
18	0	+	+	+	305800	420800		+
19	0	-	+	-	2280	35		-
20	0	-	+	-	123500	1390		-
21	1	-	-	-	6	0	+	-
22	1	-	-	-	1		+	-

+, Positive, -, negative, Time 0 <24 hours; Time 1 ≥24 hours. Cell count indicates met predetermined criteria for "+" or "-."

both cases an aneurysm was detected. In the current series SAH was detected in 20 of 455 (4%) patients presenting to an ED with severe headache and 20 of 107 (19%) patients with the worst headache of their life. In both the current and the Dutch series about 2% of patients reporting a worst-ever headache whose CT scan results were negative had a CSF-detectable SAH. The Dutch investigators used spectrophotometry only in patients with blood-stained CSF or when RBCs were detected. The current study shows the potential for false-positive results in this circumstance. In 3 patients with less than 6 RBC in tube 1, postcentrifuge spectrophotometry yielded positive results, but in all 3, tube 4 was negative for spectrophotometric xanthochromia, suggesting a traumatic tap. Perhaps because of the high sensitivity and low specificity of spectrophotometry, its best use is in patients with a considerable time interval from symptom onset who no longer have CSF RBCs, but may in fact have remaining detectable blood degradation products. Van Gijn and colleagues^{11,12} suggest that spectrophotometric xanthochromia after centrifugation is the best CSF test for SAH. Although we agree that this method is very sensitive, it lacks specificity. The D-Dimer assay also does not appear to discriminate SAH from traumatic LP as others suggest.¹³ In the current study 4 of the 22 patients with any positive spinal fluid test results had a positive D-dimer assay result, and 1 met criteria for SAH. Further study is needed to delineate whether spectrophotometry and visual xanthochromia improve sensitivity and specificity of SAH diagnosis at various times after symptom onset. This research is limited by the absence of a true gold standard in the diagnosis of SAH.

Van Gijn and van Dongen¹⁴ also call attention to the fact that head CT becomes less sensitive to blood with time, particularly after more than 48 hours. These authors also point out that LP may not demonstrate SAH until at least 12 hours after ictus since time is required for hemoglobin release after RBC lysis. In the current study, CT detected 4 patients with SAH after more than 24 hours (Figure 1). Of the 36 patients presenting more than 24 hours after symptom onset with CSF studies only 1 had positive results. This suggests that CT is still sensitive more than 24 hours after ictus, although a precise time course of effectiveness was not established in this study. Of the 17 patients with LP within 12 hours, 4 had positive spectrophotometry results and 1 met criteria for SAH, suggesting spectrophotometry's sensitivity soon after ictus.

Caution is necessary when interpreting the results of the current study. Angiography was not used to determine whether patients with any positive CSF test result had a detectable aneurysm. Of the 22 patients with any positive CSF test result, 2 met our criteria for SAH. All but 2 of the

remaining 20 were available for follow-up and were without sequelae more than 2 years after ictus. Community studies suggest that SAH follows warning leaks within a month.⁶ We believe it is unlikely that these 20 patients had an aneurysmal SAH. Angiography carries risk, expense, and the concern that a small clinically silent aneurysm may be blamed for a traumatic LP. Although 170 patients were eligible for this study, 107 were enrolled and complete analysis was performed on 97. Patient displeasure with LP likely explains why, despite its recognition as a "standard of care" in patients with CT-negative worst headache, only 50% at our center had an LP before our study. We attempted to rigorously define CSF diagnosis of SAH, but our criteria have not been validated and it is conceivable that patients with SAH were missed because of the lack of sensitivity of our criteria.

The quality of the headache is an important historical factor suggestive of SAH. The Dutch series¹⁰ found a much higher proportion of headache patients with SAH than the current series. This result is likely due to their selection of patients with sudden headache onset, a clinical clue to SAH. However, several of the patients with SAH in the current series did not have sudden onset of symptoms, suggesting that absence of sudden onset of symptoms does not exclude the diagnosis of SAH.

This study suggests that with modern CT imaging approximately 2% of patients reporting worst headache symptoms who have a negative CT result will have an SAH detectable by CSF analysis. Because of the relatively small size of this study, the 95% confidence intervals for missing SAH on CT range from .3% to 8.8%. Although this number is lower than with early-generation CT scanners, a role for CSF analysis remains. We recommend that patients with the worst headache of their life presenting to the ED undergo noncontrast head CT. If the CT result is negative, informed consent should be obtained for LP. Patients should be counseled that although the yield of CSF analysis was just 2% in this study, it could range as high as 8.8%. LP should be recommended because SAH is devastating and the opportunity for early intervention is crucial.

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