Diagnosis of Subarachnoid Hemorrhage
Time to Change the Guidelines?

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See related articles, p 2115.

Although the most concerning diagnosis in patients presenting with thunderclap headache (abrupt onset of a severe unusual headache) is nontraumatic subarachnoid hemorrhage (SAH), only 8% to 12% of neurologically intact patients with thunderclap headache will have SAH; most have benign causes.[1] Of those with aneurysmal SAH, 40% to 50% of patients will present neurologically intact. Therefore, diagnostic testing beyond history and physical examination is necessary. The initial test of choice is a noncontrast CT scan of the brain.

Although CT is an excellent test for SAH, its sensitivity is both a function of timing from the onset of the headache as well as severity of the hemorrhage.[1] CT sensitivity is extremely high early but rapidly diminishes with time. Clinicians frequently encounter neurologically normal patients with a thunderclap headache and a negative CT scan. Even using third-generation scanners, CT by itself is insufficient to exclude SAH.[2] Therefore, guidelines recommend that a lumbar puncture (LP) be performed in these patients whose CT scans are negative or nondiagnostic.[3,4] Although LP is a relatively benign test, it adds time, patient discomfort, and, sometimes, diagnostic ambiguity from a traumatic tap.

Prior studies of CT sensitivity do not adequately account for the issue of timing in the earliest hours after the hemorrhage. In this issue of *Stroke*, Backes et al[5] present data suggesting that CT scan is 100% sensitive for SAH if performed within 6 hours of the headache onset and apart from 2 caveats, the authors recommend a change in the guidelines. Are their data strong enough to warrant such a change?

First let us consider the caveats. The first is that the <6-hour rule only applies to patients presenting with headache. This is because they identified a single early-presenting patient with acute neck pain and a negative CT who had SAH due to a cervical arteriovenous malformation. This is an important caveat because up to 8% of patients with SAH will present without thunderclap headache.[6] The second caveat is the study setting; experienced neuroradiologists at a referral center interpreted the scans.

Are there any other limitations that we must consider? Aside from its retrospective design, one limitation of this Dutch study is that the incidence of SAH was 42% (50% of those patients presenting within 6 hours). This is far higher than the incidence of SAH in patients with thunderclap headache seen in routine practice.[1] As well, they excluded patients whose SAH was confirmed at the transferring hospital, another factor that could skew their results. That said, their principal findings are compatible with 2 other relevant studies.

The first is a 2010 Danish report that concluded that CT was 100% sensitive if performed within 3 days of the headache.[7] Similar to the current report, this was a referral population to a neurosurgical center; however, unlike the Backes study, the Danish study included patients with focal or generalized neurological deficits. The incidence of SAH in this study was 59% (67% if they presented in the first 24 hours).

Both of these studies are retrospective reports of referral populations whose incidence of SAH is 5 to 6 times what is reported in the literature. Although Backes and colleagues state otherwise, test performance characteristics are in part related to the incidence and severity of the disease that they test for in a given population.

Classic statistical theory teaches that the sensitivity and specificity of a test are fundamental characteristics of the test and independent of disease prevalence. However, there are numerous examples of a diagnostic test performing well in a study population but failing to yield the same results in other populations.[8] In 1978, Rasenhoff and Feinstein[9] described the phenomenon of spectrum bias as the performance of a diagnostic test varying according to the case mix (a combination of disease severity and prevalence) of the population tested. Since that time, a growing body of literature has emerged suggesting that spectrum bias is common, leading to the concept that diagnostic tests perform better in populations of patients with more severe disease or higher prevalence.[10]

As an example of the relationship between prevalence and sensitivity, the prevalence of SAH is higher in early-presenting patients than in those presenting later.[5,7] So given these issues of spectrum bias, can the Dutch and Danish reports be used to support a change in current guidelines? What will happen when CT is used in a population more reflective of real-world practice in which the severity and prevalence of SAH are much lower?

Fortunately, a third study helps to resolve this conundrum. The 2011 Canadian report by Perry et al[11] is a prospective study of 3132 neurologically intact patients with thunderclap headache presenting to 11 different Canadian emergency departments. Two hundred forty patients (7.7%) had SAH, a

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number much more representative of the population of patients to which these results will be applied. Of the 3132 patients, 953 were scanned within 6 hours of onset of headache. All 121 of these early-presenting patients were CT-positive. Like with the other 2 studies, the prevalence of SAH in the earlier presenting group (12.7%) was over twice that of patients who presented >6 hours (5.5%).

Numerous radiologists, both general and neuroradiologists from across multiple institutions, interpreted the scans in the Canadian study There were 3 instances in which CT scans read as negative by emergency physicians were later read as positive by a radiologist. In a fourth instance, the false-negative reading was by a radiology trainee. This underscores the importance of having well-trained, experienced physicians interpret the CT scans.

Although not all patients underwent LP after a negative CT, the patients who received an LP did not differ substantially from those who did not. As well, because of the healthcare system in Canada, the researchers were able to obtain healthcare follow-up on >97% of the patients and were able to show that they were alive and had not been subsequently diagnosed with a SAH. We believe that the strengths of this article far outweigh the weaknesses.

As CT technology has become increasingly accurate and available, some have begun to suggest that cerebral CT angiography be performed after a negative to CT instead of an LP for the work-up of patients with possible SAH. We believe that this "technology creep" only leads to diagnosis of asymptomatic aneurysms (not the hemorrhage) and has many other unintended negative consequences.[12] The Dutch, Danish, and Canadian studies reinforce this notion.

Like with any guideline, it is just as important to know when it does not apply. It does not apply to patients with abnormal neurological examinations. It also does not apply if the history and physical examination suggest other diagnoses beyond SAH (cerebral venous sinus thrombosis, arterial dissections, cerebellar infarction, etc). Lastly, it only applies to patients who can be scanned within 6 hours of headache onset and specifically does not apply to patients presenting with isolated neck pain. This reinforces both the public health mandate as well as emergency department operations to focus on the rapid recognition and evaluation of patients with symptoms suggesting stroke.

Given this analysis, we believe that practice should change. Neurologically intact patients who present with thunderclap headache and undergo CT scan within 6 hours of symptom onset no longer need an LP to exclude SAH if the CT scan is negative. Physicians and hospitals must ensure the expertise of the individuals who are interpreting these scans.

Disclosures

Dr Edlow has served as an expert witness in medico-legal cases for both defense and plaintiff firms.

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KEY WORDS: cerebral aneurysm ■ CT scan ■ diagnosis ■ lumbar puncture ■ subarachnoid hemorrhage

Time-Dependent Test Characteristics of Head Computed Tomography in Patients Suspected of Nontraumatic Subarachnoid Hemorrhage

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Background and Purpose—A recent study suggested that in patients with acute headache suspicious of nontraumatic subarachnoid hemorrhage (SAH), cerebrospinal fluid (CSF) analysis is not needed to rule out SAH if head CT performed ≤6 hours after ictus is negative. Before implementation in daily practice, these results need replication. Therefore, we investigated test characteristics of head CT in patients with a clinical suspicion of SAH.

Methods—Patients suspicious of SAH and a normal level of consciousness presenting to our tertiary care hospital between 2005 and 2012 were included. All patients had a head CT interpreted by experienced neuroradiologists and CSF spectrophotometry if head CT was negative or inconclusive. We determined test characteristics with 95% confidence intervals (CI) for nontraumatic SAH of head CT performed ≤6 or >6 hours after onset of headache.

Results—Sensitivity of head CT ≤6 hours after ictus (n=137) was 98.5% (95% CI, 92.1%–100%), diagnosing all patients with aneurysmal and perimesencephalic SAH, but not with a cervical arteriovenous malformation. Sensitivity of head CT performed >6 hours after ictus (n=113) was 90.0% (95% CI, 76.3–97.2). After exclusion of patients with an atypical presentation without headache, sensitivity, specificity, negative predictive value, and positive predictive value of head CT ≤6 hours were all 100%.

Conclusions—In patients presenting with acute headache and a normal head CT ≤6 hours after ictus, as interpreted by experienced neuroradiologists, there is no added value of CSF analysis. In patients with an atypical presentation without headache and in patients presenting >6 hours after ictus, CSF analysis is still indicated. **(*Stroke*. 2012;43:2115-2119.)**

Key Words: cerebrospinal fluid ■ computed tomography ■ headache ■ lumbar puncture ■ neck pain ■ spectrophotometry ■ subarachnoid hemorrhage

See related article, p 2031.

The diagnosis of nontraumatic subarachnoid hemorrhage (SAH) can be challenging. One-third of patients with SAH present with headache as the only symptom.[1] Conversely, in patients presenting to general practice, sudden headache is caused by SAH in only 12% of patients.[2] Nevertheless, a diagnosis of aneurysmal SAH should never be missed, because early diagnosis and treatment of aneurysmal SAH are associated with better functional outcomes.[3]

Common practice for diagnostic evaluation of patients suspected of having SAH is a head CT and a subsequent lumbar puncture for cerebrospinal fluid (CSF) analysis if head CT is negative or inconclusive.[4,5] A recent study suggested that a lumbar puncture is not needed if a third-generation head CT scan performed within 6 hours after headache onset and interpreted by a qualified radiologist excludes the presence of blood in the subarachnoid space.[6] Criticisms of that study are that not all patients received lumbar puncture after a negative head CT scan and data were not replicated in a separate data set.

The purpose of the present study was to determine the test characteristics of head CT scan performed ≤6 hours after ictus in a cohort of patients with a clinical suspicion of SAH. All patients with negative or inconclusive CT scan underwent a lumbar puncture.

Materials and Methods

This study was conducted at the University Medical Center Utrecht, the Netherlands, which is a tertiary referral center for patients with SAH. Approval was obtained from the Institutional Research Ethics Board. We included all patients presenting to our emergency department between January 1, 2005, and January 1, 2012, with a clinical suspicion of nontraumatic SAH and a normal level of consciousness (defined as Glasgow Coma scale score of 15).[7] Patients were retrieved from 2 prospective databases. The first

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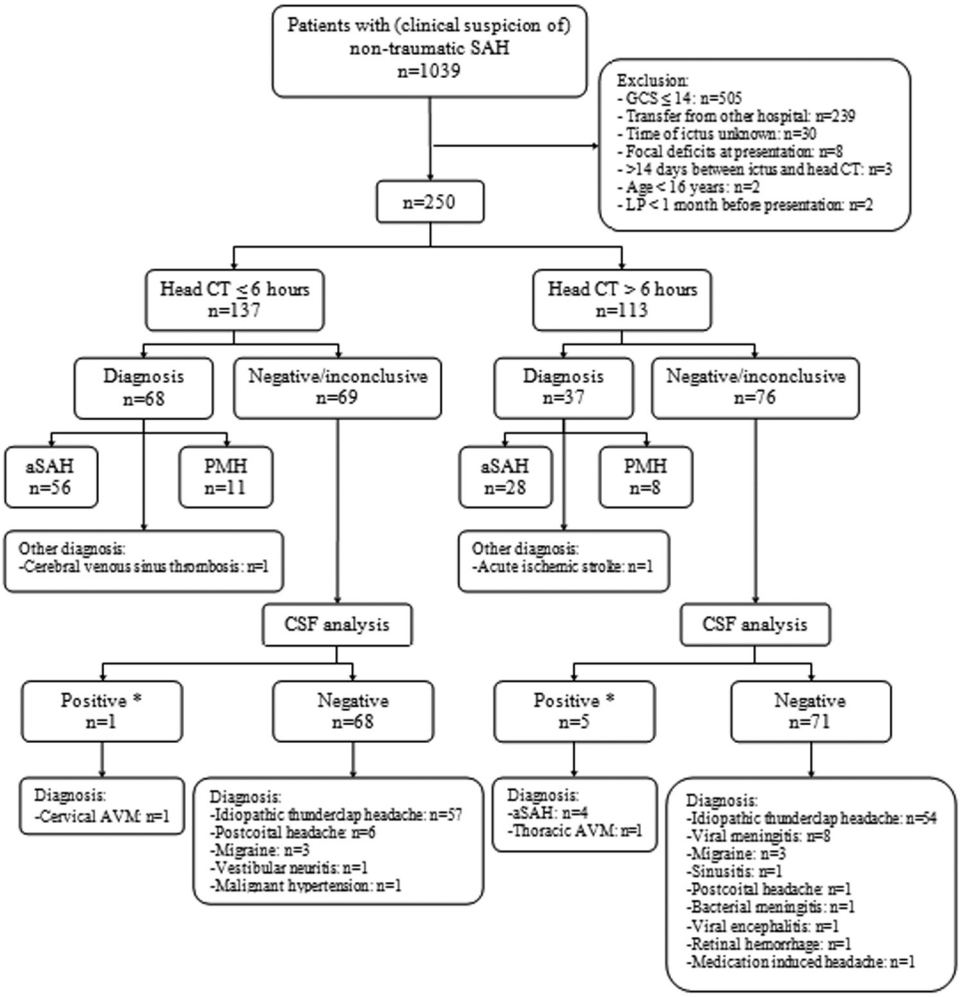

Figure 1. Flow chart. SAH indicates (aneurysmal) subarachnoid hemorrhage; GCS, Glasgow Coma Scale; CT, computed tomography; LP, lumbar puncture; PMH, perimesencephalic hemorrhage; CSF, cerebrospinal fluid; AVM, arteriovenous malformation. *Positive result was based on absorption spectrophotometry with a cut off value >0.05 at 458 nm for bilirubin.

database included consecutive patients with confirmed SAH and the second included all patients receiving lumbar puncture with CSF spectrophotometry. Exclusion criteria were: (1) Glasgow Coma scale score ≤14; (2) referral from another hospital with a confirmed diagnosis of SAH; (3) unknown time of ictus; (4) focal deficits at presentation; (5) >14 days between ictus and diagnostic work-up; (6) age younger than 16 years; and (7) lumbar puncture in the month before presentation.

According to our institutional protocol, all patients with a clinical suspicion of SAH undergo a plain head CT scan as part of their diagnostic work-up. If the CT scan does not reveal a diagnosis, then a lumbar puncture is performed for CSF analysis at least 12 hours after ictus. Our institutional protocol did not change during the study period. All patients were scanned with a modern 16 to 256 slices per rotation multidetector row third-generation scanner with a slice thickness of 5 mm. All scans were interpreted by experienced neuroradiologists. The CSF was protected from (day)light in aluminum foil and centrifuged at 1500 rotations per minute during 10 minutes. The supernatant was stored at 4°C until analysis. The CSF was analyzed using visual inspection and absorption spectrophotometry for the presence of bilirubin. Spectrophotometry was performed with a Beckman DU 650 spectrophotometer (Beckman Coulter). The diagnosis of SAH was made if plain head CT scan showed blood in the subarachnoid space or if CSF spectrophotometry was positive for bilirubin, which was defined as an absorption level >0.05 at wavelength 458 nm. Data regarding time of ictus and time of head CT were extracted from electronic patient files.

We calculated sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value of head CT scans for nontraumatic SAH with 95% confidence intervals. Test characteristics of head CT were determined in all patients and in subgroups of patients with head CT ≤6 hours and >6 hours after ictus.

Table 1. Baseline Characteristics

Characteristics	All Patients, N=250	Head CT ≤6 Hours After Ictus, N=137	Head CT >6 Hours After Ictus, N=113
Median age, y (range)	48 (17–88)	47 (18–83)	49 (17–88)
Women (%)	167 (66.8)	91 (66.4)	76 (67.3)
Median VAS (range), n=147	10 (4–10)	10 (5–10)	9 (4–10)
Symptoms at ictus (%)			
Headache	247 (98.8)	135 (98.5)	112 (99.1)
Vomiting	119 (47.6)	71 (51.8)	48 (42.5)
Neck pain	99 (39.6)	59 (43.1)	40 (35.4)
Worst headache of life	113 (45.2)	66 (48.2)	47 (41.6)
Transient loss of consciousness	39 (15.6)	24 (17.5)	15 (13.3)
Neck stiffness at presentation	72 (28.8)	40 (29.2)	32 (28.3)

CT indicates computed tomography; VAS, visual analogue scale.

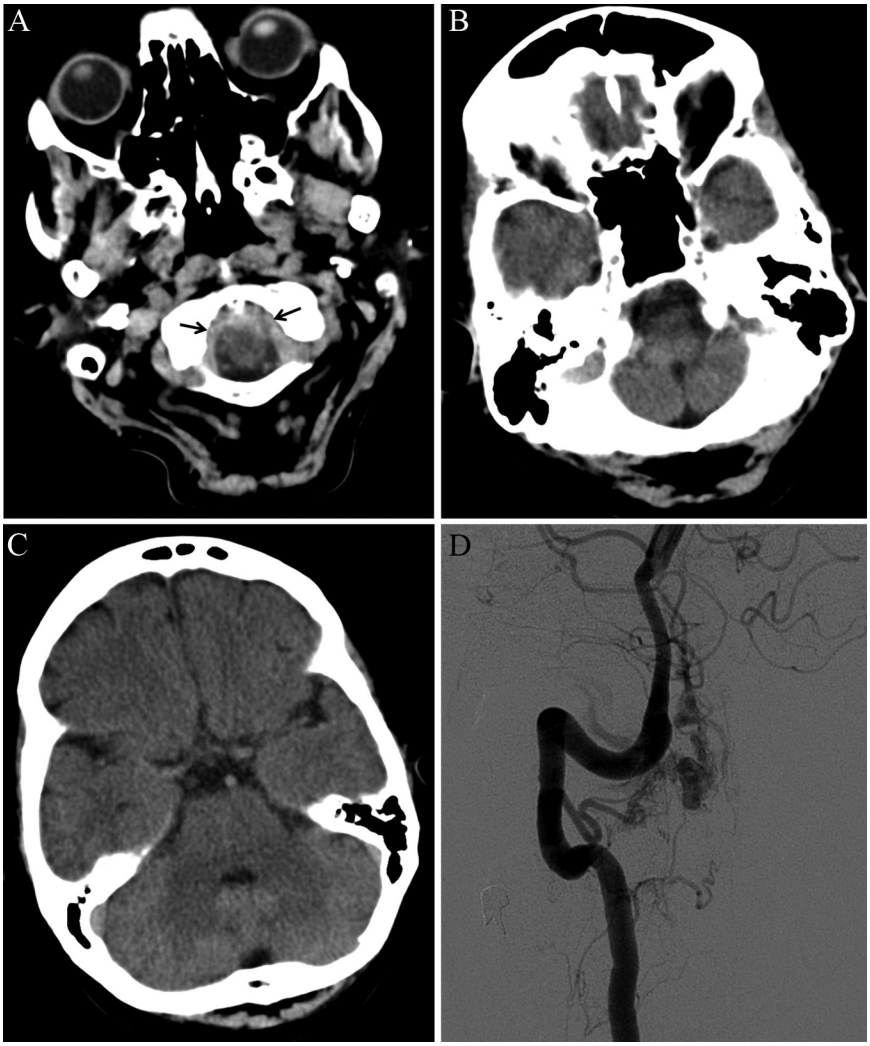

Figure 2. Head computed tomography (CT) and conventional angiography of patient with cervical arteriovenous malformation. Imaging results in a patient who presented with acute neck pain, nausea, and neck stiffness. Head CT (panels **A**–**C**) showed hyperdensity at the level of the foramen magnum (arrows), but was determined inconclusive. Conventional angiogram (panel **D**) showed the presence of a cervical arteriovenous malformation.

Results

During the study period, 1039 patients presented to our hospital with a clinical suspicion or diagnosis of SAH. A total of 789 patients were excluded, mainly because of a Glasgow Coma scale score of ≤14 on admission or initial presentation to another hospital, leaving 250 patients for further analysis (Figure 1). Baseline characteristics of included patients are shown in Table 1.

A head CT scan was performed within 6 hours after symptom onset in 137 patients (54.8%), which revealed a diagnosis in 68 patients (Figure 1). In the 69 patients with negative or inconclusive CT results, a lumbar puncture was performed that was positive for bilirubin in 1 patient. This patient presented with acute neck pain, nausea, and neck stiffness, but no headache, had an inconclusive CT scan, and finally had bleeding from a cervical arteriovenous malformation diagnosed. Head CT and digital subtraction angiography of this patient are shown in Figure 2.

A head CT scan was performed >6 hours after ictus in 113 patients (45.2%), which revealed a diagnosis in 37 patients (Figure 1). In the 76 patients with a negative or inconclusive head CT, lumbar punctures were performed that were positive for bilirubin in 5 patients (aneurysmal SAH, n=4; thoracic arteriovenous malformation, n=1). The patients with aneurysmal SAH and negative or inconclusive head CT were scanned between 27 hours and 10 days after ictus.

Table 2. Test Characteristics of Head Computed Tomography in Patients Presenting With a Clinical Suspicion of Subarachnoid Hemorrhage Stratified by Timing of Scan

Time From Onset of Symptoms to Head CT	N of Patients	% Sensitivity (95% CI)	% Specificity (95% CI)	Likelihood Ratio (95% CI)		% Predictive Value (95% CI)	
				Positive	Negative	Positive	Negative
All patients	250	95.4 (89.5–98.5)	100 (97.4–100)	Infinity	0.05 (0.02–0.11)	100 (96.5–100)	96.6 (92.2–98.9)
≤6 hr	137	98.5 (92.1–100)	100 (94.8–100)	Infinity	0.02 (0.00–0.10)	100 (94.6–100)	98.6 (92.3–100)
>6 hr	113	90.0 (76.3–97.2)	100 (95.1–100)	Infinity	0.10 (0.04–0.25)	100 (90.3–100)	94.8 (87.2–98.6)

CI indicates confidence interval; CT, computed tomography.

Table 3. Test Characteristics of Head Computed Tomography in Patients Presenting With a Clinical Suspicion of Subarachnoid Hemorrhage and Acute Headache Stratified by Timing of Scan

Time From Onset of Symptoms to Head CT	N of Patients	% Sensitivity (95% CI)	% Specificity (95% CI)	Likelihood Ratio (95% CI)		% Predictive Value (95% CI)	
				Positive	Negative	Positive	Negative
All patients	247	97.2 (91.9–99.4)	100 (97.4–100)	Infinity	0.03 (0.01–0.09)	100 (96.5–100)	97.9 (94.0–99.6)
≤6 hours	135	100 (94.6–100)	100 (94.8–100)	Infinity	0.00 (0.00–0.04)	100 (94.6–100)	100 (94.8–100)
>6 hours	112	92.3 (79.1–98.4)	100 (95.1–100)	Infinity	0.08 (0.03–0.23)	100 (90.3–100)	96.1 (88.9–99.2)

CI indicates confidence interval; CT, computed tomography.

The sensitivity of head CT for the entire study population was 95.4% (95% CI, 89.5–98.5; Table 2). In patients who underwent head CT within 6 hours after symptom onset, sensitivity was 98.5% (95% CI, 92.1–100). In patients scanned >6 hours after ictus, sensitivity was 90.0% (95% CI, 76.3–97.2; Table 2). The sensitivity, specificity, positive predictive value, and negative predictive value of head CT performed within 6 hours after ictus were all 100% when only patients with acute headache were analyzed (Table 3).

Discussion

Head CT is a very sensitive diagnostic test in patients with a clinical suspicion of nontraumatic SAH and a normal level of consciousness on admission. In patients who had CT imaging within 6 hours after onset of acute headache, a negative CT ruled out SAH. However, CT within 6 hours after symptom onset failed 1 patient with only neck pain who had an inconclusive CT; finally, bleeding from a cervical arteriovenous malformation was diagnosed.

Previous studies on test characteristics of head CT for SAH found sensitivities ranging between 90% and 100%.[4,8–12] The discrepancy of most studies with our findings can be explained by longer cut-off points for time delay between onset of headache and imaging ranging from 12 to 24 hours after ictus, the use of first- or second-generation CT scanners, and the use of tests other than absorption spectrophotometry as a gold standard. The majority of these studies only calculated sensitivity but not specificity, negative predictive value, or positive predictive value, because only patients with a final diagnosis of SAH were included.[8–10,12] Only 1 previous study investigated test characteristics of head CT scan for the diagnosis of SAH with 6 hours as a cut-off point, and the results of that study are in line with those of our study.[6] However, there are a few differences between the previous study and our study. The diagnosis of SAH can be difficult because not all patients with SAH present with acute headache; however, they may present with atypical features such as isolated neck pain, back pain, chest pain, or an acutely confused state.[13–18] Therefore, we included all patients who had a diagnostic work-up for a clinical suspicion of SAH, including those with a less obvious clinical presentation without headache. Also, in our study all patients with a negative CT underwent lumbar puncture, which is, in our view, a better gold standard than the absence of rebleeding during follow-up, which was previously used in a substantial proportion of patients to rule out in retrospect the diagnosis of SAH.[6] The incidence of SAH was much higher in our study compared with the previous study.[6] This difference most likely results from a lower threshold in the previous study to give patients presenting with headache a diagnostic work-up of SAH. It is unlikely that the difference in the incidence of SAH influenced test characteristics.

Our results imply that in patients with a clinical suspicion of SAH presenting with acute headache and a negative head CT within 6 hours after ictus, there is no longer a need to perform a lumbar puncture for CSF analysis. However, in patients with an atypical presentation without headache and a negative or inconclusive head CT within 6 hours after ictus, a lumbar puncture is still needed because it may reveal the presence of bilirubin secondary to a hemorrhage from a spinal arteriovenous malformation.[16]

The strength of our study is that all included patients with a normal head CT had a lumbar puncture for CSF analysis including absorption spectrophotometry. It is unlikely that we missed any patients with SAH because this method has 100% sensitivity for the diagnosis of SAH when it is performed between 12 hours and 2 weeks after ictus.[19] A limitation of our study might be the retrospective design. We were unable to retrieve the time of symptom onset in 30 patients, which might have resulted in selection bias. However, we know from daily practice that some patients simply do not remember the exact time of onset. Finally, our results cannot be extrapolated to low-volume centers with radiologists who are less experienced to diagnose SAH on head CT scans. Our study was conducted in a high-volume tertiary care hospital and head CT scans were interpreted by qualified neuroradiologists who routinely interpret head CT images.

Conclusions

In conclusion, we showed that in patients with acute headache and a normal level of consciousness, third-generation head CT performed within 6 hours after symptom onset is a perfect tool to diagnose SAH. There is no added value of CSF analysis for absorption spectrophotometry in this group of patients. However, a lumbar puncture for CSF analysis is still necessary to rule out SAH in a subgroup of patients presenting within 6 hours after ictus with an atypical presentation without sudden headache, and in all patients presenting >6 hours after symptom onset if head CT is negative or inconclusive. We emphasize that our results only can be extrapolated to high-volume tertiary care centers where head CT scans are interpreted by experienced neuroradiologists.

Disclosures

None.

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