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CLINICAL ARTICLE

The added value of cerebrospinal fluid analysis in patients with subarachnoid hemorrhage after negative noncontrast CT

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OBJECTIVE In patients presenting within 6 hours after signs and symptoms of suspected subarachnoid hemorrhage (SAH), CSF examination is judged to be no longer necessary if a noncontrast CT (NCCT) scan rules out SAH. In this study, the authors evaluated the performance of NCCT to rule out SAH in patients with positive CSF findings.

METHODS Between January 2006 and April 2018, 1657 patients were admitted with a nontraumatic SAH. Of these patients, 1546 had positive SAH findings on the initial NCCT and 111 patients had an NCCT scan that was reported as negative in the acute setting, but with positive CSF examination for subarachnoid blood. Demographic data, World Federation of Neurosurgical Societies grade, and SAH time points (ictus, time of NCCT, and time of lumbar puncture) were collected. All 111 NCCT scans were reevaluated by an experienced neuroradiologist.

RESULTS Of the 111 patients with positive CSF findings, SAH was initially missed on NCCT in 25 patients (23%). Reevaluation of 21 patients presenting within 6 hours of symptom onset confirmed NCCT negative findings in 12 (5 aneurysms), an aneurysmal SAH (aSAH) pattern in 8 (7 aneurysms), and a perimesencephalic pattern in 1 patient. Reevaluation of 90 patients presenting after 6 hours confirmed negative NCCT findings in 74 patients (37 aneurysms), aSAH pattern in 10 (4 aneurysms), and a perimesencephalic pattern in 6 (2 aneurysms).

CONCLUSIONS CSF examination is still mandatory to rule out SAH as NCCT can fail to show blood, even within 6 hours after symptom onset. In addition, the diagnosis SAH was frequently missed during initial reporting.

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KEYWORDS subarachnoid hemorrhage; spinal puncture; cerebrospinal fluid; x-ray computed tomography; aneurysm; vascular disorders

Noncontrast CT (NCCT) is the first diagnostic step when a subarachnoid hemorrhage (SAH) is suspected.[1,2] High diagnostic accuracy for SAH is of the utmost importance because the risk of recurrent bleeding in the aneurysmal subgroup is high, and recurrent bleeding significantly contributes to a poor clinical outcome.[3]

Previous studies have shown that, in the first 3 days after onset of symptoms, the sensitivity of NCCT to detect subarachnoid blood was between 90% and 100%.[4–7] Two studies, one of which was prospective, even described a sensitivity and specificity of 100% (range 97%–100%) within 6 hours of symptom onset when performed on third-generation or later CT scanners and interpreted by a neuroradiologist.[8,9] In addition, it has been shown that general radiologists in nonacademic hospitals were able to make the diagnosis with similar sensitivity and specificity.[10] These findings are not yet included in European and American guideline recommendations in which lumbar puncture (LP) is still judged to be necessary and no time restrictions are given to refrain from it.[1,2]

We therefore retrospectively analyzed all patients admitted to our hospital with an initially negative NCCT scan and a positive LP for subarachnoid blood to assess the diagnostic value of NCCT in excluding or confirming the presence of SAH.

Methods

This observational cohort study was performed according to the STROBE statement.[11] The study protocol and analysis of data were approved by the medical ethics

ABBREVIATIONS aSAH = aneurysmal SAH; CTA = CT angiography; DSA = digital subtraction angiography; IQR = interquartile range; LP = lumbar puncture; NCCT = noncontrast CT; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.

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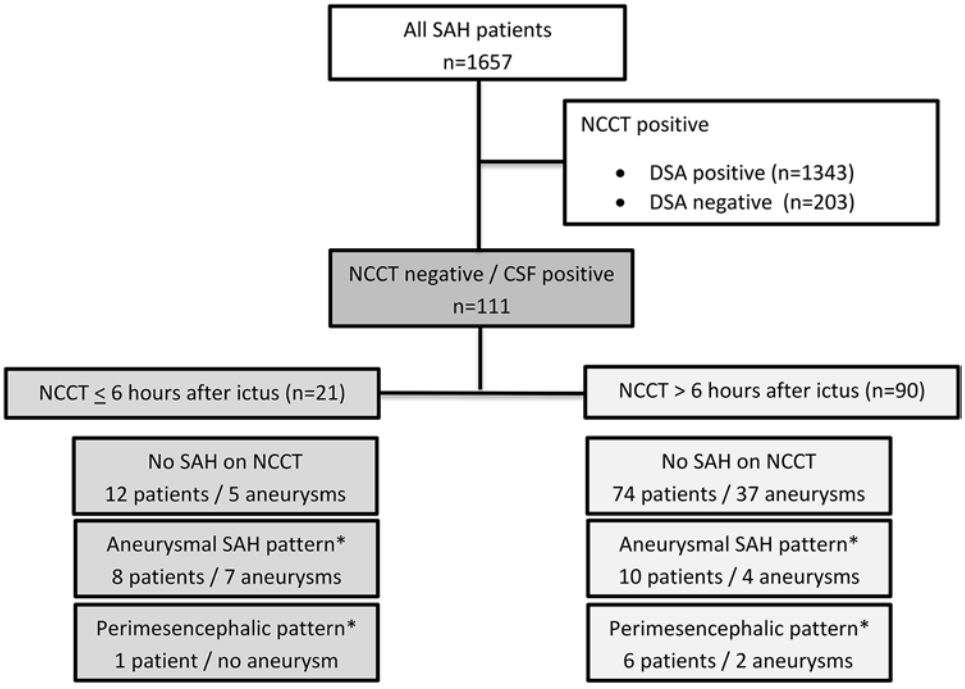

FIG. 1. NCCT findings in CSF-positive patients with SAH divided by time interval from ictus to execution of NCCT. *Patients with a normal initial NCCT report but after reassessment showed positive findings of SAH on NCCT, either in an aneurysmal or perimesencephalic pattern.

committee of our institution and no informed consent was deemed necessary.

Patient Population and Data Collection

Data were collected from a database in which all consecutive patients with SAH are registered from 2006 to the present. Between January 2006 and April 2018, 1657 patients with a nontraumatic SAH were primarily admitted to our center or referred from local hospitals. Amsterdam University Medical Centers (location AMC) is a tertiary referral center, serving a total population of approximately 2.4 million people. Of these patients, 1546 (91.8%) had an NCCT-positive SAH (Fig. 1). The remaining 111 patients (8.2% of the total), in whom SAH was diagnosed by means of a positive LP, form the core of this study. Most of these patients presented with the typical "worst ever headache," but a minority of patients with more indistinct clinical findings, who underwent both NCCT and subsequent LP, were included under the clinical suspicion of meningitis or vasculitis.

Patient demographics (age and sex), World Federation of Neurosurgical Societies (WFNS) grade on admission, and the following study-specific time (interval) parameters were analyzed: time of ictus, time of first hospital admission (referring center and/or tertiary center), time interval from ictus to first CT scan (including patient and referral delay), and time interval from ictus to LP. Because some patients were scanned in referring centers, a variety of CT scanners from different vendors were used and NCCT was performed according to the local protocol. In all referring centers, the volumetric NCCT data set was used to obtain 3- to 5-mm-thick reconstructions and these were sent for review to our center. All CT scanners were at least third-generation scanners. The presence of subarachnoid blood on the NCCT in the original radiological report from referring centers, as well as reassessment at the time of hospitalization in our center, was recorded. In all patients, CT angiography (CTA) was performed to find an aneurysmal or other vascular cause of the SAH. When imaging was judged to be of insufficient diagnostic quality, NCCT and/or CTA were repeated in our center. In cases of negative or equivocal CTA findings, diagnostic digital subtraction angiography (DSA) was performed. If no causative aneurysm was detected and all relevant intracranial arteries (including external carotid artery injections) were sufficiently evaluated, a delayed DSA was performed after 2 weeks.

For the purpose of this study, all NCCT scans (encompassing the 3- or 5-mm reconstructions and the source images, if available) were again reassessed by an experienced interventional neuroradiologist (R.V.D.B., with more than 20 years of experience) for the presence and pattern of subarachnoid, parenchymal, or intraventricular blood, without knowledge of other clinical, imaging, or outcome data. A diagnosis of perimesencephalic hemorrhage could only be made if the NCCT scan was performed within 72 hours after ictus showing the typical perimesencephalic distribution.[12]

CSF Analysis

LPs were performed at least 12 hours after symptom onset. CSF was analyzed and interpreted according to local laboratory criteria. Qualitative and/or quantitative assessment of oxyhemoglobin and bilirubin concentrations

TABLE 1. Demographics of 111 NCCT-negative, CSF-positive patients

Variable	Value
Mean age (range), yrs	54 (19–84)
Females, n (%)	57 (51)
Median time from ictus to NCCT scan (range), hrs	72 (1– 600)*
Subgroup ≤6 hrs, n = 21	3 (1–6)
Subgroup >6 hrs, n = 90	96 (8–600)*
Presence of aneurysms, n (%)	56 (50)
WFNS SAH grade, n (%)†	
I	101 (91)
II	8 (7)
III	0 (0)
IV	2 (2)

* Delay includes patient delay.
† WFNS grade on first admission.

on spectrophotometry needed to be positive to make the diagnosis of SAH. Additional support for the diagnosis was the pre-centrifuge appearance of the CSF on inspection and supernatant CSF with positive signs of xanthochromia.

Statistical Analysis

Continuous variables are presented as either mean (with range, normally distributed) or median (interquartile range [IQR], not normally distributed), and categorical variables are presented as counts (%). The Shapiro-Wilk test, together with normality plots, was used to assess normal distribution of the continuous variables. Statistical analysis was performed using SPSS (version 23.4, IBM Corp.). No funding was received for the study design, data collection, data analysis, data interpretation, or writing of research, authorship, and/or publication of this report.

Results

The patient demographics of all 111 NCCT-negative, CSF-positive patients are presented in Table 1. Contrary to the usual distribution, no female predominance was found. The vast majority of patients (91%) presented with a WFNS grade I SAH. Two patients presented with a WFNS grade IV SAH: one developed hydrocephalus, the other seizures.

After reassessment of the NCCT, findings were confirmed negative for subarachnoid blood in 86 (77%) of the 111 patients (Fig. 1). Of these 86 patients, 12 presented within 6 hours after symptom onset (14%, and 0.7% for the entire SAH cohort). In 5 (42%) of these 12 patients, an aneurysm was detected. In the 74 patients presenting later than 6 hours after ictus, an aneurysm was seen in 37 patients (50%).

On reassessment, subarachnoid blood was noted on NCCT in 25 (23%) of the 111 patients: NCCT was incorrectly judged to be negative in referring centers in 20 patients and during out-of-office hours in our center in 5 patients. The NCCT report was already corrected at hospitalization in 16 patients. After reevaluation, an aneurysmal SAH (aSAH) pattern was seen in 18 of the 25 patients, in conjunction with 11 aneurysms. A perimesencephalic pattern was noted in 7 patients, revealing 2 aneurysms. Both aneurysms were treated; one was clipped and was judged to be nonruptured during surgery.

Discussion

In this single-center large cohort study of patients, a negative NCCT scan performed within 6 hours after symptom onset did not always exclude the presence of subarachnoid blood. In a relevant proportion of patients with a confirmed negative NCCT scan, the diagnosis of SAH was solely dependent on CSF examination. These findings differ from the conclusions of a systematic review and meta-analysis that a negative NCCT scan within 6 hours may be considered sufficient to rule out SAH under specific circumstances.[13]

Our findings give support to the European and American recommendations that if NCCT is nondiagnostic and the clinical suspicion of SAH is high, it should be followed by an LP (performed more than 12 hours after symptom onset) to investigate the CSF.[1,2] Although the absolute number of patients with a false-negative NCCT scan within 6 hours is small in our cohort, the risk of failing to diagnose an aneurysmal SAH is not negligible as the consequences of a rebleed are quite severe.[3] Perry et al. implemented the "Ottawa SAH rule and 6 hour CT rule" in a prospective cohort of patients with SAH, and in 5 patients the diagnosis of SAH was missed. Nevertheless, it was concluded that the 6-hour CT rule was highly sensitive.[14] A more cautious strategy was proposed in an external validation study by Mark et al. because the imaging rule of a negative NCCT scan within 6 hours failed to detect SAH in 20% of patients.[15] Stewart et al. focused on imaging within 12 hours after symptom onset, with incorrect negative NCCT findings in 2 of 40 patients but none within 6 hours.[16]

Another important finding in our study is the number of NCCT reporting errors on the presence of subarachnoid blood. Differences in diagnostic performance between neuroradiologists in high-volume centers and less experienced radiologists in low-volume centers to detect small quantities of SAH have already been acknowledged and are confirmed in this cohort study.[8–10] In addition, our results show that even in high-volume centers the diagnosis SAH can be missed, especially during out-of-office hours. Improvements in the detection of even small amounts of SAH might come from deep learning algorithms. Kuo et al. demonstrated an end-to-end network that performs joint classification and segmentation of acute intracranial hemorrhage on head CT using deep learning with examination-level classification comparable to that of experts.[17] However, additional comparative studies focused on the detection of small amounts of SAH are needed to determine the added value of deep learning in these specific conditions.

In approximately half of our LP-positive, NCCT-negative patients an aneurysm was detected, both before and after the 6-hour cutoff point. These data are consistent with other reports describing a high diagnostic yield to detect

an aneurysm in LP-positive patients.[18–20] The high rate of detected aneurysms is far above the aneurysm prevalence in the general population of 3.2%.[21] Although the presence of an aneurysm in an LP-positive patient with SAH can be merely an incidental finding, albeit a very serendipitous one, it should be regarded as ruptured until proven otherwise.[13,15] The same argument holds true for patients with a perimesencephalic pattern of SAH. A concomitant aneurysm diagnosed with CTA will upgrade the diagnosis from perimesencephalic to an aSAH once an aneurysm has been detected.[22,23] We might even underdiagnose aneurysm presence in patients with a perimesencephalic distribution of blood because 3D rotational angiography is no longer recommended per se in the instance of classic perimesencephalic aSAH.[1]

One of the limitations of this study is that we did not reevaluate all CT scans from our cohort of 1657 patients with SAH, but only focused on patients with positive CSF findings for SAH. Therefore, no calculation of sensitivity, specificity, or positive or negative predictive values was possible, nor can we give a clear recommendation about which clinical conditions warrant additional CSF examination. This might have positively influenced the detection of SAH at reevaluation and is not immediately comparable to the real-life clinical situation during initial assessment. However, even in this biased retrospective situation, no blood could be detected on the NCCT scan within 6 hours after symptom onset, which is important for the main finding of this study. A second limitation of our study is that because of the retrospective analysis, the time of ictus was sometimes difficult to extract from the patient files, making it difficult in some cases to determine the exact time interval until execution of the NCCT. Another limitation of the study is that because we are a referral center for patients with (nontraumatic) SAH we depend on the judgment of other centers for proper SAH patient identification. We might not have included SAH patients with a more ambiguous neurological course in our database, especially those in whom the admission NCCT scan did not show subarachnoid blood, and the LP failed or was refused by the patient. Moreover, the technique used and reference values for CSF examination varied among referring centers, making it possible that we missed some patients with SAH, or that patients with ambiguous findings were unnecessarily referred, leading to overdiagnosis.

Conclusions

We advocate a low threshold for CSF examination in patients suspected of SAH with a negative NCCT scan, even when scanned within 6 hours after onset of symptoms, and emphasize referral to dedicated neurovascular centers for accurate judgment of the NCCT. Although this might involve a relatively small number of patients of the total population with SAH, almost half of these patients will have an underlying aneurysm, which, if left untreated, will carry the risk of a rebleed.

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Disclosures

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Author Contributions

Conception and design: van den Berg, Verbaan, Vandertop. Acquisition of data: van den Berg, Jeung, Post. Analysis and interpretation of data: Jeung, Hoogmoed, Verbaan. Drafting the article: van den Berg, Jeung. Critically revising the article: Coert, Coutinho, Majoie, Verbaan, Emmer, Vandertop. Reviewed submitted version of manuscript: Jeung, Post, Coert, Hoogmoed, Coutinho, Majoie, Verbaan, Emmer, Vandertop. Approved the final version of the manuscript on behalf of all authors: van den Berg. Statistical analysis: van den Berg, Verbaan. Study supervision: van den Berg, Hoogmoed, Vandertop.

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