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Is there a role for lumbar puncture in early detection of subarachnoid hemorrhage after negative head CT?

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Abstract
To investigate the role of lumbar puncture (LP) after a negative head computed tomography (CT) when ruling out subarachnoid hemorrhage (SAH) within 24 h of symptom onset. In a single-center, retrospective cohort study, we studied a consecutive series of patients from 2011 to 2015. All patients underwent CT or CT following LP to rule out SAH. Patients were categorized into four groups depending on the time of symptom onset to initial head CT: 0–6 h, 6–12 h, 12–24 h, and over 24 h. Experienced radiologists interpreted all CT scans. We investigated the sensitivity, specificity, and negative predictive value (NPV) of noncontrast CT in detecting SAH. Of 539 patients with suspected SAH and negative CT, 280 (51.9%) had their CT performed within 24 h of symptom onset. None of these patients had SAH. Five (1.9%) out of 259 patients with CT performed after 24 h of symptom onset had SAH diagnosed, and two turned out to be aneurysmal. When CT was performed within 24 h of symptom onset it had a sensitivity of 100% (95% CI 95–100%), specificity of 98% (95% CI 96–99.7%), and NPV of 100% (95% CI 98–100%) in detecting SAH. Modern CT scanners seem to have high sensitivity and specificity in the diagnosis of SAH when performed within 24 h of symptom onset. Beyond this point, CT seems to lack sensitivity and further investigation with LP is required.

Keywords Cerebrospinal fluid · Subarachnoid hemorrhage · Headache · Computed tomography · Lumbar puncture

Background

Headache is a common complaint, and accounts for 2% of visits in the emergency department (ED) [1]. Amongst headache patients, aneurysmal subarachnoid hemorrhage (aSAH) remains one of the most concerning underlying conditions for its high mortality and morbidity. 12% of aSAH patients die suddenly before receiving medical attention [2], and one in five patients who are admitted die within 1 month [3]. Amongst aSAH patients 10–43% experience a warning leak (or sentinel bleed) from an aneurysm up to a few weeks before aneurysm rupture [3]. This warning leak is characterized by an abrupt onset of severe, unusual headache, and may or may not be accompanied by a brief loss of consciousness, nausea, vomiting, and meningismus.

Current international and Finnish guidelines recommend noncontrast head computed tomography (CT) for diagnosis of subarachnoid hemorrhage (SAH) and lumbar puncture (LP) if the initial head CT is negative for SAH [4, 5]. A lumbar puncture can reveal xanthochromia or small amounts of blood in the cerebrospinal fluid (CSF) undetected by the CT that can be a sign of a warning leak. Due to advances in third generation CT scanners, several recent studies have challenged the value of LP after negative head CT if the patient is neurologically intact, and CT is performed within 6 h of onset of a headache [6–8]. In addition, a lumbar puncture can cause pain, discomfort, and sometimes complications, of which post-lumbar puncture headache (PLPH) is the most common [9].

This study aims ED to evaluate the role of LP in the diagnostics of a suspected SAH. This study primarily focuses on evaluating how reliably a negative head CT using a third generation scanner can rule out SAH when performed within 24 h of symptom onset.

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Materials and methods

Study design

This was a retrospective cohort study conducted in Central Finland Central Hospital, a nonacademic hospital with annual ED visits of approximately 85,000.

A third generation CT scanner (Toshiba aquilion 64) with 5 mm slices was used in the ED during the study period. An attending radiologist interpreted all CT scans. In some cases, a radiology resident interpreted the scan first, and an attending radiologist reviewed the scan afterward. One neuroradiologist, who was consulted if needed, was working in the study hospital during the time of the study. The attending radiologist's report was used as a standard for this study. CSF was analyzed for red blood cells (RBCs), white blood cells, and xanthochromia visually and with spectrophotometry using UK National guidelines [10], which is the standard in Finland and many other European countries.

In the final analysis, a patient was considered to be positive for aSAH if (1) CT was positive for SAH and subsequent vascular imaging revealed an aneurysm, (2) CSF contained more than five RBCs and subsequent vascular imaging revealed an aneurysm, or (3) CSF had xanthochromia either visually or with spectrophotometry and subsequent vascular imaging revealed an aneurysm. A patient was considered negative for aSAH if CT was negative for SAH and either (1) CSF contained less than five RBCs, (2) CSF contained more than five RBCs, but subsequent vascular imaging revealed no aneurysms, (3) CSF had xanthochromia either visually or with spectrophotometry and subsequent vascular imaging revealed no aneurysm, or (4) CSF contained more than five RBCs and within 6-month follow-up patient had not suffered any form of SAH.

We hypothesize that no cases of SAH would be missed within 24 h of symptom onset. To test this hypothesis we estimated that 252 patients need to have CT performed within 24 h from symptom onset based on a previous study [11].

Institutional Ethics approval was not required as the study had no interventions or deviations from routine practice. The study was approved by the Central Finland Central Hospital District and was registered under local guidelines.

Selection of participants

Study participants were identified from two electronic databases. The first database contained consecutive patients who underwent LP in the ED between January 1st, 2011 and December 31st, 2015. All patients who had LP performed for suspicion of SAH after CT were included. Patients were excluded if they had refused LP, no CT was performed or if LP was performed for other reasons, such as meningitis and encephalitis. If patient records were ambiguous as to why LP was performed exclusion criteria were: (1) no complaint of a headache, (2) a trauma-related headache, (3) fever over 38°, and (4) a headache lasting longer than 14 days. The second database contained consecutive patients with International Classification for Diseases, ninth revision (ICD-9), codes I60.0 through I60.9 for SAH used on their visit to any department of the hospital during the study period. From this database, patients diagnosed with nontraumatic SAH were included. The study included patients who were 16 and older at the time of examination as in our institution (and most other in Finland) patients aged 16 and older are treated as adult patients. All patients included in the study had a noncontrast head CT and LP performed.

The following information were collected from patients' medical records: gender, age, time from symptom onset to initial head CT, result of CT, RBC count of CSF, visual and spectrophotometry analysis of CSF, whether patient presented with other symptoms besides a headache, whether an aneurysm was found in subsequent imaging studies, whether patient with positive head CT had been investigated for SAH with CT in 6 months prior to the hemorrhage, and whether patients revisited ED for complication due to LP. Patients' hospital and general practitioner records can be easily found in the same database of the studied hospital district. Both the records were also reviewed up to 6 months after LP to ensure no new episode of SAH had occurred. A structured phone call performed by first author MT was used to establish that the patient had not suffered a new episode of SAH within the follow-up period if medical records were considered inadequate. 18 patients had incomplete medical records through the follow-up period and were contacted by phone. After an introduction to the study, patients were asked about the time they were being investigated for SAH and whether they had ever since been investigated for SAH or had an episode of SAH.

Study patients were categorized into four groups based on the time from symptom onset to the initial head CT derived from the previous studies [8, 12, 13]: 0–6 h, 6–12 h, 12–24 h, and over 24 h.

Results

During the 5-year study period, 647 patients who presented to the hospital were identified as being suspected of SAH and underwent head CT or CT and LP. Median age was

Table 1 Characteristics of patients

	All patients ($N=647$)	Negative CT ≤ 24 h ($N=280$)	Negative CT > 24 h ($N=259$)	p
Median age, year (range)	47 (17–96)	45 (17–90)	43 (17–88)	
Women (%)	381 (55.8)	208 (58.1)	153 (52.9)	< 0.32
Symptoms besides headache (%)	128 (19.8)	47 (16.8)	24 (9.3)	< 0.02
Sensory impairment	31	16	12	< 0.57
Motor impairment	10	2	3	< 0.67
Speech disturbance	10	6	3	< 0.5
Brief LOC	22	9	3	< 0.14
Seizure	14	11	0	< 0.001
Unconscious at presentation	28	1	0	< 0.51
Other	13	2	3	< 0.67

LOC loss of consciousness

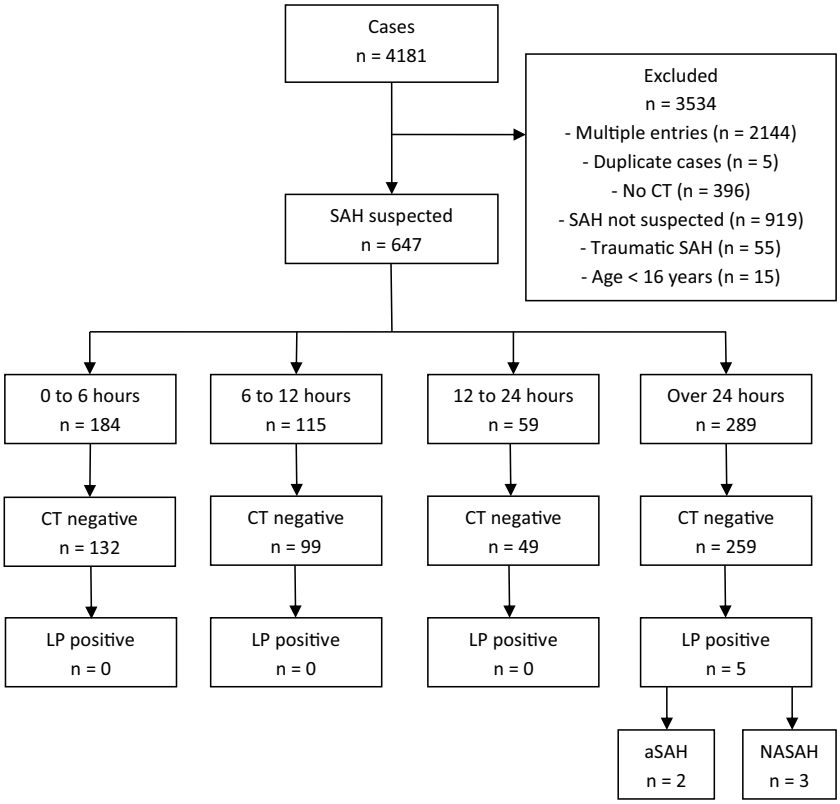

Fig. 1 Flowchart of study participants. *aSAH* aneurysmal subarachnoid hemorrhage, *NASAH* nonaneurysmal subarachnoid hemorrhage

47.2 years (range 17–96), and 361 patients (55.8%) were female (Table 1). Initial head CT was reported positive for SAH in 108 patients (16.7%) (Fig. 1).

The remaining 539 patients had negative head CT and underwent LP. The initial head CT was performed within 6 h in 132 patients (24.5%), 6–12 h in 99 patients (18.4%), 12–24 h in 49 (9.1%), and over 24 h from symptom onset in 259 patients (48%). Five patients had positive LP for SAH after a negative head CT (Table 2), and two of these patients had an aneurysm discovered. All five patients had their initial head CT performed more than 24 h after symptom onset. Out of 280 patients who underwent CT within 24 h from symptom onset, none had aSAH. Noncontrast CT had overall sensitivity of 95% (95% CI 89–98%), specificity of 99% (95% CI 97–99.7%), and negative predictive value (NPV) of 99% (95% CI 97–99.6%). When CT was performed within 24 h of symptom onset, it had a sensitivity of 100% (95% CI 95–100%), specificity of 98% (95% CI 96–99.7%), and NPV of 100% (95% CI 98–100%).

Table 2 Characteristics of patients with SAH diagnosis after negative noncontrast head CT

Age	Sex	Time from symptom onset	Symptoms	CSF RBC[a]	Xanthochromia[b]	Vascular anomaly	Diagnosis
80	F	~48 h	Ptosis, non responsive pupil	300,000	Yes/yes	Aneurysm	aSAH
27	M	~48 h	Thunderclap headache	20,000	Yes/yes	None	NASAH
32	M	1 week	Thunderclap headache	17	Yes/yes	None	NASAH
58	M	1 week	Brief LOC and headache	27,000	No/N/A	None	NASAH
71	F	4 weeks	Thunderclap headache	30,000	Yes/yes	Aneurysm	aSAH

N/A not available, *LOC* loss of consciousness

[a]CSF *RBC* Red blood cell count in the third vial of cerebrospinal fluid

[b]Visual xanthochromia/spectrophotometry

Out of the 539 patients with negative head CT, 71 (13.2%) had other symptoms besides a headache (Table 1). Patients with symptoms besides a headache were more likely ($p < 02$) to be examined within 24 h of symptom onset. Patients who had a seizure were more likely to be examined within 24 h of symptom onset ($p < 001$).

111 (20.6%) patients with head CT negative for SAH went through subsequent vascular imaging (Fig. 2). Modalities included CT angiography (CTA) in 78, magnetic resonance angiography (MRA) in 29, and digital subtraction angiography (DSA) in 4 patients. A new aneurysm was discovered in 9 (8%), 2 (2%), and 0 patients, respectively, and 9 of these patients had an aneurysm, but no SAH was suspected in noncontrast CT. One patient had an RBC count of 300,000 in CSF 2 days after symptom onset of ptosis and mydriasis but no headache. This patient had an aneurysm pressing against the oculomotor nerve, and the patient died from aSAH the next day while waiting for a DSA. Another patient had 30,000 RBCs in CSF with positive spectrophotometry 4 weeks after symptom onset of a headache. This patient's aneurysm was treated, and the patient had a good recovery. All other nine patients had aSAH ruled out with negative LP, aneurysms ruled as incidental, and patients were considered to be CT negative for SAH.

Four patients (3.7%) out of 108 patients with positive head CT had a CT performed within 6 months before the incident of SAH. Only one patient had CT performed to investigate possible SAH. This patient had a history of intracerebral hemorrhage, several known inoperable aneurysms and 2 weeks of headache before a seizure. The CT was negative for SAH. No LP was performed. 3 months later one of the aneurysms ruptured, and the patient died.

Three patients (0.6%) out of 539 with negative head CT died within the 6-month follow-up. The first patient with 300,000 RBCs in CSF is described in the previous paragraph. The second patient had zero RBCs in CSF a few days after the onset of symptoms, and died a month later from an aortic dissection. The third patient had 2500 RBCs in CSF negative for xanthochromia within 6 h of symptom onset, and further investigation was withheld after consultation with a neurosurgeon due to the patient's old age and comorbidities. This patient died from complications of chronic illnesses 1 1/2 months later. Apart from the patient who died from aSAH, we found it unlikely that the other two patients

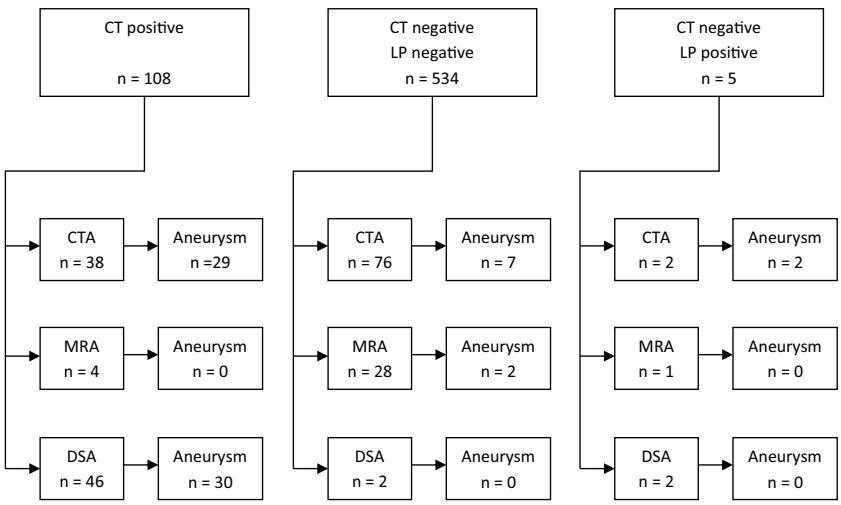

Fig. 2 Flowchart of patients who received further imaging. *CTA* computed tomography angiography *MRA* magnetic resonance angiography, *DSA* digital subtraction angiography

had aSAH or warning leak as the cause of their symptoms. We explored a worst-case scenario, and in this scenario we considered the third patient as being missed aSAH. In the worst-case scenario sensitivity was 98% (95% CI 92–99.7%), specificity was 98% (95% CI 96–99.6%), and NPV was 99.6% (95% CI 97–99.9%) for CT performed within 24 h of symptom onset.

Out of 539 patients with LP performed, 54 patients (10.0%) revisited the ED after developing PLPH and 45 (83.3%) of them were treated with an epidural blood patch. Other complications from LP were not found.

Limitations

The retrospective study design is always inherent to problems relating to proper record keeping. We included patients from two different databases. The first database included consecutive patients who underwent LP in the ED. Lumbar puncture is performed in the ED setting typically to diagnose SAH, infectious and inflammatory diseases of the CNS and sometimes multiple sclerosis or idiopathic intracranial hypertension. The study included all patients who had LP performed to rule out SAH as mentioned in the patient records.

Some patient records did not contain information as to why LP was performed. Selection bias due to occasional poor record keeping was minimized by including these patients with few exceptions. We acknowledge that some patients may have been included where SAH was not the primary concern of the treating clinician but the goal was not to miss any cases of SAH. We further recognize that these patients could skew the confidence level of our analysis, but since no cases of SAH were found within 24 h, the sensitivity, specificity, and NPV would remain 100% even if some patients would be excluded.

The second database search was conducted to find all possible cases of SAH diagnosed in the hospital. This database contained all patients with ICD-9 diagnosis codes for SAH used during any visit to the hospital. Out of 2378 cases, 102 patients were included after exclusion of duplicate cases, multiple entries for the same patient, and traumatic forms of SAH. The high number of excluded cases is due to the patients with SAH diagnosis making multiple visits to clinics and rehabilitation wards and all these visits are recorded with ICD-9 codes. 106 patients with CT positive for nontraumatic SAH were diagnosed in the ED and two in other wards of the hospital.

Our study did not include patients who had CT performed for suspicion of SAH but for one reason or another had no LP performed after a negative CT scan. To mitigate the possibility of a missed SAH in CT we reviewed the past 6-month history of all the patients with positive head CT for SAH. Only one patient had CT performed to rule out SAH after 2 weeks of a headache.

Prospective study design could overcome these limitations. As a single-center study, a suitably sized study population would be unattainable.

Discussion

Headache remains a common complaint in the ED with a small subgroup suffering from SAH. Patients with SAH tend to be younger, and have less comorbidity than patients suffering from other forms of stroke [14]. Thus, delays in diagnosis of SAH can lead to devastating outcomes for otherwise healthy individuals. Traditionally LP has been considered the gold standard for ruling out SAH. It is accurate in diagnosing SAH when performed within 2–3 weeks from symptom onset, and severe complications are infrequent [15]. Thus noncontrast CT is required to achieve the same high accuracy as LP if the use of LP is to be considered obsolete. Our study found CT, using a third generation scanner, to have high sensitivity when ruling out SAH within 24 h of symptom onset.

The first studies looking into the improved diagnostic accuracy of SAH with newer CT scanners found high sensitivity within days from symptom onset. A small study in a level 1 trauma center found CT to have a sensitivity of 100% [16]. In this study, a neuroradiologist interpreted all CT scans, which is not a reality in most EDs. A retrospective study from Denmark in 2010 found CT to have 100% sensitivity in the first few days of a headache in ruling out SAH [6]. Again, the study was criticized for the lack of generalizability given that it was conducted in a university hospital with neuroradiologist on call 24 h a day. Another study investigating the results of LPs after negative head CT from 2015 found five patients out of 706 (0.7%) to have aSAH diagnosed with LP using spectrophotometry [17]. One of the patients had a negative head CT 2½ h after headache onset but did have a less severe headache a few weeks before the diagnostic workup. All other patients had CT performed over 24 h of symptom onset.

In an effort to find a time frame in which head CT could be considered accurate, a multicenter prospective study in Canada found CT to have a sensitivity of 100% in identifying SAH if performed within 6 h of symptom onset in tertiary care ED [8]. This study used CT slices up to 10 mm at the start of the study and up to 7.5 mm by the end of the study. These thicker slices, compared to 5 mm slices used in our study, in the CT protocol could partly explain why only patients who underwent CT within 6 h of symptom onset had CT sensitivity of 100%. This study also had a large population gathered from multiple centers, which could explain as to why CT sensitivity of 100% could not be expanded

beyond 6 h from symptom onset. Backes et al. found a 98.5% sensitivity for CT within 6 h of symptom onset as one patient without a headache had a hemorrhage from cervical arteriovenous malformation (AVM). Four patients with SAH were diagnosed after 6 h from symptom onset. Two of these cases were nonaneurysmal subarachnoid hemorrhages (NASAH), and only two aneurysmal forms were diagnosed over 24 h from symptom onset [18]. Other retrospective studies have also found CT to be highly sensitive in distinguishing SAH within 6 h of symptom onset in nonacademic hospitals [7, 13]. One study with 760 patients had one missed perimesencephalic hemorrhage, a form of NASAH, in a nonacademic ED with a good outcome.

A new meta-analysis from 2016 concludes that if CT is performed within 6 h, LP is likely to benefit only a small subgroup of patients with suspicion of SAH [19]. In fact, neurologists from Helsinki University Hospital have recommended in 2016 that the routine use of LP for ruling out SAH in patients who have negative head CT within 6 h of symptom onset should be relinquished [20]. Such a practice has not yet spread to other hospitals in Finland to the best of our knowledge.

Our study seeks to find out if a negative CT could be used to rule out aneurysmal forms of SAH. Other studies have included all forms of SAH, even CT negative NASAH as missed cases. Rupture of a saccular aneurysm causes most cases (80%) of spontaneous SAH. In approximately 15–20% of SAH patients, the cause of hemorrhage cannot be identified and are thus labeled as NASAH. Patients with NASAH fare much better than those with aSAH, and the clinical course of the disease is even better when the amount of hemorrhage shown in CT is small [21, 22]. One could postulate that if initial CT remains negative for hemorrhage and patients were to be diagnosed with NASAH with LP, no increase in mortality compared to the general population could be recognized. This raises a question whether hundreds of patients need to go through LP to diagnose one NASAH that requires no intervention and poses minimal long-term risk to the patient.

Although LP is a moderately straightforward procedure, it predisposes the patient to complications such as PLPH, nerve root irritation, low back pain, infections, and bleeding complications [23]. The 10% rate of PLPH in this study is in accordance with previous results [9]. A lumbar puncture can cause bleeding, called traumatic tap, which complicates the diagnostic process. Some authors use an RBC count of 400 (which causes visible discoloration of CSF) or an arbitrary number such as 1000 or 2000 for traumatic tap [24]. As not all the study patients with negative CT underwent vascular imaging or had spectrophotometry analysis completed appropriately, we cannot be sure whether some cases of excess RBCs in CSF were caused by traumatic tap or NASAH. A traumatic tap can lead to uncertainty among treating physicians, further investigations, and possible harm to patients. Given that in all patients with RBC count over five, aSAH was ruled out with either appropriate spectrophotometry or 6-month follow-up, we feel confident that no cases of aSAH were missed.

The rate of new aneurysms discovered in our study was comparable to the general population. Although 10% of patients who underwent vascular imaging had a new aneurysm found, most of these patients had an aneurysm suspected in initial head CT. Only 2% of patients with no aneurysm suspected in noncontrast CT had a new aneurysm discovered in subsequent vascular imaging. These numbers are comparable to the prevalence of aneurysms in the general population [25]. Furthermore, this study identified 21 new cases of spontaneous SAH per year in the hospital, which is analogous to a large study from Finland from 2016 [26].

Some patients present symptoms besides a headache. Although we found significance between additional symptoms and examination time, if seizures are excluded, the significance disappears ($p < 14$). This is almost certainly because patients with seizures are rushed to the hospital and examined promptly.

Conclusions

This retrospective study found no added benefit from LP after negative head CT in ruling out SAH when CT was performed within 24 h of symptom onset. After 24 h of symptom onset CT was not sufficient in ruling out SAH, and thus LP is still recommended in clinical practice, although other modalities (i.e., CTA/MRA) may be useful for further evaluation.

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Compliance with ethical standards

Conflict of interest Authors MT, TT and KM have no relevant conflict of interest to declare in relation to this work.

Statement of human and animal rights All procedures performed in our studies were in accordance with ethical standards of the 1964 Helsinki declaration and its later amendments. Our article does not contain any studies with human and animals performed by any of the authors.

Informed consent Informed consent was not required as the study had no interventions or deviations from routine practice and was a retrospective study. Informed consent was obtained from patients contacted for additional information. The study was approved by the Central Finland Central Hospital District and was registered under local guidelines.

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