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Pooled analysis of patients with thunderclap headache evaluated by CT and LP: Is angiography necessary in patients with negative evaluations?

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ABSTRACT

Background: Severe, abrupt onset headache raises concern for aneurysmal subarachnoid hemorrhage (SAH). The current standard work-up is brain CT scan followed by LP if the CT is non-diagnostic in patients with a normal neurological exam. Some have suggested that angiography is also indicated in this common clinical situation. Is evaluation with brain CT and LP for thunderclap headache to rule out SAH sufficient and is angiography needed?

Methods: We systematically searched for studies that followed neurologically-intact patients with thunderclap headache and normal CT and LP for at least 1 year. The primary outcome was SAH. We estimated the proportion of patients who developed SAH and the one-sided upper 95% confidence bound.

Results: Seven studies including 813 patients were identified. None of the patients developed SAH during follow-up (pooled proportion=0, upper 95% confidence bound=0.004).

Conclusion: Although our methods have important limitations, we believe that this analysis will give clinicians better tools to decide whether or not to pursue further work-up with angiography in patients with thunderclap headache and normal neurological exam, CT, and LP.

1. Introduction

Thunderclap headache raises concern for several life threatening conditions including subarachnoid hemorrhage (SAH). The traditional work-up includes a non-contrast head computed tomography (CT) followed by a lumbar puncture (LP) if the CT is non-diagnostic. Case reports, however, suggest that even when the CT and LP both show no evidence for hemorrhage, cerebral angiography is necessary to exclude a symptomatic aneurysm at acute risk of rupturing [1–4]. These cases have stimulated others to follow neurologically-intact patients presenting with thunderclap headache who had a negative CT and LP. There have been 7 longitudinal studies combining more than 800 patients followed for at least six months [5–11]. Most patients did not have angiography. None had a SAH or died suddenly in the subsequent year. These studies support the view that aneurysms detected on angiography in patients with thunderclap headache may be incidental.

This distinction is important because CT angiography (CTA) has been introduced as a less invasive, rapid and widely available approach to detect aneurysms. Some are suggesting its use to primarily "diagnose" SAH (as opposed to diagnosing aneurysms) [12]. One study found an aneurysm in 6 out of 116 patients with sudden headache. Three of the 6 had a normal CT and LP; of the other 3 patients, one had a false positive CTA and 1 declined surgery and was well 12 months later [12]. There are costs to performing angiography including renal failure, hypersensitivity reactions and stroke, downstream financial costs of procedures and hospitalization for potential treatments, and psychological costs including anxiety over needing a procedure and aneurysmal rupture.

Should the work-up for thunderclap headache include angiography if CT and LP are negative to rule out a subarachnoid hemorrhage? This question has been the focus of recent controversies in the medical literature [13,14]. We addressed this question by performing a meta-analysis of the 7 longitudinal studies to determine the incidence of SAH in patients with thunderclap headache and a normal head CT and LP.

2. Methods

We followed the MOOSE guidelines regarding meta-analysis of observational studies [15]. A systematic search of the literature for relevant studies was conducted and included a Medline search for articles with the words "subarachnoid hemorrhage," "thunderclap headache" "normal head CT," "normal CSF," and "aneurysm" as well as the bibliographies of retrieved papers and review papers on subarachnoid

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hemorrhage or thunderclap headache. Studies were excluded if they did not specify if the patients had a normal neurological examination, head CT and CSF. We found 7 articles in which patients with thunderclap headache, normal head CT and normal cerebrospinal fluid (CSF) were followed for a defined period of time. We included all 7 studies from which we abstracted salient aspects of design (e.g., patient demographics, duration, method of follow-up, intensity of follow-up investigations, results of diagnostic testing, percentage of patients with follow-up information and clinical outcomes).

The main outcome from each study was expressed as a cumulative incidence of adverse outcome (SAH or sudden unexplained death) at 6 months. We calculated one-sided 95% confidence intervals for each study [16]. The pooled cumulative incidence of SAH or sudden unexplained death was calculated weighting each study estimate by its sample size [17].

Statistical analysis was performed in SigmaPlot version 10 (San Jose, CA).

3. Results

We first assessed the aspects of clinical heterogeneity between the 7 studies (Table 1). All studies shared the same clinical presentation of sudden and severe headache. All patients in these studies presented to an ED or were referred into the hospital. The evaluation in each study included only a head CT and an LP. The type of head CT was not specified in most of the studies. Only two studies specified the method of xanthrochromia measurement (spectrophotometry in one; visual inspection in the other). Two studies did not indicate the method of follow-up; the other 5 used a subsequent clinic visit or telephone interview.

Table 1

a. Patient characteristics

Study	Number of patients	How were patients referred into the study	Age range	Onset of HA defined	Other characteristic of HA specified
Wijdicks	71	Admitted to neurology service at university hospital	15–67	Yes	Sudden, severe, unusual
Harling	14	Admitted to general hospital	NS	Yes	Sudden, severe, generalized, "worst ever"
Marcus	16	Presented to ED	29–63	Yes	Sudden, severe, unusual maximal by 1 min, "worst ever"
Linn	59	Referred by GP to hospital	NS	Yes	Sudden, severe, >1 h
Landtblom	114	Referred to ED or seeking ED	18–86	Yes	Maximal in 10 s, sudden
Duffy	8	Admitted to neurosurgical service	NS	Yes	Sudden, severe
Perry	531	Presented to ED	≥15	Yes	Sudden, severe

b. Evaluation of patients

Study	Physical examination — neurological findings	Head CT: what model	CSF analysis description
W	No deficits	NS	Normal
H	No deficits	NS	Normal
M	No deficits	NS	Normal
Linn	No deficits	NS	No xanthrochromia
Landt	No deficits	GE 9800	No xanthrochromia
Duffy	No deficits	NS	Normal
Perry	No new deficits	NS	No xanthrochromia

c. Follow-up characteristics

Study	Percentage of patients followed	Method of f/u (chart/phone/etc)	Duration of f/u	Recurrent h/a
W	100%	Clinic visit or telephone	1–7 years (mean 3 years)	17%
H	100%	NS	18–36 months	NS
M	100%	Telephone	14–21 months	25%
Linn	100%	NS	12 months	20%
Landt	100%	Telephone interview	12 months	24%
Duffy	100%	Clinic visit	12 months	NS
Perry	89.6%	Clinic visit or telephone	>6 months	NS

NS = not specified.

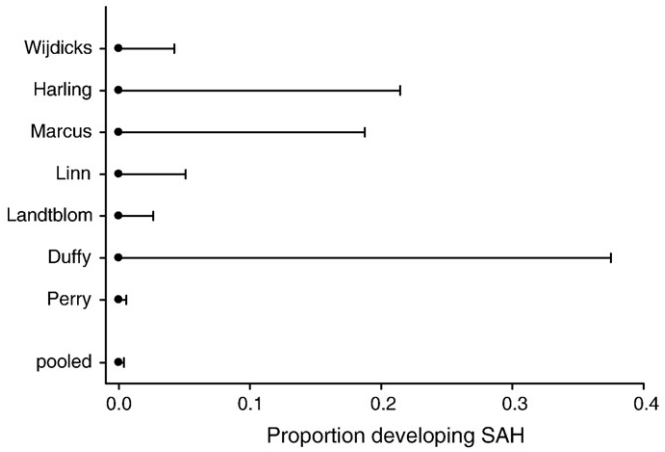

Fig. 1. Forest plot showing one-sided confidence intervals on the probability of hemorrhage in 12 months follow-up. For individual studies, the upper, one-sided, exact 95% confidence intervals are shown.

The incidence of hemorrhage or sudden death was zero, even in those studies with follow-up greater than 1 year. The upper 95% confidence bounds ranged from 0.006 in the study of 531 patients to 0.38 in the study of 8 participants (Fig. 1). The pooled cumulative incidence was 0 with an upper 95% confidence bound of 0.004.

4. Discussion

Our analysis indicates that the probability of missing a subsequent SAH in neurologically-intact patients presenting with thunderclap headache with normal CT and LP is less than roughly 0.4%. In terms of number needed to harm [18], we are reasonably confident that the number would not exceed one missed case for every 250 such patients.

Our methods have important limitations. There is no well-accepted method to perform meta-analysis on low frequency events when there are few studies with small numbers of patients. For the pooled estimate of cumulative incidence, we used sample size weighting [17] which assumed that a fixed effects model was appropriate. We did not directly calculate estimates of within- or between-study variance or extent of between-study heterogeneity because no participant in any study developed the outcome of interest. It is unlikely that the true risk of SAH following a thunderclap headache with negative CT and LP is 0. Even if these headaches are unrelated to SAH, patients would likely have the same risk of SAH as the general population. However, the calculated upper 95% CI of 0.004 gives some reassurance that the risk is not high. In addition, meta-analysis cannot overcome weaknesses of the underlying studies. Of particular concern, 65% of the patients in the pooled analysis came from a study with less than 100% follow-up [11].

The incidence of missing a hemorrhage from this analysis should be balanced against the morbidity of performing cerebral angiograms, which carry a similar quantifiable risk of complications such as stroke. In addition, the risk of missing a hemorrhage should be balanced against the detection of false positives on CTA [12]. The 5.6% incidence of aneurysms reported in 1 study [12] is about what one would expect in an unselected population given that the incidence of aneurysms is 2–6% [19].

Our results, despite their intrinsic limitations, should help clinicians to decide whether angiography is indicated, and to better communicate the risk of missing SAH to patients as part of informed decision-making. Of course, in some highly selected patients whose history suggests diagnoses that CT and LP would be expected to miss (e.g., arterial dissection, cerebral venous sinus thrombosis and pituitary apoplexy), other imaging may be indicated [14]. Overall, our analysis supports the contention that a head CT and an LP constitute a sufficient work-up for SAH in most patients with thunderclap headache but it must be acknowledged that clinicians may need to consider other causes of acute severe headache for which CT and LP may be negative such as cerebral venous thrombosis and arterial dissection.

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