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Brief Report

Validation of cerebrospinal fluid findings in aneurysmal subarachnoid hemorrhage☆,☆☆,★

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ABSTRACT

Background: Recently proposed cutoff criteria for cerebrospinal fluid (CSF) analyses might safely exclude a diagnosis of aneurysmal subarachnoid hemorrhage (aSAH).
Objective: The objective of this study was to examine the sensitivity of a CSF red blood cell (RBC) count greater than 2000×10^6/L (ie, 2000 RBCs per microliter) or the presence of visible CSF xanthochromia in identifying patients with aSAH.
Methods: We identified a retrospective case series of patients diagnosed with aSAH after lumbar puncture (LP) in an integrated health delivery system between January 2000 and June 2013 by chart review. All identified patients had at least 1 cerebral aneurysm that was treated with a neurosurgical or endovascular intervention during the index hospitalization. The lowest CSF RBC count was used for validation analysis. Cerebrospinal fluid color was determined by visual inspection. Xanthochromia was defined as pink, orange, or yellow pigmentation of CSF supernatant.
Results: Sixty-four patients met study inclusion criteria. Of these, 17 (33%) of 52 underwent LP within 12 hours of headache onset, and 49 (84%) of 58 exhibited CSF xanthochromia. The median CSF RBC count was $63\,250 \times 10^6$/L. The sensitivity of a CSF RBC count of greater than 2000×10^6/L in identifying aSAH was 96.9% (95% confidence interval, 89.3%-99.1%). Additional consideration of CSF xanthochromia resulted in a sensitivity of 100% (95% confidence interval, 94.3%-100%).
Conclusions: All patients in this case series of patients with aSAH had either a CSF RBC count greater than 2000×10^6/L or visible CSF xanthochromia, increasing the likelihood that this proposed cutoff strategy may safely identify patients who warrant further investigation for an aneurysmal cause of subarachnoid hemorrhage.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) occurs with an annual incidence of approximately 1 in 10 000 among North American populations [1]. Although most aSAH cases are identified by cranial computed tomography (CT), the imperfect sensitivity of CT combined with the increased morbidity associated with delays in diagnosis makes lumbar puncture (LP) the definitive test to exclude a diagnosis of aSAH [2]. Cerebrospinal fluid (CSF) is examined for the presence of red blood cells (RBCs) and xanthochromia, the latter being determined either by visual inspection or by spectrophotometry depending on local practices. Although some advocate that xanthochromia is a sine qua non factor for a diagnosis of aSAH, this assumption is based on LP performance at 12 or more hours from ictus combined with the use of spectrophotometry to detect CSF bilirubin, neither of which are usual practices within North America [3-5].

As a result, when abnormal numbers of RBCs are present in the CSF of a patient with possible “CT-negative” SAH (subarachnoid hemorrhage), angiography is often recommended to exclude a vascular etiology of hemorrhage [6-8]. Unfortunately false-positive LPs because of elevated RBC counts are common, most often attributed to traumatic technique (“traumatic taps,” with reported rates up to 30%) [9-11]. Resultant workups can result in unnecessary and potentially harmful diagnostic testing; rates of neurologic complications after cerebral digital

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subtraction angiography (DSA) have been reported as high as 1.3% [12]. In addition, when considering that there is a 1% to 2% background prevalence of cerebral aneurysms in the general population, unplanned surgical treatment of incidental aneurysms becomes a real concern [13,14].

Researchers have proposed various methods to identify traumatic taps. Although often suggestive, analyses using the percentage decrease in RBCs between sequential tubes have failed to produce a clearly accepted cutoff value [9-11,15]. This is largely because CSF collection volumes are not standardized, and also because traumatic taps and SAH are not mutually exclusive conditions. Two prior retrospective studies have examined potential CSF RBC count cutoffs below which SAH can be excluded; one reported a negative predictive value of 100% for a cutoff of 500×10^6/L or less (ie, 500 cells per microliter or per cubic millimeter) in detecting 11 cases of SAH with vascular etiologies among a cohort of 594 patents, and the other reported 100% sensitivity for a cutoff of 100×10^6/L among 26 cases of SAH of varying etiologies [9,10]. However, neither of these studies specifically examined patients with aSAH, the diagnosis that carries the most potential morbidity from delayed recognition and treatment [16].

Recently, data from the largest prospective study examining diagnostic testing for SAH revealed that, among 1739 patients undergoing LP, the presence of either a CSF RBC count 2000×10^6/L or more or visible xanthochromia identified 15 patients with aSAH with 100% sensitivity (95% confidence interval [CI], 74.7-100.0) [11]. Given this potentially promising approach, we sought to provide a narrower CI for sensitivity by applying these CSF analysis criteria to a 13-year case series of patients diagnosed with aSAH after LP.

2. Methods

2.1. Case cohort selection and setting

Chart review data from 2 independent studies with overlapping study periods spanning January 2000 through June 2013 were used to assemble the case series. Both studies were approved by the Kaiser Foundation Research Institute Institutional Review Board with a waiver of the requirement for informed consent. In both cases, electronic health records of patients treated within the Kaiser Permanente Northern California (KPNC) integrated health delivery system were screened for case inclusion if they had an emergency department (ED) or hospital encounter with an associated *International Classification of Diseases*, *Ninth Revision* (*ICD-9*), diagnosis code of subarachnoid hemorrhage (430). During the study period, emergency care within KPNC was provided at between 17 and 21 community EDs serving between 2 and 3.4 million Kaiser Foundation Health Plan members. Patients were electronically excluded from further screening if they were younger than 18 years or had an *ICD-9*–coded diagnosis of head or neck trauma within 24 hours of the index encounter.

Inclusion criteria for this case series included initial presentation to a KPNC ED, performance of an LP in the ED, and subsequent cerebral angiography demonstrating an aneurysm that was treated with neurosurgical or endovascular intervention during the index hospitalization. We chose urgent aneurysm repair as part of our case inclusion criteria to avoid inclusion of incidentally discovered aneurysms. However, we also identified patients who had cerebral aneurysms identified but did not undergo urgent surgical or endovascular repair for use in a sensitivity analysis.

2.2. Methods and measurements

Three emergency physician abstractors (D.G.M., M.K.V., and S.R.O.) blinded to the current study hypothesis conducted structured explicit chart reviews. Data on age, sex, and race were electronically collected. Abstractors manually documented the study inclusion criteria (age, performance of LP in the ED, aneurysm on cerebral angiography, and subsequent treatment) along with CSF RBC counts, the presence of CSF xanthochromia, the official written radiology interpretation of the initial cranial CT, the location and size of the culprit aneurysm, and whether the time to LP was 12 hours or greater from headache onset, when available. It is common practice in our system for patients with negative initial cerebral angiography to undergo a second imaging study within the following 2 weeks, most often cerebral DSA, and these studies were also reviewed for delayed recognition of a cerebral aneurysm.

Computed tomography examinations were performed without contrast using multislice cine technology. General radiologists or neuroradiologists made the final interpretation of CT images. A blinded review of 40% of the final sample was conducted by 2 emergency physicians (D.R.V. and D.W.B.) to establish the inter-rater agreement on the following variables: time to LP of 12 hours or greater from headache onset, presence of CSF xanthochromia, and lowest CSF RBC cell count.

Cerebrospinal fluid was assessed for xanthochromia by visual inspection of the supernatant against a white background, as per usual practice in North American laboratories [17]. Although xanthochromia in its literal interpretation means "yellow color," spectrophotometric evidence of bilirubin, the primary colorimetric breakdown product of RBCs responsible for yellow CSF supernatant discoloration, has been observed in CSF ranging from red to green [18]. As such, it is now common practice to refer any discoloration of CSF supernatant as xanthochromia, particularly pink, orange, and yellow [19-21]. Thus, we explicitly considered any of these reported CSF colors (pink, orange, or yellow) as representative of xanthochromia, in addition to explicitly reported xanthochromia. We did not include red discoloration in our definition of xanthochromia because significant amounts of oxyhemoglobin (causative of red discoloration of CSF supernatant) are detectable by spectrophotometry within 1 hour in ex vivo CSF samples containing RBCs greater than 20000×10^6/L [21].

We used the lowest available CSF cell count for our primary analysis for 2 principal reasons: (1) cell count and color analysis were only performed on a single tube in multiple instances and (2) it is not uncommon for tubes to be either reported or collected out of order, resulting in inaccurate apparent trends in RBC counts. Thus, for practical purposes, we assumed that the lowest RBC count represented the last tube collected in all cases, consistent with the definition used in the derivation study of interest [11].

2.3. Outcomes and analysis

The outcomes of interest were the independent and combined sensitivities of a CSF RBC count greater than 2000×10^6/L and/or the presence of visible CSF xanthochromia in identifying patients with aSAH. Binomial CIs were calculated using the Wilson method [22]. All statistical analyses were performed using STATA v 13.0 (College Station, TX).

3. Results

A total of 2236 charts were reviewed for inclusion criteria. Sixty-four patients with LP results who underwent urgent treatment of aSAH were identified, comprising the final case series. The median age at diagnosis was 51.5 years, and 69% were female. Twenty-four (38%) had evidence of SAH noted on the final CT report. Nineteen patients (30%) had only a single CSF tube analyzed for cell count and/or color. One patient had only CSF color results reported because of a clotted sample, and 6 patients did not have CSF color results reported. The median RBC count was 63250×10^6/L (range, 408-721000×10^6/L), and 49 (84%) of 58 exhibited CSF xanthochromia (47% reported as "xanthochromia" and 38% reported as "pink" – the remaining were 16% reported as "colorless"). The median percentage decrease in cell counts between tubes was 17% (range, 0%-83%). Of charts with available data, 17 (33%) of 52 underwent LP within 12 hours of headache onset. The most common aneurysm location was the anterior communicating artery (38%) followed by the posterior communicating artery (33%). Cohort characteristics are summarized in Table 1. Inter-rater agreement was 100%