Clearing of Red Blood Cells in Lumbar Puncture Does Not Rule Out Ruptured Aneurysm in Patients with Suspected Subarachnoid Hemorrhage but Negative Head CT Findings

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BACKGROUND AND PURPOSE: **In evaluating the results of lumbar puncture (LP), a decrease in the number of red blood cells (RBCs)/mm^3 between the first and fourth tubes collected (clearing) has often been assumed to indicate a traumatic puncture rather than the presence of subarachnoid hemorrhage (SAH). We tested the hypothesis that, in the setting of severe headache, CSF clearing coupled with an unremarkable unenhanced CT scan was negatively predictive of the presence of aneurysm and could be used to reduce the need for conventional arteriography.**

METHODS: **Cerebral angiography was performed to evaluate suspected SAH in 123 consecutive patients over 2 years at a university teaching hospital. Records of these patients were reviewed. Among the subset without SAH on CT scan, LP results were evaluated for clearing. Clearing was arbitrarily defined as a 25% reduction in RBCs between the first and fourth tubes. This subset's records were also reviewed for the presence of aneurysm at cerebral angiography or at follow-up 6 weeks later. Data were analyzed for correlation between clearing and aneurysm.**

RESULTS: **Of the 123 patients whose records were reviewed, 22 did not show an SAH on CT scan. Of those 22 patients, eight had aneurysm at angiography and 14 did not. Clinical diagnoses in the other 14 included trauma, herpes meningitis, sickle cell disease, and cocaine use. CSF clearing was noted in 25% of those with an aneurysm (two of 8) and 21% of those without an aneurysm (three of 14). In the two cases with aneurysms, RBCs cleared from 3550 to 2550 (−28%) and from 24,686 to 17,842 (−28%), respectively. In the remaining six cases with aneurysms, RBCs increased a mean of 1370% between the first and fourth tubes (range, −22% to 7700%). Two of these six had a reduction that did not meet our criteria for clearing (−22% and −5.3%, respectively). In the 14 cases without aneurysms, RBCs increased a mean of 70% between the first and fourth tubes (range, −99% to 895%). In addition to the three of these 14 that met our criteria for clearing (−99%, −99%, and −43%), four cases had a reduction that did not (range, −0.7% to −14%).**

CONCLUSION: **A 25% reduction in RBC concentration between the first and fourth tubes of CSF in patients with suspected SAH but negative CT findings occurs even in cases of ruptured aneurysms. Formal evaluation for the presence of an aneurysm is still necessary in this scenario.**

When subarachnoid hemorrhage (SAH) from a ruptured aneurysm is suspected clinically, the recommended confirmatory test is unenhanced CT of the head (1). Unfortunately, head CT scanning has been reported to be falsely negative for SAH in up to 7% of patients later confirmed to have ruptured aneurysms (2, 3). When the clinical suspicion for subarachnoid bleeding is high but CT shows none, lumbar puncture (LP) is performed to detect blood in the CSF.

Usually, after the L4–L5 interspace is blindly punctured, four sequential aliquots of CSF are placed into numbered tubes and sent for analysis (4). If RBCs and xanthochromia are absent from any of these tubes (a "champagne tap" for the happy intern), acute SAH is confidently excluded (5–7). Unfortunately,

Received March 22, 2004; accepted after revision August 16.

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true champagne taps occur in less than one-third of all LPs, even in experienced hands (8). In the remainder, RBCs in the CSF sample may represent either true SAH or contamination from a "traumatic tap," and the diagnosis remains uncertain. Traumatic taps can result from incidental perforation of the ventral or dorsal epidural venous plexus or cauda equina vessels during puncture (9).

The rapid distinction of true SAH from a traumatic tap is not simply of academic interest. Early diagnosis and treatment of ruptured intracranial aneurysms has repeatedly been shown to result in decreased disability and death (10). Conversely, the incorrect diagnosis of SAH in a patient without hemorrhage needlessly exposes him or her to the risk of angiography and expense of hospitalization. Permanent neurologic deficit can occur in as many as 1% of persons undergoing cerebral angiography (11–14). Although CT angiography (CTA) does hold great promise as a noninvasive diagnostic tool, at our institution it is not used as the definitive examination in the emergent setting. Also, in light of the fact that anywhere from 1–3% of the general population may have asymptomatic aneurysms (15, 16), such a course might also lead the patient to have untimely intervention.

The literature discusses several methods for distinguishing true SAH from a traumatic tap. The simplest is the operator's impression of whether the LP was traumatic, which has been shown to be wholly unreliable (17). Alternatively, the LP can be repeated at a different interspace. Although this may or may not yield CSF free of RBCs, it will certainly be unwelcome to the patient. Opening pressure can be elevated in as many as 60% of patients with SAH (9). In our experience, opening pressure is usually not measured in the emergency department setting.

Laboratory analyses of CSF that have been investigated in this setting include the presence of either xanthochromia or D-dimer and the leukocyte-to-erythrocyte ratio. Each has its disadvantages. Xanthochromia refers to a pink, yellow, or orange tint to centrifuged CSF that indicates that RBCs have lysed and that the hemoglobin has been converted to oxyhemoglobin, methemoglobin, and bilirubin. Fresh blood from a traumatic tap will not yield xanthochromia unless it is allowed to stand (18). Therefore, xanthochromic CSF at the time of LP indicates SAH; however, xanthochromia can take as long as 12 hours to develop (19), and delaying an LP for that long after ictus to ensure its appearance may be unacceptable. In addition, low-level xanthochromia (<360 RBC/mm^3) may be invisible to the naked eye (18). The spectrophotometers necessary to detect such cases are not widely used in North American emergency departments (20, 21). The presence of D-dimer in CSF can be seen with SAH, but both false-positive and false-negative results have been reported (3, 22). Elevation of the leukocyte-to-erythrocyte ratio in CSF from the normal 1:700 is said to occur when SAH irritates the meninges but requires 3–5 days to manifest (9).

The clearing of RBCs from the CSF—that is, the progressive decrease in concentration of RBCs from the first tube to the fourth—has long been taught at the bedside to indicate a traumatic tap (18). In past years this has also been called the "three-tube method," although CSF is now usually collected in four. Unlike spectrophotometry for xanthochromia and assays for D-dimer, it uses common and rapidly available instrumentation. Unlike visual inspection for xanthochromia and the leukocyte-erythrocyte ratio, its validity is not associated with when it is performed relative to the acute SAH.

The reliability of CSF clearing as a diagnostic tool has been discussed by many authors over the past 50 years (9, 17, 18). Although common sense suggests that it is an intrinsically limited test—a traumatic tap in a patient with actual underlying SAH might yield some degree of clearance of RBCs between tubes 1 and 4—it has not been reassessed in the era of easily available neuroimaging. We considered the possibility that the CSF studies of the subset of patients with no visible subarachnoid blood on CT scans could be interpreted with a higher level of confidence. In addition, we are unaware of any prior prospective attempts to quantify what degree of RBC count decrease constitutes "clearing."

We tested the hypothesis that CSF clearing was negatively predictive of the presence of aneurysm and could be used to reduce the need for angiography by distinguishing traumatic taps from true SAH in patients whose initial head CT findings are negative.

Methods

The records of consecutive patients for whom conventional cerebral angiography was performed to evaluate suspected aneurysmal rupture over 2 years at a university teaching hospital were reviewed. In addition, the results of head CT and LP preceding angiography in these patients were retrospectively queried. LP results were evaluated for clearing, with attention to the subset whose head CT report showed no evidence of SAH. We arbitrarily defined clearing as a 25% reduction in RBCs between tubes 1 and 4. This subset's cerebral angiogram reports were also reviewed for the presence of aneurysm. Data were analyzed for correlation between clearing and aneurysm.

Results

Records were reviewed of 123 consecutive patients over 2 years who underwent conventional angiography to evaluate SAH or an otherwise suspected aneurysm. Twenty-two of the 123 (18%) patients studied did not have SAH on head CT and are discussed below. Ninety-nine were excluded from our analysis because SAH was positively diagnosed on head CT scan. Of these 99, seven also had LPs, with varied findings. In three RBCs were had "too numerous to count," two had more than 50,000 RBCs/mm^3, and two had 40 RBCs/mm^3 or fewer. Two additional patients were excluded from analysis because they had negative head CT scans and no RBCs in the CSF but nonetheless underwent angiography on the basis of strong clinical suspicion of SAH. Both had normal angiograms and were discharged with the clinical diagnosis of migraine headaches.

Of those 22 patients without evidence of SAH on head CT, eight had an aneurysm at angiography (Table 1). CSF clearing, as defined by our hypothesis, was noted in two (25%) of those eight. Fourteen of the 22 did not have aneurysms on angiography (Table 2). CSF clearing was noted in three of those 14 (21%). In all patients, the subjective description of CSF color was noted. Opening pressures were not recorded for any patient.

In the patients without an aneurysm, clinical diagnoses were made in nine of the 14 that satisfactorily explained the patient's presentation. These included trauma, infectious meningitis, sickle cell disease, migraine headache, and cocaine use. In four of the 14, no satisfactory etiology was found for the clinical presentation. In all four, follow-up cerebral angiography (either conventional or MR) was repeated 6 weeks later and findings were normal in each case. One patient of the 14 was lost to follow-up. Among all 14 without an aneurysm, the percentage of change in RBCs between the first and fourth tubes ranged from a 99% decrease to an 895% increase (average, 70% increase). Seven of these 14 had an increase in RBC count from the first to the fourth tube and seven had a decrease, but only three cleared more than 25%.

Among the eight patients with an aneurysm, the percentage of change in RBCs between the first and fourth tubes ranged from a 28% decrease to a 7700% increase (average, 1360% increase). Half showed an increase in RBC from the first to the fourth tube, and half showed a decrease. Of those four patients with a decrease, only two cleared more than 25%. The median interval between onset of symptoms and head CT was 3 days (range, 3 hours to 24 days). On average, LP was performed within 4.1 hours of head CT scanning (range, 6 hours before to 9 hours after).

Discussion

We investigated whether patients with suspected acute SAH but whose head CT scans showed none could be spared angiography on the basis of a 25% decrease in RBCs between the first and fourth tubes of CSF during lumbar puncture. Our data show that this arbitrary threshold would not be useful in avoiding diagnostic angiography in patients without an aneurysm or in confirming the need for angiography in patients with one. In the former group, only three of the fourteen patients without an aneurysm met the standard of clearing. They hypothetically would have been spared conventional angiography. In the latter group, two of eight patients with an aneurysm did meet the standard for clearing. They would have been incorrectly (and possibly fatally) diverted from further evaluation and treatment in our scenario.

Methodological errors alone are unlikely to explain this result, but they should be considered. Our sample size may be too small to have adequate statistical power. It is also possible that our data may be tainted by errors in collection or measurement. For example, the inaccurate numbering of CSF tubes at the bedside in a busy emergency department or hospital ward

TABLE 1: Patients with negative head CT findings and aneurysms on angiography

Patient	Time from Symptom Onset to Head CT	Time from Head CT to LP	Tube 1 ($RBCs/mm^3$)	CSF Description	Tube 4 ($RBCs/mm^3$)	CSF Description	% Change from Tube 1 to 4	Angiographic Result
1	**4 days**	**5 hours**	**3550**	**Cloudy**	**2550**	**Slightly bloody**	**−28.2**	**Basilar artery dissecting aneurysm**
2	**3 days**	**5 hours**	**24,686**	**Cloudy**	**17,842**	**Bloody**	**−27.7**	**Right posterior communicating artery aneurysm**
3	8 days	2 hours before CT	14,325	Xanthochromic	11,207	Xanthochromic	−21.8	Anterior communicating artery aneurysm
4	7 days	1 hour	2249	Cloudy	2129	Bloody	−5.3	Left vertebral artery dissection
5	3 hours	3 hours	29,710	Cloudy	33,700	Bloody	13.4	Anterior communicating artery aneurysm
6	2 days	6 hours before CT	69	Clear	100	Clear	45	Right middle cerebral artery aneurysm
7	24 days	2 hours	192	Clear	1150	Slightly bloody	499	Anterior communicating artery aneurysm
8	3 hours	9 hours	80	Clear	6225	Slightly bloody	7700	Right anterior communicating artery aneurysm

TABLE 2: Patients with negative head CT findings and no aneurysms on angiography

Patient	Tube 1 (RBCs/mm^3)	Tube 4 (RBCs/mm^3)	% Change from Tube 1 to 4	Angiographic Result	Clinical Diagnosis
1	**293**	**2**	**−99**	**Normal**	**None. Normal follow-up cerebral MRA.**
2	**6230**	**60**	**−99**	**Normal**	**Traumatic SAH**
3	**711**	**404**	**−43.2**	**Normal**	**Cocaine use or migraine**
4	2450	2100	−14.3	Normal	Sickle-cell disease
5	414,750	364,875	−12.0	Normal	None, normal follow-up cerebral MRA
6	117,600	105,400	−10.4	Normal	Varicella and cryptococcal meningitis (HIV+)
7	1634	1623	−0.7	Normal	Sickle-cell disease
8	65,363	68,750	5.2	Normal	None, normal follow-up cerebral angiography
9	33,525	36,425	8.7	Normal	None, normal follow-up cerebral angiography
10	120	149	24.2	Normal	Systemic lupus erythematosus and antiphospholipid antibody syndrome
11	69,090	91,035	31.8	Normal	None; patient lost to follow-up
12	992	1776	79.0	Normal	Migraine headache
13	37	119	220	Normal	Traumatic SAH
14	837	8330	895	Normal	Varicella encephalitis (HIV+)

Note.—Bold entries indicate cases in which the 25% threshold for clearing was met.

could either create the appearance of clearing when there was none or hide actual clearing. Likewise, in the automated counting of RBCs, properly coincident errors might create the false impression of clearing if the concentration of RBCs in each tube was relatively low. Prediction rules, however, must take these clinical realities into account. It is improbable that such errors would occur more or less frequently than in other hospitals or during some other period at our institution.

We re-examined our arbitrary definition of clearing to determine whether a more robust one could be derived from the data. We had prospectively chosen a 25% decrease as our threshold to define significant clearing after first performing a literature search via PubMed by using the phrases “subarachnoid hemorrhage,” “clearing,” “traumatic tap,” “lumbar puncture,” and “aneurysm rupture,” singly and in various combinations. Two articles discovered during this search both defined clearing as any decrease at all between the first and last tubes of CSF (17, 18). No other article suggested an alternate definition. Because a 1% decrease (e.g., from 1000 RBC/mm^3 to 990 RBC/mm^3) would not be likely to be interpreted as clinically significant clearing in practice, we arbitrarily chose a higher threshold of 25%.

Retrospectively raising the threshold to a RBC decrease of 50% or more eliminated the two false-negative results from our analysis. This change, however, further decreased the threshold’s practical value. One of the patients without an aneurysm had a 43% decrease between the first and fourth tubes but would be redefined as “not clearing” with the higher threshold, yielding a false-positive result. This patient was one of the three (of a total of 14 without an aneurysm) who would have been spared further workup if the 25% threshold were used.

The redefinition of clearing as a drop below an absolute threshold rather a percentage drop was considered but was ruled out on empirical grounds. We first considered it because one of the two false-negatives (patient 2 in Table 1) had nearly 18,000 RBC/mm^3 in tube 4. Pragmatically, it would be imprudent to regard such bloody CSF as entirely due to a traumatic tap without further investigation, and we sought to alter the definition to take this into account, although setting the threshold level was problematic. Other authors (8, 23) have suggested that a traumatic tap be defined as any in which <1000, or even 400, RBC/mm^3 were found. Our results do not support such a contention. Aneurysms were found in patients whose CSF contained as few as 40, 69, and 80 RBC/mm^3. Although it possible that one of these was an unruptured aneurysm found incidentally in a patient who both had a dramatic headache and underwent a traumatic LP, it seems improbable to ascribe all three to that scenario. Thus, an absolute threshold is impractical in distinguishing traumatic taps from real SAH.

A potential solution is to combine relative reduction in RBC count between tubes 1 and 4 with an absolute threshold below which the count must fall. Clearing could be defined as a 25% relative decrease in of RBC/mm^3, provided that the concentration fell below some floor. In light of our data, we could set that floor anywhere between 500 and 2000 RBC/mm^3 and eliminate the two false-negative results. The rate of false-positives would be unchanged. In any event, the new hypothesis would require validation against a separate group of patients.

The problem may lie not with methodology or details of the definition but with the idea of “clearing” itself. On the basis of our data, clearing, however defined, is not by itself a strong predictor of the presence or absence of a ruptured aneurysm. Therefore, its clinical role is likely limited to that of a single datum among others used in formulating a clinical impression or hypothesis. This idea is immediately relevant at the bedside. It will become even more relevant if CTA is rigorously proved accurate. Because the procedural risk of CTA is reduced in comparison to conventional angiography, there should be an accordingly lower threshold for going on to CTA even in the presence of "clearing."

Our data do contain some other insights. First, although multiple authors have reported that head CT is more sensitive for the detection of SAH when performed soon after ictus (3, 24–26), this is only a generalization. Table 1 shows that, among our patients with aneurysms, head CT scans showed no evidence of SAH in patients who were scanned within hours of symptom onset and those who waited days or weeks to seek medical attention. Second, negative head CT findings do not correlate with a low concentration of erythrocytes in the CSF. Two of our patients with ruptured aneurysms and no SAH seen on head CT scans had concentrations as high as 34,000 and 24,000 RBC/mm^3. These patients both had their LPs performed within 5 hours of scanning, which was a typical interval in this group. This may be related to the third point: traumatic taps can yield astonishingly high levels of blood in the CSF. Three of the patients in Table 2 had upwards of 60,000 RBC/mm^3 in the CSF despite having neither an aneurysm nor any other pathologic condition identified at presentation or follow-up. Fourth and finally, SAH can be due to causes other than aneurysmal rupture. Several patients without aneurysms did have diseases known to cause vasculopathy and vasculitis (e.g., sickle cell disease, systemic lupus erythematosus, meningitis), and some of these actually may have had minor associated SAH despite normal angiograms.

It is notable that the 22 angiograms performed in patients with negative head CT findings constituted 18% of the 123 patients in whom aneurysmal SAH was suspected at our institution over 2 years. This is higher than the 7% rate of CT-negative SAH found in the literature. It is impossible, however, to know *a priori* which patients with negative CT findings will fall into that 7%. As with surgery for appendicitis, a certain rate of intervention for patients without the suspected disease is tolerated so that those with it will not be missed. For example, some patients in this series presented with histories of trauma vague enough that an aneurysm could be suspected as a cause for the trauma. It is reasonable to expect a person who has a sudden aneurysmal bleed while driving to then be involved in a motor vehicle accident.

Conclusion

A 25% reduction in RBC concentration between the first and fourth tubes of CSF in patients with suspected SAH, but negative head CT findings, occurs even in cases of ruptured aneurysms. Formal evaluation for aneurysm is still necessary in this scenario.

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