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Research

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Sensitivity of Serum D-dimer for Spontaneous Subarachnoid Hemorrhage

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ABSTRACT

Study Objective: Subarachnoid hemorrhage (SAH) activates the fibrinolytic system and increases serum D-dimer levels. These levels could prove diagnostically useful if reliably elevated in patients with SAH. Our goal was to calculate the sensitivity of serum D-dimer in detecting spontaneous subarachnoid hemorrhage.
Methods: We reviewed case records of all patients diagnosed with spontaneous SAH at our institution from 1990-2012. We excluded patients who had SAH from traumatic injuries, known intracranial pathology, as well as those having intracerebral hemorrhage. We recorded whether the D-dimer level was assessed in each patient, as well as the timing of the D-dimer measurement.
Results: We identified 368 patients who received a diagnosis of SAH, including 237 meeting inclusion criteria. One hundred eighty-five of these patients had a positive serum D-dimer after symptom onset, yielding a sensitivity of 78.1% (95% confidence interval (CI): 72.9-83.8%). Twenty-two patients had a serum D-dimer drawn within 12 hours of symptom onset, including 19 with positive D-dimer results, to yield a sensitivity of 86.4% (95% CI: 65.1-97.1).
Conclusions: Serum D-dimer levels exhibit high sensitivity among patients with spontaneous SAH. This finding warrants further investigation.

KEY WORDS: Subarachnoid hemorrhage; D-dimer; Spontaneous sensitivity.

ABBRIVATIONS: SAH: Subarachnoid hemorrhage; CFR: Case Fatality Rate; CT: Computerized Tomography; CSF: Cerebrospinal fluid; CTA: Chicago Transit Authority; MRI: Magnetic Resonance Imaging.

INTRODUCTION

Background

Headache accounts for 2% of Emergency Department (ED) visits, and subarachnoid hemorrhage (SAH) accounts for 1-3% of these headaches.[1-5] It is infrequent, yet deadly, with a case fatality rate (CFR) reported as high as 40-50%.[2] It can be difficult to diagnose, as neurologically intact patients presenting with only headache can account for half of all SAH at initial presentation.[6] The current diagnostic gold standard is high-resolution computerized tomography (CT) scanning, followed by lumbar puncture in patients with negative imaging.[7] The requirement for lumbar puncture is not ideal. It is often troublesome to patients, can be technically difficult and cumbersome, and can be fraught with complications including postural headache, nerve injury, epidural hematoma and both local tissue and CSF infections.[1] Furthermore, the cerebrospinal fluid (CSF) red-blood-cell (RBC) cut-off for the diagnosis remains unclear, and a traumatic puncture can lead to further uncertainty.[8] A more streamlined approach to quickly diagnosing SAH would be welcome.

Importance

Serum D-dimer, a product of fibrin degradation, is physiologically activated in the acute stage

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of SAH,[9,10] and is higher in patients with poor clinical outcomes after SAH, traumatic intracranial hemorrhage and intracerebral hemorrhage.[10-16] If the serum D-dimer level was reliably elevated in patients with SAH, it might provide a diagnostic alternative to lipoprotein (LP).

Goals of this Investigation

In this study, we calculated the sensitivity of serum D-dimer in patients with spontaneous SAH, to determine if serum D-dimer could be an objective marker to help diagnose SAH.

METHODS

Study Design

We conducted a review of the medical records of human subjects. The project was reviewed and approved by the institutional human subjects review board.

Study Setting and Population

All patients admitted to a large tertiary care hospital with a diagnosis of SAH (ICD-9, 430), between the years 1990-2012.

Study Protocol

Our inclusion criteria were: age>18, spontaneous SAH, and symptoms starting before serum was drawn. Patients were excluded if they had evidence of head trauma, subarachnoid blood from iatrogenic intervention, intracerebral hemorrhage, or concomitant intracranial pathology.

Our 2 formally trained data abstractors completed numerous "*practice*" abstractions prior to collecting data for the study. Periodic meetings were held with the abstractors to monitor progress and ensure uniform handling of the data. One-hundred-ninety charts were randomly selected to be reviewed by both abstractors to assess for inter-rater reliability. Both abstractors were aware of the purpose of the study. Disagreements between the 2 abstractors were resolved by a study author directly involved with the training of the abstractors.

Methods and Measurements

Information abstracted included the patient age, sex, race, final diagnosis (including type of SAH), radiologist interpretation of all brain imaging (including CT, computed tomography angiography (CTA), and magnetic resonance imaging (MRI)), lumbar puncture results (if performed), time symptoms began, time serum D-dimer was collected and whether serum D-dimer was positive or negative. Patients that were "*found down*" were considered to have spontaneous SAH if no obvious trauma was seen on brain imaging.

For studies of deep venous thrombosis (DVT), a serum D-dimer cut-off of 500 ng/ml has traditionally been used. It has been extrapolated for cerebral venous thrombosis (CVT) and aortic dissection.[17-20] The same cut-off was used in this study for serum D-dimer's that resulted after 2002.

Analysis

We used Microsoft Excel (Office XP, Microsoft Corp, Redmond, WA, USA) to tabulate data and calculate the overall sensitivity of serum D-dimer for diagnosis of spontaneous SAH. This study was reviewed and approved by the Institutional Review Board (IRB) under expedited status. Informed consent was waived.

RESULTS

Characteristics of Study Subjects

We identified 368 patients who received a diagnosis of SAH during the study period. Two hundred and thirty-seven met inclusion criteria, and formed the final cohort. Our chart abstractors exhibited a kappa coefficient 0.75 in determining D-dimer outcome.

All but 4 patients were initially diagnosed *via* a non-contrast CT brain study. Two patients were diagnosed *via* lumbar puncture and 2 were diagnosed *via* MRI (Table 1).

Main Results

One hundred eighty-five patients had a positive serum D-dimer after symptom onset, yielding a sensitivity of 78.1% [95% CI: 72.9-83.8%]. Twenty-two patients had a serum D-dimer drawn within 12 hours of symptom on set (Table 2). Nineteen had positive D-dimer results, yielding a sensitivity of 86.4% [95% CI: 65.1-97.1%]. All 22 patients in the 12-hour subset were diagnosed on the initial non-contrast CT brain scan.

Limitations

This study has no table limitations. It is based on medical record review, therefore our conclusions are a reflection of the quality of the data in the patient records, and some data were not obtainable. For example, many patients did not have D-dimer levels assessed, and among those who did, the exact time of critical events such as symptom onset was frequently not recorded. Serum D-dimer testing is not mandatory at our institution, and its use in patients with SAH is arbitrary in terms of which patients underwent testing, and the timing of that testing. Most of these tests were ordered as part of a neurosurgical admission package at University of California, Los Angeles (UCLA) and were not prompted by specific presentations. Ideally, analysis of the serum D-dimer of numerous patients within the time frame of a typical ED visit would afford better understanding of the utility of this test in the setting of suspected spontaneous subarachnoid hemorrhage. Under the constraints of a retrospective chart analysis, few patients were identified with serum D-dimer levels

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	All	Positive D-dimer	Negative D-dimer
N (%)	237	185 (78.1)	52 (21.9)
Age- median (IQR)	55.5 (45.3, 68.0)	58.0 (46.0, 71.0)	50.5 (43.5, 64.5)
Sex (%)			
Male	89 (37.5)	67 (36.2)	22 (42.3)
Female	148 (62.4)	118 (63.8)	30 (57.7)
Race (%)			
Caucasian	132 (55.7)	99 (53.5)	33 (63.5)
African American	15 (6.3)	13 (7.0)	2 (3.8)
Asian/Pacific Islander	37 (15.6)	32 (17.3)	5 (9.6)
Unknown	4 (1.7)	3 (1.6)	1 (1.9)
Latino	49 (20.7)	38 (20.5)	11 (21.2)
SAH Type (%)			
Aneurysm	160 (67.5)	129 (69.7)	32 (61.5)
AVM	30 (12.7)	21 (11.4)	9 (17.3)
AVM and Aneurysm	2 (0.8)	1 (0.5)	1 (1.9)
Ependymal Bleed	3 (1.3)	1 (0.5)	2 (3.8)
Other/Unknown	42 (17.7)	33 (17.8)	8 (15.4)
How Diagnosed (%)			
CT non-contrast	233 (98.3)	182 (98.4)	51 (98.1)
CTA	0 (0)	0 (0)	0 (0)
LP	2 (0.8)	2 (1.1)	0 (0.0)
MRI	2 (0.8)	1 (0.5)	1 (1.9)

Table 1: Patient demographic totals.

	All	Positive D-dimer	Negative D-dimer
N (%)	22	19 (86.4)	3 (13.6)
Age: median (IQR)	58.0 (46.0, 68.8)	58.0 (46.0, 66.5)	70.0 (50.0, 72.0)
Sex (%)			
Male	3 (13.6)	2 (10.5)	1 (33.3)
Female	19 (86.4)	17 (89.5)	2 (66.7)
Race (%)			
Caucasian	8 (36.4)	7 (36.8)	1 (33.3)
African American	2 (9.1)	2 (10.5)	0 (0.0)
Asian/Pacific Islander	4 (18.2)	2 (10.5)	2 (66.7)
Unknown	1 (4.5)	1 (5.3)	0 (0.0)
Latino	7 (31.8)	7 (36.8)	0 (0.0)
SAH Type (%)			
Aneurysm	21 (95.5)	18 (94.7)	3 (100.0)
AVM	1 (4.5)	1 (5.3)	0 (0.0)
AVM and Aneurysm	0 (0.0)	0 (0.0)	0 (0.0)
Ependymal Bleed	0 (0.0)	0 (0.0)	0 (0.0)
Other/Unknown	0 (0.0)	0 (0.0)	0 (0.0)
How Diagnosed (%)			
CT non-contrast	22 (100.0)	19 (100.0)	3 (100.0)
CTA	0 (0.0)	0 (0.0)	0 (0.0)
LP	0 (0.0)	0 (0.0)	0 (0.0)
MRI	0 (0.0)	0 (0.0)	0 (0.0)
Minutes to D-dimer drawn: median (IQR)	533 (351, 598)	437 (320, 620)	554 (544, 565)

Table 2: Patient demographics of 12 hr subset.

analyzed within the time of a typical ED visit resulting in clearly underpowered results. It is also possible that uniform testing under specified time constraints and with more enrolled patients would yield different outcomes. The study was conducted at single institution and is based on a small sample size, this therefore limits generalizability and robustness of our results.

The method of D-dimer measurement at our institution changed during the study. Patients enrolled from 1990-2001 had a serum D-dimer that was a latex agglutination assay reported in ratios, producing an overall output of "*positive*" or "*negative*". Patients enrolled from 2002-2012 had a mini VIDAS high sensitive D-dimer reported in ng/ml and fibrinogen equivalent units. While it is unclear the effect this had on the study, only 2 patients out of the 22 in the 12-hour subset had the outdated D-dimer test.

It is also worth noting that all of the patients in this study had a hemorrhage that was visible on high-resolution head

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CT. In contrast, serum D-dimer levels are most likely to be useful in establishing a diagnosis in patients who have unremarkable head imaging results. It is unclear whether our results apply to patients with CT-negative SAH.

DISCUSSION

To our knowledge, no previous study has examined the use of serum D-dimer as a diagnostic tool for assessing patients with spontaneous SAH. In this preliminary investigation, we found that serum D-dimer exhibited a sensitivity of 86.4% in detecting spontaneous SAH in the 1st 12 hours after symptom onset, a level of sensitivity similar to that of CSF xanthochromia.[21] While our findings are based on a very small set of patients, this observation naturally leads to the question of whether it would be possible to replace an analysis of CSF obtained by lumbar puncture (xanthochromia) with a measurement of a serum marker obtained on a peripheral blood draw (D-dimer). While patients are likely to embrace this option, the answer to this question will require further research and a larger population of test subjects. In particular, CSF analysis is not used in establishing the diagnosis of SAH in most patients, but is typically used to assess patients with unremarkable or non-diagnostic head CT results and small hemorrhages. If D-dimer measurements are to be clinically relevant, they too must retain high sensitivity among this same cohort. While high sensitivity is essential for establishing the routine use of D-dimer measurements, a lower sensitivity might still be acceptable in assessing patients who refuse lumbar puncture. It is also important to note that outside 12 hours, our observed sensitivity dropped to 78.1%. This is in agreement with previous studies showing that systemic coagulation and fibrinolytic system activation occurs after SAH.[9-16] The decrease in sensitivity with time may limit the utility of serum D-dimer assessment among patients with delayed presentations.

As newer CT scanner models develop improved sensitivity and a lower rate of false negatives in detecting SAH, there is increasing discussion over the utility of CSF analysis.[22] There is also evidence that obtaining CTA or magnetic resonance angiogram (MRA) can rule out aneurysm bleed with enough sensitivity to effectively make lumbar puncture obsolete.[23] Underfunded hospitals and those in third world countries, however, may rely on older model scanners unable to produce results with the sensitivity to rule out SAH without adjunctive testing. However, given the relative ease and affordability of measuring the serum D-dimer, further studies into the sensitivity of serum D-dimer in the detection of spontaneous SAH and its utility in the work up of these patients are warranted.

This study was a preliminary investigation, and our goal was to find a sensitive serum biomarker to aid in the diagnosis of SAH. Specificity of serum D-dimer for spontaneous SAH was not calculated. Specificity for DVT is strongly dependent on pre-test clinical probabilities and has been found to be as low as 35-54.7% given that elevated D-dimer are frequently found in hospitalized patients, the elderly, those with malignancy, trauma, hemorrhage, recent surgery and cancer, among other causes.[24-27] It would likely be similarly poor for SAH.

Further studies with refined methodology and larger sample sizes are needed before serum D-dimer can be used in clinical practice for the detection of spontaneous SAH in our patients. If future studies reveal high sensitivities, serum D-dimer could be a viable modality to rule out SAH in patients with a negative CT brain scan, thus providing an alternative to lumbar puncture for low risk patients. This finding could be exceedingly helpful in the work up of patients with suspected SAH in underfunded or third world hospitals.

CONCLUSIONS

In summary, serum D-dimer appears to be sensitive in detecting spontaneous SAH in our small patient population. Results from this study suggest a need for further investigations into its clinical use and potential incorporation into diagnostic algorithms for spontaneous SAH patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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