Do Normal D-dimer Levels Reliably Exclude Cerebral Sinus Thrombosis?

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Background and Purpose—Cerebral sinus thrombosis (CST) needs to be considered in the differential diagnosis of all patients with acute headache. Early diagnosis is essential because early treatment may prevent morbidity and may even be life-saving. Definite exclusion, however, needs advanced neuroradiologic diagnostics, which are not readily available in many hospitals. Because measurement of D-dimers has been demonstrated to be helpful in excluding thromboembolic disease, our aim was to investigate whether D-dimers would be also sensitive enough to exclude CST.

Methods—We undertook a prospective multicenter study over a 2.5-year period including all patients who came to the emergency departments with symptoms suggestive of CST. All patients were diagnosed either by magnetic resonance venography, spiral computed tomography scan venography, or intra-arterial digital subtraction angiography. D-dimer levels were measured at admission and analyzed by the same method in all patients.

Results—A total of 343 patients were included. CST was diagnosed in 35 patients, of whom 34 had D-dimers above the cutoff value (>500 μg/L). From the 308 patients not having CST, D-dimers were elevated in 27. Sensitivity of D-dimers was 97.1%, with a negative predictive value of 99.6%. Specificity was 91.2%, with a positive predictive value of 55.7%. D-dimers were positively correlated with the extent of the thrombosis and negatively correlated with the duration of symptoms (Spearman rank correlation coefficients 0.76, −0.58, respectively).

Conclusions—D-dimer measurement is useful in patients with suspected CST. Normal D-dimers make the presence of CST very unlikely. (Stroke. 2004;35:2820-2825.)

Key Words: cerebrovascular disorders • computerized tomography • magnetic resonance imaging • thromboembolism

Headache is one of the most frequent chief symptoms leading to emergency room consultations. Although the cause of headache for the majority of these patients may be benign, it is essential to identify the small subset of patients with severe neurological diseases that are life-threatening and need immediate therapy. One of the most challenging diagnoses for the clinician in this context is cerebral sinus thrombosis (CST). In most cases, the headache is typically of subacute onset and may be the only symptom at the patient’s first visit. The absence of focal neurological signs and papilloedema is not sufficient to exclude CST.1–4 Cranial computed tomography (CT) scan is frequently used to exclude severe neurological conditions in headache patients but has a low sensitivity for diagnosing CST.3 Cerebral angiography is still the gold standard to diagnose CST, but other imaging techniques such as magnetic resonance imaging (MRI) with MR venography or spiral CT with contrast-enhanced venography have been demonstrated to be equally sensitive and specific.5–11 Thus, in all cases in which CST is a possible diagnosis, patients have to undergo costly radiological procedures that have limited emergency availability.

Under comparable diagnostic settings in which acute venous thromboembolic disease is suspected (deep vein thrombosis and/or pulmonary embolism), quantitative measurement of circulating D-dimer levels has been shown to be a very useful diagnostic tool. Under certain circumstances, normal D-dimers almost exclude presence of thromboembolic disease.12,13 Techniques for the quantitative detection of circulating D-dimers have improved such that the assay is now inexpensive and readily available.12,14

The aim of this study was to determine whether D-dimer measurement would be sensitive enough to reliably detect thrombosis in cerebral sinuses, a condition in which the clot volume is often considerably smaller than it is in extracranial venous thromboembolic disease.

Materials and Methods

Study Design

The study was powered to demonstrate whether the sensitivity of elevated D-dimers is at least 0.95. Using exact confidence intervals

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(CIs) for binomial probabilities, we calculated that even under optimal conditions (ie, all patients with CST are found to have elevated D-dimers) we would need at least 29 radiologically proven CST cases for the lower 95% confidence bound to be $>0.90$. With an expected number of 3 to 10 patients with a newly diagnosed CST per year in each study center, we decided that an inclusion period of 2.5 years would be appropriate. Inclusion period was from March 2001 until October 2003. The study was approved by the Ethical Committee of the Medical Faculty, Aachen and was in accordance with institutional guidelines.

**Inclusion/Exclusion Criteria**

In all participating study centers, patients with a chief symptom of headache were primarily seen by a neurologist in the emergency department, where they were included into the trial. Included into the study were all patients reporting headaches that were suggestive of CST and in which further radiological diagnostics seemed mandatory to the neurologist. Patients were included if reporting headaches in combination with one of the following: symptoms suggestive of increased intracranial pressure (nausea/vomiting, visual disturbances, papilloedema, disturbance of consciousness); focal signs on neurological examination; or seizures. Also included were patients reporting subacute headache of increasing intensity that was entirely new to the patient and could not be explained otherwise.

Exclusion criteria were thromboembolic disease (deep venous thrombosis/pulmonary embolism) within the past 4 weeks; known malignancy; acute nephrotic syndrome; signs of disseminated intravascular coagulopathy; pregnancy or termination of pregnancy within the past 4 weeks; patients younger than age 18 years; patients with signs of septic sinus thrombosis; and thrombosis limited to either inner brain veins or bridging veins. After patients underwent further diagnostic procedures, all patients were kept under medical observation for at least 24 hours.

**D-dimer Analysis**

After written informed consent was obtained, blood samples were collected either directly before further radiological diagnostic procedures were performed or soon afterward (maximum of 12 hours). Blood plasma was separated, frozen at $-80^\circ$C, and sent on dry ice to the study center. D-dimers were measured with a widely used quantitative latex assay (Tinaquant; Roche GmbH), which reaches a sensitivity for detection of thromboembolic disease of $>95\%$, with a cutoff value of 500 μg/L.

**Radiological Examination**

Radiological examination followed a standardized protocol for all study centers in which patients were examined primarily either by MRI with gadolinium-enhanced venography or by spiral CT scan with contrast enhanced venography. In cases in which diagnosis was still unclear after CT scan with contrast enhanced venography, patients were further examined by MRI with gadolinium-enhanced venography. In patients in whom diagnosis was unclear after MRI with gadolinium-enhanced venography, intra-arterial digital subtraction angiography was performed. Patients with elevated D-dimers had to undergo 2 of the 3 different possible radiological procedures before it was determined that the diagnosis was not CST. The decision about the necessity of further diagnostic work-up was made by radiologist and neurologist at each study center. D-dimers were measured with a wide-ranging radiological examination approach applied to individual cases.

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**Statistical Analysis**

Data were arranged in a 2×2 contingency table and statistical analysis was performed using a commercially available software package for exact statistical inference (StatXact-4; Cytel Software Corp; Mehta & Pate, 1999), which allows for estimation of specificity, sensitivity, and positive and negative predictive values including exact 95% CIs. Statistical comparison of D-dimer levels between groups was performed using the nonparametric Mann–Whitney U test. Correlations for D-dimer levels to either duration of symptoms or number of sinuses affected were calculated using the nonparametric Spearman rank correlation coefficient.

**Results**

A total of 543 patients were included into this study. On the basis of neuroradiological examination, 35 patients (10.2%) were found to have CST. In the other 308 patients, migraine or tension headache were the most frequent final diagnoses (142 patients, 46%). Other frequent diagnoses were viral meningitis (38 patients, 12.3%), intracerebral hemorrhage or ischemia (32 patients, 10.4%), systemic viral infection or sinusitis accompanied by severe headache (22 patients, 7.1%), idiopathic intracranial hypertension (19 patients, 6.2%), epilepsy (18 patients, 5.8%), drug-induced headache (18 patients, 4.5%), and giant cell arteritis (9 patients, 2.9%). Other final diagnoses were papillitis (2 patients, 0.7%), neuroborreliosis (2 patients, 0.7%), Mycoplasma pneumoniae-associated encephalitis (1 patient, 0.3%), gliomatosis cerebri (1 patient, 0.3%), neurosarcoidosis (1 patient, 0.3%), and brain tumor (WHO grade III astrocytoma) (1 patient, 0.3%). In addition to these patients, another 8 had CST diagnosed during the observation period in our study centers and were not included into this trial because of exclusion criteria: 5 patients because of pregnancy, 2 were younger than age 18, and 1 had a preexisting malignancy.

Within the groups of CST and non-CST patients, there were no statistical differences regarding age, gender, and duration of symptoms at the time patients were examined for suspected CST (Table). Risk factors for venous thrombosis (obesity, oral contraceptives, cigarette smoking, history of thromboembolic disease) were found more frequently in patients with CST, but differences were not statistically significant.

D-dimer levels were elevated ($>500$ μg/L) in 61 trial patients (17.8%), among whom 34 had CST diagnosed. The D-dimer levels (mean±SD) were significantly higher in patients with CST than in patients in whom CST could be excluded ($2052±1286, 375±368$, respectively; $P<0.0001$).
Figure 1. Representative examples of CT scans and MRI from CST patients, including grading of extent of thrombosis. Case 1, CT scans (A to F) of a patient with isolated thrombosis of left transverse and sigmoid sinus (grading, 1; D-dimers, 966 μg/L). A, unenhanced axial CT shows high-density thrombus in the left transverse sinus (arrow). B to E, Images from spiral CT venography with occluded sinus (arrows) and (F) recanalization 3 months later on follow-up CT venography (arrow). Case 2, (G to L) MRI of a patient with thrombosis of the left transverse and sigmoid sinus and anterior part of the sagittal sinus (grading, 2; D-dimers, 1969 μg/L). Note the different signal characteristics of the thrombus (arrows) on T2-weighted (G) and T1-weighted (H) images. Time-of-flight (TOF) MR angiography (I) and 3-dimensional phase contrast MR venography (maximum intensity projections), lateral (K) and axial (L) projections, show partial thrombosis of the superior sagittal sinus (arrows) and complete thrombotic occlusion of the left lateral transverse and sigmoid sinus.
From the 35 neuroradiologically proven CST cases, there was only 1 (2.8%) who had a normal D-dimer level (350 μg/L). In the 27 patients who had no CST, increased D-dimer level could be related mostly to infectious disease (18 patients) or age older than 60 years (9 patients).

The sensitivity of an elevated D-dimer level to detect CST in this trial was 97.1% (95% CI: 83.1% to 99.9%) and the specificity was 91.2% (95% CI: 87.5% to 94.1%). We calculated a positive predictive value of elevated D-dimers for diagnosis of CST of 55.7% (95% CI: 43.4 to 67.5), with a positive likelihood ratio of 11.1 (95% CI: 7.7 to 16). The negative predictive value of a normal D-dimer level to exclude CST was 99.6% (95% CI: 98 to 100), with a negative likelihood ratio of 0.03 (95% CI: 0 to 0.2).

To explain the high variability in the degree of D-dimer elevation in CST patients, we tested the influence of age, gender, duration of symptoms, extension of CST according to our grading, presence of a parenchymal lesion, and presence of focal neurological signs. For age, gender, presence of parenchymal lesion, and presence of focal neurological signs, there was no significant difference in the D-dimer level between the 2 levels of each of these factors (t test, all P>0.1). However, there was a significant correlation, however, between the D-dimer level and the extensiveness of CST in our grading (Spearman rank correlation r = 0.76, P<0.0001) (Figure 2). We also found that D-dimer levels were lower with a longer duration of symptoms with a significant negative correlation (Spearman rank r = 0.58, P<0.001). The impact of age, duration of symptoms, and extension of CST on D-dimer level was studied in a multiple linear regression analysis. There was a highly significant multiple correlation (r = 0.78, P<0.001) when all 3 parameters were considered. However, only duration of symptoms and extension of CST had an independent significant contribution (both P<0.05) to the prediction of the D-dimer level.

## Discussion

This study clearly demonstrates that in a clinical situation in which a patient is suspected to have CST, measurement of D-dimers is a helpful diagnostic tool. We found a sensitivity of >95% and a negative predictive value of 99.6% in favor of having no CST when D-dimers were normal. This makes this test extremely valuable for exclusion of CST in patients with clinically suspected CST.

Specificity (91.2%) and positive predictive value (55.7%) of elevated D-dimer levels for detection of CST were also relatively high in this study in contrast to other trials in which D-dimers were evaluated for detection of peripheral thromboembolic disease. This might be explained by restrictive exclusion criteria in this trial like pregnancy and malignancies, which are known to cause elevated D-dimers.

Only 1 patient in this study had CST with D-dimer levels <500 μg/L. It is interesting that this patient reported headaches for >3 weeks before diagnosis. Other groups have described normal D-dimer levels in CST patients with rather chronic headaches lasting for >3 weeks.15,16 It is known that in acute deep venous thrombosis of the legs, initially raised D-dimer levels may decline to normal within the first week.17 If this is also the case in CST, then we hypothesized that D-dimer levels might be inversely correlated with duration of symptoms. Our data confirm this hypothesis and the decline of D-dimer levels with duration of symptoms before diagnostics suggests that D-dimer levels are only helpful for exclusion of CST when symptoms do not last >2 weeks (Figure 2).

Similar to findings in patients with thromboembolic disease, this study demonstrates that the extent of thrombosis, here expressed as a semi-quantitative measure by the number of sinuses affected, is positively correlated with the elevation of D-dimers (Figure 2). This correlation could not be attributed to any of the other possible confounding factors that we
tested (age, gender, duration of symptoms, presence of parenchymal lesion, presence of focal neurological signs). But the number of CST patients in this study is certainly too low to exclude a possible joint influence of all variables together. Nevertheless, our findings suggests that D-dimers might be not only suitable in the context of diagnosing CST but also may be helpful in estimating severity of disease and might also turn out to be a tool for monitoring course of disease, therapeutic success, or for distinguishing between acute and chronic CST. Studies measuring D-dimers during the course of the disease will be necessary to address these questions accurately.

Some smaller patient series have been published, which addressed the issue of D-dimers in the context of CST. In a pilot study Wildberger et al published on 6 patients with MRI-proven CST, it was found that D-dimers were elevated in all patients using a qualitative bedside test (SimpliRED).18 Talbot et al described 5 CST patients, of whom 2 had D-dimers <500 μg/L and concluded that D-dimers were not helpful for exclusion of CST.19 Interestingly the 2 patients with normal D-dimer levels would have been excluded in our trial because 1 had septic CST of the left sigmoid sinus accompanied by left sided mastoiditis, and the other patient was younger than age 18. Recently, Tardy et al published a report of 18 patients with CST who had symptoms for <2 weeks and found elevated D-dimers in all subjects.15 In this study, 34 control patients without CST were selected by a matched design and it was therefore impossible to calculate specificity of D-dimer measurement. Lalive et al published a series of 12 patients with CST and found D-dimers elevated in 10.16 In accordance with our findings, they calculated a high sensitivity (83%), but because of the limited size of their trial the range of their 95% CI was 52% to 98%, so the precision of the sensitivity estimate of this finding was still questionable. Our study confirms the 2 other studies with a high negative predictive value of normal D-dimers to exclude CST.

A limitation of our study is that some patients were excluded from this study because of pregnancy, puerperium, or malignancy, although it is known that these comorbidities increase the risk of CST.2 In fact, the 6 patients with CST who were excluded from this study because of pregnancy or malignancy all had elevated D-dimer (>500 μg/L) levels. Although specificity of D-dimers for diagnosing CST is certainly lower in these patients, we would thus predict that normal D-dimers have a similar negative predictive value than those we found in patients without these comorbidities. Further studies need to address this issue more directly.

Figure 2. D-dimer levels in patients with cerebral sinus thrombosis (CST) in relation to (A) the extent of the thrombosis expressed as the number of thrombosed sinuses (see Materials and Methods for details); (B) the period of time that the patient was reporting symptoms when CST was diagnosed; (C) the presence or absence of focal neurological signs on admission; and (D) the presence or absence of parenchymal lesions on MRI or CT scans. D-dimer levels were significantly (P<0.0001) correlated with the extent of thrombosis and inversely correlated with the duration of symptoms. The dotted line in (A) represents the results of regression analysis under the assumption of a linear association. The dotted horizontal line in each graph indicates the cutoff value of D-dimers at 500 μg/L.
A specific challenge for early diagnosis of CST are patients who present with headaches that are not accompanied by any focal neurological abnormalities, because CST might be most easily overlooked in this subgroup of patients. In 20 of our 35 patients having CST, focal neurological signs were absent. However, D-dimmers were significantly elevated in all of these patients and are thus extremely helpful in identifying the headache patients who need immediate further radiological diagnostics.

In summary, our data together with published studies suggest that D-dimers are useful in the diagnostic evaluation of headache patients who consult emergency departments and are clinically suspected of having CST. If the native CT scan is normal, then elevated D-dimers can be very helpful to identify the subset of patients who need further radiological diagnostics to exclude CST. With normal D-dimer levels, CST is very unlikely in all patients who have symptoms for ≤2 weeks and who are 18 years or older.

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References