DIAGNOSTIC VALUE OF D-DIMER MEASUREMENT IN PATIENTS SUSPECTED TO HAVE CEREBRAL VENOUS THROMBOSIS

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Abstract- Among the causes of headache, cerebral venous and/or dural sinus thrombosis (CVT) is an important challenge because of its variable clinical presentation, having negative brain CT in up to 30% of cases and unavailability of MRI in some situations. On the other hand as D-Dimer (DD) test has been reported to be a sensitive test for the exclusion of venous thromboembolism, we sought whether it could be useful in the diagnosis of cerebral venous thrombosis. A prospective study of 104 consecutive patients with headache or unusual ischemic stroke (infarction in brain CT, but not compatible with any brunch of cerebral arteries), suggesting CVT was conducted between 2003 and 2005. D-Dimer test determined for all patients in the emergency ward before MRI or MRV was performed. Titers above 500 ng/ml were regarded as positive test. From a total 104 patients, 21 cases (20.2%) were confirmed (by MRI and/or MRV) to have CVT, 20/21 (95.7%) of whom had positive DD test. In the remainder 83 (without CVT) it was only positive in 16.8% (14/83), which was statistically meaningful ($P < 0.001$). Specificity, sensitivity, negative and positive predictive values of DD test were 83.1, 95.2, 98.6 and 58.8%, respectively, so application of this test would be useful in the diagnosis of CVT and values below 500 ng/ml make acute thrombosis unlikely.

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Key words: Cerebral venous thrombosis, headache, D-Dimer

INTRODUCTION

Cerebral venous thrombosis (CVT) is a life threatening condition with a broad range of clinical presentations and mode of onset that can lead to a great diagnostic problem (1-3). Brain CT is negative in up to 30% of cases (2). MRI coupled with MRV is the gold standard diagnostic procedure, but is not always available and is expensive.

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Headache is the most common initial presentation usually associated with other signs including focal neurological deficits (4, 5). Regarding the fact that only minority of headache admissions to the emergency are due to CVT, it is not advisable to perform MRI or MRV in every patient presenting with headache. Furthermore, the value of DD (a degradation product of cross-liked fibrin) measurement to rule out venous thromboembolism (DVT, pulmonary embolism) has been already well established (6-10), though controversy still exists (11, 12). Because of the above mentioned reasons we decided to study the value of DD test in patients with headache or unusual stroke, suggesting CVT.

MATERIALS AND METHODS

In this cross-sectional prospective study, 104 consecutive patients suffering from unusual headache and/or cerebral ischemic infarct and addressed to emergency room of our center were included with specific criteria. Inclusion criteria were: 1) unusual acute, subacute and chronic headaches without any history of cluster, migraine or tension headache, 2) headaches with unusual localization or type of pain, worsening with lying down, unusual long duration and/or unresponsive to usual medication, and 3) unusual recent ischemic stroke (infarct in CT, but not compatible with any brunch of cerebral arteries). Patients with history of stroke during the 3 months prior to admission and headache due to cranial trauma, hypertension, infection, intra-cerebral mass lesion and hemorrhage were excluded. Conditions such as inflammation, pregnancy, rheumatoid arteritis which may increase DD titers were also omitted in this study.

The study achieved approval of University ethics committee. After obtaining written informed consent, blood samples were drawn before any imaging procedures and soon afterward (maximum of 24 hours) plasma was separated, frozen at -80 °C and sent to the laboratory. D-Dimer titers were measured by using a conventional ELISA (Asserachrom Ddi, Slago, France). As in many previous researches (15), titers more than 500 ng/ml were considered positive tests. Final definite diagnosis was made by MRI and/or MRV.

SPSS software and Epi info 2000 were applied for statistical analysis. Student *t* test, chi square and Fisher exact test were used for evaluation of variables relationship with CVT occurrence. For description of D-Dimer levels first and third quartiles (Q1, Q3) were taken. The sensitivity, specificity, negative and positive predictive values were calculated by Fisher exact test. To assess agreement between the diagnostic capacities of D-Dimer test and radiologically confirmed diagnosis kappa statistic was applied.

RESULTS

Cerebral thrombosis was detected in 21/104 (20.2%) of patients, which were all located in dural sinuses. Mean ± SD age of patients with and without CVT were 31.2 ± 9.4 and 27 ± 12.8 years, respectively. 61.9% (13.21) of cases with CVT and 74.7% (62/83) of patients without thrombosis were female. These findings indicated that age and gender had no effect in CVT occurrence. Oral contraceptive (OCP) consumption was a major risk factor for CVT occurrence, because 92.3% of cases with thrombosis used OCP whereas only 22.6% of non-thrombotic patients had consumed OCP (Table 1).

The mean ± SD titers of DD test in patients with and without CVT were 1380 ± 920 and 388 ± 205 ng/ml, respectively, which were statistically meaningful (P = 0.001) (Table 2). Positive DD test was found in 95.3% (20/21) of thrombotic and 16.8% (14/83) of non-thrombotic patients. This was also statistically significant (Table 3, $P < 0.001$).

Specificity, sensitivity, negative and positive predictive values of the DD test was 83.1, 95.2, 98.1 and 58.8%, respectively.

Lateral sinus was the most common site of thrombosis (11/21). Involvement of both lateral and saggital sinuses occurred in 9 cases. Saggital sinus thrombosis alone was detected in only one of the thrombotic patients.

Table 1. Characteristics and risk factors (variables) of patients

Variables	With CVT 21 cases (20.2%)	Without CVT 83 cases (79.8%)	*P* value
Age* (mean ± SD) year	31.2 ± 9.4	27 ±12.8	0.20
F/M ratio†	13/21 (61.9%)	62/83 (74.7%)	0.24
OCP consumption‡	12/13 (92.3%)	14/83 (22.6%)	0.001

Abbreviations: CVT, cerebral venous thrombosis; OCP, oral contraceptive pills.
* Student t test was used.
† Chi square test was used.
‡Fisher's exact test was used.

Table 2. Mean ± SD D-Dimer titers in patients with and without CVT

	With CVT		Without CVT			
DD titer	**No**	**Mean ± SD**	**No**	**Mean ± SD**	***P* value**	***t***
Ng/ml	21	1380 ± 920	83	388 ± 205	< 0.001	5/8

Abbreviations: CVT, cerebral venous thrombosis; DD, D-Dimer.

DISCUSSION

In our study CVT occurred in 20.2% of patients, which was nearly similar to Lalive's report (13). Mean age and female predominance in the patients with CVT also correlated with other studies (13, 14). Lateral and lateral-saggital sinuses were the most common sites of thrombosis that was in agreement with some of the previous reports (15), but in contrast with Trazzi's study (16).

D-Dimer levels were much higher in our patients with CVT than those without thrombosis, as reported by other researchers (15, 17, 18). For this reason Kelly and Hunt suggested that DD titration should be first step of investigation in venous thromboembolic events (19). We found also a high negative predictive value (98.6%) of DD test which disagrees with certain authors (18, 20) and supports others (2, 21).

All but one of our thrombotic patients showed positive DD test. The latter, who suffered from headache with duration of 5 weeks had DD level less than 500 ng/ml, which can be explained by the fact that DD level decreases progressively during the first weeks of thrombotic event (22). Some authors reported that DD level returns to normal value within 3 months after an acute deep thrombosis (23). The optimal time window in which DD test is till valid remains uncertain. According to Brill-Edward and Lee negative DD test rules out thrombosis strongly (7), but Brotman *et al.* showed that a negative test did not exclude thrombosis in older patients with long term hospitalization and high C-reactive protein (24). It is worthy to mention that other causes such as inflammation, meningitis, pregnancy and rheumatoid arthritis may increase DD levels (25, 26). In our study, positive predictive value (58.8%) was lower than Tardy's report. Our study was also in agreement with some reports (23, 26) that OCP consumption is an important risk factor of CVT.

Table 3. Frequency of positive DD test in patients with and without CVT

	With CVT	Without CVT
DD test*	**No (%)**	**No (%)**
Positive	20 (95.2)	14 (16.9)
Negative	1 (4.8)	69 (83.1)
Total	21 (100)	83 (100)

Abbreviations: CVT, cerebral venous thrombosis; DD, D-Dimer.
* Agreement between DD test with final diagnosis with Kappa statistic (K value: 0.64, *P* value < 0.001); Sensitivity: 95.2 % (CI 95: 741-99.8%); Specificity: 83.1% (CI 95: 73-90.1%); Negative predictive value: 98.6% (CI 95:912-99.9%); Positive predictive value: 58.8% (CI 95: 40.8-74.9%).

In conclusion, positive DD test with high sensitivity and negative predictive value may be a useful diagnostic approach in patients suspected to have cerebral venous thrombosis. Negative DD test can exclude thrombosis with a high certainty and MRI and/or MRV should preferably be performed only in patients with positive DD test and highly suspected cases.

Conflict of interests

We have no competing interests.

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