Diagnostic value of D-dimer’s serum level in Iranian patients with cerebral venous thrombosis

Leila Hashami,1 Vahid Rakhshan,2 Hoda Karimian,3 Mehdi Moghaddasi1
1Department of Neurology, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran; 2Department of Dental Anatomy and Morphology, Dental Branch, Islamic Azad University, Tehran; 3Department of Emergency Medicine, Iran University of Medical Sciences, Tehran, Iran

Abstract

Cerebral venous thrombosis (CVT) is a long-term debilitating vascular brain disease with high morbidity and mortality. It may be associated with rise in D-dimer level. The aim of this study was to examine this potential association and identify the critical D-dimer cut-off level corresponding to increase the risk of CVT. This case-control study was conducted on two groups of patients with and without CVT attending the Rasool Akram Hospital (Iran) during 2014 and 2015. D-dimer levels were measured by the rapid sensitive D-dimer assay. Data were analyzed by Spearman’s correlation coefficient test, independent-samples t-test, backward-selection multiple linear regression and multiple binary logistic regression analysis. Sensitivity-specificity tests were used to detect D-dimer cut-off for CVT. Differences between the D-dimer levels of the case and control groups were significant (P<0.001). It showed that each level of increase in the number of symptoms could increase the risk of thrombosis occurrence for about 3.5 times. All symptom types except for headache were associated with D-dimer level, while headache has negative association with D-dimer level. D-dimer cut-off point for CVT diagnosis was estimated at 350 ng/ml. We concluded that D-dimer serum level significantly rises in CVT patients. A rounded cut-off point of 350 ng/ml can be used as a diagnostic criterion for CVT prediction.

Introduction

For a long time cerebral venous thrombosis (CVT) was known as a rare long-term debilitating vascular brain disease of high morbidity and mortality. This disorder presents itself with a wide range of clinical signs and symptoms, like headache, cerebral hemorrhage and cerebral edema.1 Among its diagnostic challenges in the emergency department are its non-specific signs and symptoms.2 In recent years, the introduction of highly sensitive but non-invasive techniques such as magnetic resonance imaging (MRI), magnetic resonance venography, and computed tomography venography have led to the discovery of more cases.3,4 However, the difficulties associated with the use of these techniques have hindered their application as general screening methods for CVT.5 Hence, a simple, accessible and accurate method has always been of interest to neurology researchers.

D-dimer is a fibrin degradation product, the serum level of which begins to rise shortly after thrombus formation and the process of clot lysis.6 The measurement of serum D-dimer levels is nowadays used as a diagnostic method for non-CVT.7 Although D-dimer has a similar role in the diagnostic approach toward Deep Venous Thrombosis (DVT) and pulmonary thromboembolism it lacks a valid score for CVT diagnosis. Thus the role of D-dimer is still a matter of debate in the diagnostic approach toward suspected cases of CVT.8

One of the most recent statements released by the American Heart Association and American Stroke Association recommended the use of D-dimer as a useful indicator in the detection of suspected cases of CVT.9 Elsewhere, D-dimer evaluation yielded positive results in most but not all cases of CVT.10 However, sufficient research has not been conducted on the sensitivity and specificity of D-dimer in the diagnosis of CVT. Moreover, a conclusive D-dimer cut-off point has not been determined for CVT risk estimation for various ethnicities such as eastern ones. Considering the significance of timely diagnosis of CVT and the uncertainty surrounding the use of D-dimer in its diagnosis, we conducted this study to determine the serum levels of D-dimer in suspected patients attending Rasool Akram Hospital and in an Iranian population.

Materials and Methods

This case-control study was performed on all the available records of patients attending the Rasool Akram Hospital during 2014 and 2015. The ethics were approved by the Research Committee of Iran University of Medical Sciences, in accordance with the Helsinki declaration.

This study was conducted on two groups of patients with and without CVT. All patients attending Rasool Akram Hospital during 2015-2016 with adequate neuroimaging (MRI) data were originally evaluated to diagnose CVT according to classical neuroimaging signs. They were divided into two groups of patients with CVT (cases) and without CVT (controls). The sample size was determined based on a pilot study, which included a minimum of 90 patients in both groups (30 cases and 60 controls). The following data were gathered from all the participants: age, gender, weight, height, body mass index, cigarette smoking status, pregnancy, menopause status in women, intake of oral contraceptive pills (OCPs) in women, and their dosage if taken.

The participants’ clinical signs and symptoms were assessed as well: isolated headache; headache and papilledema; and encephalic signs (seizure, focal weakness, consciousness, etc.). Relevant CVT risk factors [pregnancy, menopause status, OCPs use, factor V Leiden, Body Mass Index (BMI), smoking] were assessed and identified. Before starting any treatment or medications, including anticoagulant drugs in the case group, all the participants had blood tests conducted. Their D-dimer levels were measured by the rapid sensitive D-dimer assay and the results were reported.

Statistical analysis

Data were analyzed in the SPSS program (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA). Descriptive statistics (mean and median) were calculated for both groups. Associations between variables were assessed using Spearman’s correlation coefficient, independent-samples t-test, backward-selection multiple linear regression, and multiple binary logistic regression analyses. The critical D-
The D-dimer level was estimated by sensitivity analysis. The level of significance was predetermined as 0.05.

**Results**

In the case group there were 16 males and 13 females, with a mean age of 41.2±15.0 years (36.3±13.4 in females; 44.8±15.6 in males). In order to the site of thrombosis, there was 17 cases of transverse sinus (58%), 9 in sagittal sinus (31%), 2 in vein of Galen (6.9%) and one in vein of Labbe (3.5%). In the control group (patients clear of thrombosis diagnosis), there were 35 males and 24 females, with a mean age of 42.2±13.8 years (39.4±11.3 in females; 44.9±45.2 in males).

The mean D-dimer level in the case group was 2545.6±753.5 ng/mg (range: 135 to 3459), 2268.8±861.5 ng/mg, and 2598.4±643 ng/mg, respectively in 29 patients, 13 females and 16 males. There was only one patient with a D-Dimer level of 135 ng/mg, and the rest of cases had D-Dimer levels above 1000 ng/mg. None of the females was smokers, while 5 males (31.3%) were smokers. Of the female cases, only 3 (23.1%) were taking OCPs. Of them, 1 (7.7%) was pregnant, 2 others (15.4%) were in their first or second postpartum weeks, and 3 (23.1%) were menopausal. The mean BMI was 25.2±2.6 kg/m² (25.4±2.4 in females; 25.1±2.8 in males). The factor V Leiden was positive in 1 woman (7.7%) and 3 men (18.8%). Of the 29 cases, 55.2%, 41.4%, and 3.4% had respectively 1, 2, and 3 symptoms. Headache, hemiparesis, and seizure were reported by 48.3%, 27.6%, and 58.6% of the cases, respectively. Other symptoms (confusion, visual problems, ataxia, etc.) were reported by 10.3% of the cases. In the control group, D-dimer levels were 27.7±7.2 (range: 12 to 43), 29.8±6.6, and 26.3±7.3, respectively in the controls i.e. 24 females, and 35 males. Twelve males (34.3%) were smokers. There were no female smokers. Of the female controls, only 1 (4.2%) was pregnant. The mean BMI of control group was 24.7±2.0 ng/mg (24.9±1.8 in females; 24.6±2.1 in males). Among the 59 controls, 79.7% and 20.3% had respectively 1 and 2 symptoms (i.e., only headache and seizure). Headache, hemiparesis, and seizure were reported by 100%, 0.0%, and 20.3% of the controls, respectively. Other symptoms (confusion, visual problems, ataxia, etc.) were not reported by any of the control group participants.

**Subgroup analyses**

**Case (cerebral venous thrombosis-positive)**

The backward-selection multiple linear regression on the case group data (n=29) showed that of all the above mentioned variables (excluding symptom types), only age (beta=0.472; P=0.015) significantly predicted D-dimer levels (all other variables were insignificant). According to the analyses performed on the case group data (n=29), among the symptoms, headache (beta=-0.438; P=0.011) negatively predicted D-dimer levels. The symptoms hemiparesis, and seizure were not associated with D-dimer levels. However, other symptoms (confusion, ataxia, visual problems) were collectively associated with D-dimer levels (beta=0.352; P=0.036).

**Control (cerebral venous thrombosis-negative)**

The backward-selection multiple linear regression on the control group data (n=59) showed that of all the above-mentioned variables (symptom types excluded), only age (beta=0.303; P=0.018) and female gender (beta=0.293; P=0.022) positively predicted D-dimer levels in the controls, and all other variables were insignificant. None of the symptoms was associated with D-dimer levels in the control group.

**Analysis of complete data**

Based on the t-test results, the difference between the D-dimer level of the case and control groups was significant (P<0.001). A regression analysis was performed over the whole data (n=88). The variables included all the items in above-mentioned regressions as well as the number of symptoms present in patients, but excluding the types of symptoms. Only age (beta=0.086; P=0.022) and thrombosis (beta=0.940; P=0.000000) were predictors of D-dimer levels. A separate analysis was performed on symptom types only. According to the linear regression, all symptom types except headache were positively associated with D-dimer levels, while headache was negatively associated with D-dimer levels (Table 1). Spearman’s coefficient showed excellent correlations between thrombosis occurrence, D-dimer levels, and symptoms (Table 2). The multiple binary logistic regression analysis was used to assess the association of all variables except D-dimer and symptom types with thrombosis occurrence. It showed that each level of increase in the number of symptoms could increase the risk of thrombosis occurrence for about 3.5 times (odds ratio (OR)=3.4, Table 3).

**D-dimer’s cut-off value for cerebral venous thrombosis prediction**

The rounded critical D-dimer cut-off point was estimated to be 350 ng/mg (rounded from 342.5 ng/mg), above which, patients are at a much increased risk of thrombosis (receiver-operator curve’s P<0.0001).

**Discussion**

D-dimer increases in the serum following fibrinolysis of blood clots. Assessment of its serum levels can confirm the process of clot formation and fibrinolysis. Based on our results the serum level of D-dimer was significantly higher in CVT patients than in the control group. Furthermore, all the CVT signs were associated with the D-dimer level, except for headache. An increase in the number of symptoms was associated with an increased risk of thrombosis. Age and the female gender were positively associated with the D-dimer level.

The D-dimer level was significantly different in the CVT group when compared to the control group in 350 ng/mg cut-off level. Other studies have confirmed elevated levels of serum D-dimer following CVT, but critical cut-off value was 500 ng/mg in most studies, probably due to the prevalence of other CVT predisposing factors in different populations. Lalive and colleagues assessed the D-dimer level for the purpose of CVT diagnosis, and found the sensitivity and specificity to be 83% and 90%. Dentali and colleagues studied the diagnostic value of D-dimer serum level in CVT. The weighted mean sensitivity of D-dimer was estimated at 93.9% (95% CI 87.5-97.1) and its weighted mean specificity was estimated at 89.7% (95% CI 86.5-92.2). So, it seems that decreasing D-dimer cut-off level may increase the diagnostic value of this test in CVT. In this study, the female gender and age were D-dimer level determinants in patients.
Table 2. Spearman correlation coefficient test of D-dimer serum level in patients with and without cerebral venous thrombosis.

| Variable                  | Rho    | P       | OR       | 95% CI for OR |
|---------------------------|--------|---------|----------|---------------|
| Age                       |        |         |          |               |
| Male sex                  | 0.859  | 0.053   | 0.908    | 0.314, 2.632  |
| Number of symptoms        | 0.012  | 0.491   | 3.399    | 1.305, 8.849  |
| Smoking                   | 0.678  | 0.987   | 1.346    | 0.331, 5.478  |
| Body mass index           | 0.219  | 0.950   | 1.157    | 0.917, 1.460  |
| Thrombosis                | 0.139  | 0.005   | 0.858    | 0.491, 1.496  |
| Male sex                  | 0.859  | 0.053   | 0.908    | 0.314, 2.632  |
| Number of symptoms        | 0.012  | 0.491   | 3.399    | 1.305, 8.849  |
| Smoking                   | 0.678  | 0.987   | 1.346    | 0.331, 5.478  |
| Body mass index           | 0.219  | 0.950   | 1.157    | 0.917, 1.460  |
| Thrombosis                | 0.139  | 0.005   | 0.858    | 0.491, 1.496  |
| Male sex                  | 0.859  | 0.053   | 0.908    | 0.314, 2.632  |
| Number of symptoms        | 0.012  | 0.491   | 3.399    | 1.305, 8.849  |
| Smoking                   | 0.678  | 0.987   | 1.346    | 0.331, 5.478  |
| Body mass index           | 0.219  | 0.950   | 1.157    | 0.917, 1.460  |
| Thrombosis                | 0.139  | 0.005   | 0.858    | 0.491, 1.496  |

Conclusions

CVT may occur more in patients with a higher number of symptoms. No strong association was found between CVT risk and items such as age, smoking, or BMI. D-dimer level may be higher in older patients and those experiencing either hemiparesis, seizure, or a combination of confusion, ataxia, and visual problems, but not in those with headache (which showed a negative association and needs future research). D-dimer serum level significantly rises in CVT patients compared to the control group. A rounded cut-off point of 350 ng/ml can be used as a diagnostic criterion for CVT prediction.
References

1. Bousser MG. Cerebral venous thrombosis: diagnosis and management. J Neurol 2000;247:252-8.
2. Ageno W, Dentali F, Squizzato A, et al. Evidence and clinical judgment: treatment of cerebral vein thrombosis. Thromb Haemost 2010;103:1109-15.
3. Ferro JM, Canhao P, Stam J, et al. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 2004;35:664-70.
4. Dentali F, Gianni M, Crowther MA, Ageno W. Natural history of cerebral vein thrombosis: a systematic review. Blood 2006;108:1129-34.
5. Linn J, Brückmann H. Cerebral venous and dural sinus thrombosis: state-of-the-art imaging. Clin Neuroradiol 2010;20:25-37.
6. Kovacs MJ, MacKinnon KM, Anderson D, et al. A comparison of three rapid D-dimer methods for the diagnosis of venous thromboembolism. Br J Haematol 2001;115:140-4.
7. Bates SM, Grand’Maison A, Johnston M, et al. A latex D-dimer reliably excludes venous thromboembolism. Arch Intern Med 2001;161:447-53.
8. Gouda T, Sabry HM. Evaluation of plasma D-dimer assay as a diagnostic biomarker for cerebral venous thrombosis. Egypt J Neurol Psychiatry Neurosurg 2010;47:331-6.
9. Misra UK, Kalita J, Bansal V. D-dimer is useful in the diagnosis of cortical venous sinus thrombosis. Neurol India 2009;57:50-4.
10. Haapaniemi E, Talliisumak T. Is D-dimer helpful in evaluating stroke patients? A systematic review. Acta Neurol Scand 2009;119:141-50.
11. Tardy B, Tardy-Poncet B, Viallon A, et al. D-dimer levels in patients with suspected acute cerebral venous thrombosis. Am J Med 2002;113:238-41.
12. Wildberger JE, Mull M, Kilbinger M, et al. [Cerebral sinus thrombosis: rapid test diagnosis by demonstration of increased plasma D-dimer levels (SimpliRED) ]. Rofo 1997;167:527-9. [Article in German]
13. Lalive PH, De Moerloose P, Lovblad K, et al. Is measurement of D-dimer useful in the diagnosis of cerebral venous thrombosis? Neurology 2003;61:1057-60.
14. Dentali F, Squizzato A, Marchesi C, et al. D-dimer testing in the diagnosis of cerebral vein thrombosis: a systematic review and a meta-analysis of the literature. J Thromb Haemost 2012;10:582-9.
15. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005;352:1791-8.
16. Choi JY, Morris JC, Hsu CY. Aging and cerebrovascular disease. Neurol Clin 1998;16:687-711.
17. Bousser MG, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol 2007;6:162-70.
18. Alons IM, Jellema K, Wermer MJ, Algra A. D-dimer for the exclusion of cerebral venous thrombosis: a meta-analysis of low risk patients with isolated headache. BMC Neurol 2015;15:118.