

The Value of D-dimer Test for Diagnosis of Cerebral Venous Thrombosis in Kuwait Neurological Center

Jasem Y Al-Hashel^{1,2,*}, Samar Farouk Ahmed^{1,3}, Doaa Youssry^{1,4}, Raed A Alrouhani^{5,6}, Ismail I Ismail¹ and Periasamy Vembu¹

¹Department of Neurology, Ibn Sina Hospital, P.O. Box 25427, Safat 13115, Kuwait

²Department of Medicine, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait

³Department of Neurology and Psychiatry, Minia University, P.O. Box 61519, Minia 61111, Egypt

⁴Department of Neurology, Cairo University, Egypt

⁵Division of Neurology, Amiri Hospital, Sharq, Kuwait

⁶Neurology Clinic, Dasman Diabetes Institute, Dasman, Kuwait

*Corresponding author: Jasem Y. Al-Hashel, MD, FRCPC, FAHS, Consultant Neurologist, Chairman of Neurology, Department of Neurology, Ibn Sina Hospital, President Kuwait Neurology Society, Neurology Program Director, PO Box: 25427, Safat PO, Kuwait, Tel: +965 66400032; Fax: +965 24849226; E-mail: dralhashel@hotmail.com

Received date: May 20, 2015; Accepted date: June 15, 2015; Published date: July 22, 2015

Copyright: © 2015 Al-Hashel JY, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: Plasma levels of D-dimer shown to be elevated and sensitive for the diagnosis of deep vein thrombosis including cerebral venous thrombosis (CVT).

Objective: To assess the usefulness of serum D-dimer level, for the diagnosis of CVT.

Subjects and Methods: This retrospective analysis included 65 patients who was diagnosed with cerebral venous thrombosis proved by magnetic resonance venography (MRV) or computed tomographic venography (CTV), from Jan. 2005 up to Dec. 2014. The patient's files were collected and the data were extracted for the study. Based on these data, the usefulness of serum D-dimer level for the diagnosis of CVT, were analyzed.

Results: The records of 23 male and 42 female were taken for this clinical review. The D-dimer level were elevated in 42 patients (64.6%) versus 23 patients (35.4%) with normal level; $P < 0.018$. Eight patients had slight elevation of D-dimer level (200-500 ng/ml), 18 patients had moderate elevation of D-dimer level (500-1000 ng/ml) and 16 patients had very high level of D-dimer (1000-2000 ng/ml). The sensitivity and specificity of predicting cerebral venous sinus thrombosis using D-dimer were 64.6% and 71.5%. The pattern of venous sinuses involved, the neurological deficits were different and did not correlate with serum D-dimer levels ($r=0.18$, $P < 0.108$).

Conclusion: Raised D-dimer level are often helpful for early diagnosis of CVT and an important screening tool to determine the early need of neuroimaging in patients who are suspected of CVT.

Keywords: D-dimer; Cerebral Venous thrombosis; Kuwait

Introduction

Cerebral Venous Thrombosis (CVT) is presented with variety of clinical signs and symptoms and considered as a medical emergency. Headache is the most frequent and earliest manifestation of CVT (>80%) followed with seizures (approximately 40%), hemiparesis (approximately 40%), altered consciousness (15-20%), and papilledema (20-30%) [1-3]. The non-specificity of most of the presenting symptoms of CVT poses major problems in an emergency room setting, because it might be difficult to screen every patient with headaches for CVT by magnetic resonance imaging (MRI) [3]. One study reported that an initial misdiagnosis of CVT could occur in up to 73% of patients. In addition, delays in reaching to a diagnosis for over 10 days can also happen in 40% of patients admitted to the hospital [4].

Magnetic resonance venography (MRV), plasma levels of D-dimer, a biological marker of endogenous fibrinolysis, shown to be elevated and sensitive for the diagnosis of deep vein thrombosis including cerebral venous thrombosis [5]. A number of studies have confirmed the usefulness of D-dimer level in venous sinus thrombosis [5,6].

The aim of our study is to evaluate the usefulness of plasma D-dimer levels in diagnosis of cerebral venous thrombosis.

Subjects and Methods

This retrospective study was done at Ibn Sina Hospital which is a tertiary hospital of neurology in Kuwait. It included all patients with CVT of both sexes and all age groups who were admitted Jan. 2005 up to Dec. 2014. CVT diagnosis was proved by magnetic resonance venography (MRV) or computed tomographic venography (CTV). We excluded patients with systemic disease or states that affect d-dimer as pregnancy, puerperium, rheumatoid arthritis, septicemia, malignancy and meningitis. The patient's files were collected and the data were

extracted for the study. Demographic data (age, gender), clinical data (presentation at onset) and para clinical results (level of D-dimer, results of MRV or CTV) were collected from the files of patients. D-dimer level was measured by immune turbidimetry assay with the coagulational laboratory autoanalyzer (ACL2000; Instrumentation Laboratory, Milan, Italy). The cut-off values were equal or greater than 200 ng/l, as in accordance to the normal criteria of our laboratory. The D-dimer level was graded according to the level of estimation. Graded as normal level, when less than 200 ngm/ml, slightly elevated are 200-500 ngm/ml, moderate elevation is 500-1000 ngm/ml and severely elevated were 1000-2000 ngm/ml.

Statistical Analysis

Data Obtained were fed into computer software package (SPSS, version 19). Descriptive statistics i.e. mean (M), standard deviation (SD), range; minimum and maximum reading and frequency were calculated. Chi-square analysis was carried out to evaluate the significance between quantitative data. The sensitivity, specificity, negative and positive predictive values were calculated by Fisher exact test. Pearson Correlation Coefficient TEST “R” was calculated to measure the strength of association between variables. P-values less than 0.05 were considered to be statistically significant.

Results

A total of 65 patients who were diagnosed to have CVT were identified for study. Most of the patients (85%) were admitted within 3 days to 4 weeks of disease onset.

Their ages ranged from 15 to 60 with a median age of 30 and a male to female ratio of 1:1.8. Headache was the most common presentation in our study. It was the presenting symptom in 57 patients out of 65 (87.7%). Twenty patients out of 65 patients had focal neurological deficits such as hemi-paresis, monoparesis and/or cranial nerve palsies. Another 20 patients presented with focal or generalized seizures. Ten female patients of them had venous infarction. Fifteen patients, 7 male and 8 female had papilledema with raised cerebrospinal fluid (CSF) pressure (Idiopathic Intracranial Hypertension like syndrome). Four male and ten females had papilledema with normal CSF pressure.

The D-dimer level was elevated in 42 patients (64.6%) versus 23 patients (35.4%) with normal level; $P < 0.018$. The normal serum D-dimer levels were seen in 23 patients, 5 males and 18 females, who were having CVT. However 42 patients (64.6%) had elevated D-dimer level. Three males and five females had slight elevation of D-dimer level 200-500 ngm/ml, 6 males and 12 females had moderate elevation and six males and ten females had very high level of D-dimer (1000-2000 ng/ml) (Table 1). Single sinus involvement was found in 49 patients (75.4%) (Lateral sinus: 22, Superior sagittal sinus: 18; and straight sinus: 9 patients). Multiple sinus involvement was found in 16 (24.6%) patients. Parenchymal lesions were found in 8 (12.3%) patients, venous hemorrhagic infarction in 5 (7.7%) patients and cerebral ischemic infarction in 3 (4.6%) patients. as showed in Table 1.

The sensitivity and specificity of predicting cerebral venous sinus thrombosis using D-dimer were 64.6% and 71.5%. Negative predictive value = 84.3%, positive predictive value =60% ($p < 0.05$). There was no significant correlation between degree of D-dimer level and number of sinuses involved ($r = 0.18$; $P < 0.108$).

Variables	M±SD, N (%)
Mean age (years)	32.40 ±8.95
Gender	
Female	42 (65.6)
Male	23 (34.4)
Clinical presentation at onset	
Headache	57 (87.7)
Focal neurological signs	20 (30.77)
Seizures	20 (30.77)
Papilledema with raised CSF pressure	15 (23.1)
Papilledema with normal CSF pressure	14 (21.53)
D-dimer level	
Normal	23 (35.4)
Mild	8 (12.3)
Moderate	18 (27.7)
Severe	16(24.6)
Site of CTV	
Single CTV	49 (75.4)
Multiple CTV	16 (24.6)
Focal brain lesion	
Venous hemorrhagic infarction	5 (7.7)
Cerebral ischemic infarction	3 (4.6)
*CSF: cerebrospinal fluid, CVT: cerebral venous thrombosis.	

Table 1: Demographic, clinical and Para clinical characteristics of CVT patients (N=65).

Discussion

CVT is known for its diverse clinical manifestations with unpredictable outcome. The clinical diagnosis of CVT is difficult and often a diagnostic challenge for the physicians [5,7]. The challenge for early diagnosis of CVT is patients who present with headaches that are not accompanied by any focal neurological abnormalities. Serum D-dimer level is often helpful for early diagnosis. There was lot of improvements in the D-dimer assays in the past 20 years of its use in CVT [6].

In the present study of 65 patients with CVT, 64.6% of the patients had elevated D-dimer level. Our result is in agreement with the previous result [1,8,9]. The percentage of normal D-dimer in our study (35.4%) is more than the average which is around (3%) in patients with recent CVT in previous studies [10-13]. The higher percentage of normal D-dimer level in our study compared to previous study could be explained by that the samples in our study were taken in the different stages of the disease. It is known that in acute deep venous

thrombosis of the legs, initially raised D-dimer level may decline to normal within the first week. If this is also the case in CVT, D-dimers level might be inversely correlated with duration of symptoms [14].

In the previous published studies [11-13] none of the patients with a recent CVT (<3- to 4-week duration) had normal D-dimer level, and only 2 of the 5 patients reported by Talbot et al. [10] had a recent CVT and a normal D-dimer. In our study, there are some patients, who were proved to have cerebral venous thrombosis, had normal serum D-dimer level and positive clinical signs and symptoms. Our results are in agreement with that of Lalive et al. [11] who studied 54 consecutive patients with headaches suggestive of CVT. D-dimer level were tested for all patients in the emergency room before brain CT or MRI was performed. Twelve of the 54 patients in their study had CVT, 10 of these 12 patients had high D- dimer level. The other two patients with confirmed CVT and normal D-dimer level had a history of chronic headache of >30 days' duration. We are also in agreement with the study of Isabelle that showed that 10% of patients with CVT had negative D-dimer [15]. So normal D-dimer level will not surely exclude CVT [16]. A negative D-dimer assay in the acute stage of acute headache make the diagnosis of CVT unlikely. However, when the degree of clinical suspicion for CVT is low because of isolated headache, particularly in the absence of cause other than oral contraceptive use, a negative D-dimer does not confidently rule out CVT. This contrasts with deep venous thrombosis, where a combination of low clinical probability and a negative D-dimer assay safely excludes the diagnosis [14].

Our study showed that the sensitivity and specificity of predicting cerebral venous sinus thrombosis using D-dimer were 64.6% and 71.5%. Negative predictive value=84.3%, positive predictive value=60% ($p<0.05$). This finding suggests the importance of d-dimer level as a useful biomarker for CVST prediction. These results are in partial agreement with the previous reports on CVT [13,17]. Gouda and Sabry found that the sensitivity of D-dimer test was 85.7% and the specificity was 85.5%. These previous studies collected blood sample in the acute stage, however we collected the blood samples in both acute and subacute stages of the illness. Our figures are less than that of Meg who showed that the sensitivity (94.1%), specificity (97.5%), positive predicting value (86.5%) and negative predicting value (98.9%) of d-dimer [18]. The difference between our results and that of Meg can be explained by the difference of methodology between both studies. Meg study was prospective and involved only patients who are younger than 45 years and their symptom onset within seven-days.

Our results did not found any significant correlation between degree of D-dimer level and number of sinuses involved. This result is in disagreement with previous results [10,13,17] who found significant association between limited sinus involvement and a negative D-dimer assay.

Limitations of this Study

The retrospective design is a limitation of this study, however, missing patients are unlikely because the used data base was recorded carefully. The serum D-dimer tests were done at different time of the illness, in some cases before diagnosis and in some patients after the radiological diagnosis. There are no case control studies. The patients also were different age groups.

Conclusion

Raised D-dimer level is often helpful for early diagnosis of CVT. The D-dimer estimation in the appropriate time, can avoid more costly imaging studies and this simple blood test is less invasive. The Physician must aware of D-dimer level is raised in a variety of other conditions, other than cerebral venous thrombosis and level varies with duration of symptoms in CVT.

References

1. Bousser MG (2000) Cerebral venous thrombosis: diagnosis and management. *J Neurol* 247: 252-258.
2. Fink JN, McAuley DL (2001) Cerebral venous sinus thrombosis: a diagnostic challenge. *Intern Med J* 31: 384-390.
3. Tanislav C, Siekmann R, Sieweke N, Allendorfer J, Pabst W, et al. (2011) Cerebral vein thrombosis: clinical manifestation and diagnosis. *BMC Neurol* 11: 69.
4. Bentley JN, Figueroa RE, Vender JR (2009) From presentation to follow-up: diagnosis and treatment of cerebral venous thrombosis. *Neurosurg Focus* 27: E4.
5. Al-Hashel JY, John JK, Vembu P (2014) Venous thrombosis of the brain. Retrospective review of 110 patients in Kuwait. *Neurosciences (Riyadh)* 19: 111-117.
6. Righini M, Perrier A, De Moerloose P, Bounameaux H (2008) D-Dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost* 6: 1059-1071.
7. Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG (2005) Headache as the only neurological sign of cerebral venous thrombosis: a series of 17 cases. *J Neurol Neurosurg Psychiatry* 76: 1084-1087.
8. Cakmak S, Derex L, Berruyer M, Nighoghossian N, Philippeau F, et al. (2003) Cerebral venous thrombosis: clinical outcome and systematic screening of prothrombotic factors. *Neurology* 60: 1175-1178.
9. Misra UK, Kalita J, Bansal V (2009) D-dimer is useful in the diagnosis of cortical venous sinus thrombosis. *Neurol India* 57: 50-54.
10. Talbot K, Wright M, Keeling D (2002) Normal d-dimer levels do not exclude the diagnosis of cerebral venous sinus thrombosis. *J Neurol* 249: 1603-1604.
11. Tardy B, Tardy-Poncet B, Viallon A, Piot M, Garnier P, et al. (2002) D-dimer levels in patients with suspected acute cerebral venous thrombosis. *Am J Med* 113: 238-241.
12. Lalive PH, de Moerloose P, Lovblad K, Sarasin FP, Mermillod B, et al. (2003) Is measurement of D-dimer useful in the diagnosis of cerebral venous thrombosis? *Neurology* 61: 1057-1060.
13. Kosinski CM, Mull M, Schwarz M, Koch B, Biniek R, et al. (2004) Do normal D-dimer levels reliably exclude cerebral sinus thrombosis? *Stroke* 35: 2820-2825.
14. Fancher TL, White RH, Kravitz RL (2004) Combined use of rapid D-dimer testing and estimation of clinical probability in the diagnosis of deep vein thrombosis: systematic review. *BMJ* 329: 821.
15. Crassard I, Soria C, Tzourio C, Woimant F, Drouet L, et al. (2005) A negative D-dimer assay does not rule out cerebral venous thrombosis: a series of seventy-three patients. *Stroke* 36: 1716-1719.
16. Reber G, Bounameaux H, Perrier A, De Moerloose P (2004) A new rapid point-of-care D-dimer enzyme-linked immunosorbent assay (Stratus CS D-dimer) for the exclusion of venous thromboembolism. *Blood Coagul Fibrinolysis* 15: 435-438.
17. Gouda T, Sabry HM (2010) Evaluation of Plasma D-Dimer Assay as A Diagnostic Biomarker for Cerebral Venous Thrombosis. *Egypt J Neurol Psychiat Neurosurg* 47: 331-336. 18.
18. Meng R, Wang X, Hussain M, Dornbos III D, Meng L, et al. (2014) Evaluation of plasma d-dimer plus fibrinogen in predicting acute CVST. *Int J Stroke* 9: 166-173.