ORIGINAL ARTICLE

To find out the Interrelationship of Factor X1 and D-dimer as a Marker of Increased Risk of Deep Venous Thrombosis in Dengue Haemorrhagic Fever

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ABSTRACT

Background: Infectious diseases pose a serious hazard to human health security especially in the developing countries because of inadequate resources to fight them. These pathogens are distinguished by a special mode of pathogenesis and, some time has a vast host range.

Aim: To find the interrelationship of factor X1 and D-dimer as a marker of increased risk of deep venous thrombosis in dengue haemorrhagic fever.

Methods: The study included 81 confirmed patients of dengue hemorrhagic fever with age greater than 18 years. The data was collected by the proforma prepared for the study for variables including age, D dimmer coagulation factor XI. The patients with dengue hemorrhagic fever were divided in four grades according to WHO criteria.

Results: Majority of dengue patients were of age less than 30 years. Other patients have an age range of 30-45 yrs and 45–60 yrs. There were 53(65.4%) cases belong to DHF-I, 20(24.6%) cases belong to DHF-II, and 8(9.88%) cases belong to DHF-III, and DHF-IV. 55(67.9%) were male and 26(32.1%) were female.

The factor XI activity increased in 12 cases of DHF grade II, 8 cases of grade III & IV, while it was normal in DHF I patients. The D dimmer levels were also significantly raised among group DHF-I patients had levels <700 in DHF-II were 40%, with a range of 200- 700 and 60% with a range of 700-1200. In DHF-III 62.5% had a range of 700-1200 and 37.5% had > 1200.

Conclusion: It is concluded that direct interrelationship of factor X1 and D-dimer may be a marker of deep venous thrombosis in dengue haemorrhagic fever

Keywords: Factor X1, D-dimer, Dengue fever, Deep venous thrombosis.

INTRODUCTION

Dengue infection can demonstrate as febrile illness with thrombocytopenia, dengue haemorrhagic fever and dengue shock syndrome. Dengue infection can be either asymptomatic, or progress to involve hemorrhagic manifestations with shock[1]. Dengue infection is caused by a virus belongs to genus Flavivirus. Due to multiple serotypes of dengue virus, the epidemic is periodic[2].

Incidences of rising fatal viral infections have considerably affected human health. The frequent outbreak of dengue fever is observed in both tropical and sub-tropical regions[3]. Dengue has become a worldwide issue, widespread in more than 100 countries of South East Asia, Africa, America, Eastern Mediterranean and Western Pacific regions[4]. In Pakistan more than 15,000 patients were observed in Lahore only. Due to dengue shock and internal bleeding there is increased mortality rate in dengue patients[5].

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Hemorrhagic manifestations are known with dengue but thrombotic complications are uncommon[1] (Roy 2013). These Thrombotic events or complications affected big veins in dengue fever[6]. Human coagulation factor XI also called as plasma thromboplastin may activate blood coagulation or intrinsic pathway[7]. Factor XI have a role in clot formation and also take part in the stoppage of lysis of clot, which help in managing thromboembolism[8]. Increased levels of factor XI may enhance the chances of arterial and venous thrombosis[9].

Imbalance between pro-coagulant and anticoagulant factors enhances the chances of deep venous thrombosis. In the last steps of blood coagulation there is an activation of prothrombin, tracked by fibrin formation and its following degradation. D-dimers are exclusive fibrin splitting protein (FSPs) formed when fibin is lysed by plasmin. Compare to FSPs which show only the plasmin activation, d-dimers show the commencement of plasmin and thrombin and are precise for coagulation and fibrinolysis. Study reported that increase level of D-dimer is related with an increased the chances of arterial and venous thrombosis[10].

Level of D-dimer is therefore a sign of coagulation activity as it is observed after fibrinolysis. It is also reported as a rule-out test for venous thromboembolism[11]. concentration of D-dimer level aid in detecting the blood disorder and thrombosis associated with intravascular coagulation[12]. Additionally it is demonstrated that the course of thromboembolism is directly linked with the presence or absence of D-dimer test[13].

Thrombotic events have not been widely reported, in spite of the wide series of increased procoagulant activity during dengue illness. Study is therefore designed to find the interrelationship of factor X1 and D-dimer as a marker of increased chance of deep venous thrombosis in dengue haemorrhagic fever

SUBJECT AND METHODS

This was a cross sectional analytical study. The study included 81 confirmed patients of dengue hemorrhagic fever, more than 18 years old who agreed to participate in study and fulfill inclusion criteria i.e. blood culture negative and IgM or NS-1 positive. Dengue patients with IgG positive and bacterial culture positive were excluded from the study. The data was collected by the proforma prepared for the study for variables including age, D dimmer coagulation factor XI. The DHF patients divided in four grades according to WHO criteria. Level of D-Dimer was estimated by Latex Agglutination Slide Test. Level of factor X1 was estimated by standard kit using ELISA techniques.

Table 1: Age distribution of patients with dengue fever (n=81)

Age (years)	Frequency	%age
≤ 30	34	42.0
31 – 45	23	28.4
46 – 60	24	29.6

Table 2: Distribution of factor X1 for patients with dengue fever (n=81)

Factor X1	Frequency	%age
≤ 5.0	3	3.7
5.1 - 10.0	55	67.9
10.1 - 15.0	12	14.8
15.1+	11	13.6

Table 3: Distribution of D Dimer level for patients with dengue fever (n=81)

D Dimer	n	%age
≤ 200	2	2.5
201 – 700	59	72.8
701 - 1200	17	21.0
1201+	3	3.7

RESULTS

There were 55(67.9%) males and the most of the patients (42%) were with age < 30 years, and others were with age range 30-45 and 45–60 years (Table 1).

About 53(65.4%) cases belong to DHF-I, 20(24.6%) cases belong to DHF-II, and 8(9.88%) cases belong to DHF-III, and DHF-IV. 55 (67.9%) were male and 26(32.1%) were female.

The status of factor XI was different in all groups based on grade and showed significant difference (p value <0.001). The factor XI activity increased in 12 cases of DHF grade II, 8 cases of grade III & IV, while it was normal in DHF I patients (Table 2).

The D dimmer levels were also significantly raised among group DHF-I patients had levels <700 in DHF-II were 40%, with a range of 200- 700 and 60% with a range of 700-1200. In DHF-III 62.5% had a range of 700-1200 and 37.5% had > 1200. This shows a highly significant difference (p value <0.001) (Table 3).

DISCUSSION

Increase rate of infectious diseases pose a serious hazard to human health security especially in the developing countries because of inadequate resources to fight them. These pathogens are distinguished by a special mode of pathogenesis and, some time has a vast host range. Pakistan has suffered a great deal from infectious diseases such as dengue, Crimean-Congo fever, hepatitis, measles, and polio from few decades. Factors like climate changes, environmental pollution, global warming, and failure of biodiversity are related with these diseases and result in the appearance and reemergence of infections[5].

We observed that most of the dengue patients were of <30 years. Our study is in line with a study who reported that seroprevalence of antibodies related with dengue is high and frequent in young age.[13] In addition it is suggested increase occurrence of Dengue disease in brood to adults is due to the enhance permeability of vessels. This may enhance the incidence of dengue[14].

We found that 65.4% cases of dengue related to DHF1 class, 24.6% cases of dengue related to class DHF11 and 9.88% cases of dengue related to class DHF 111 and DHF 1V. Our study is in line with the observation of study who also noted that many cases of DHF were of DHF grade I & II, and a few patients with grade III,IV[15]. It is suggested that changes in genotype of dengue, the strains and structure of dengue viruses may relate with pathogenesis and also increase the severity of disease[16].

Present study observed an increased level of D-dimer and factor X11 in cases with Dengue hemorrhagic fever 1 compared to type 11, 111 & 1V.

Several systems may take part in the pathogenesis of bleeding due to dengue disease which may include thrombocytopenia, vasculopathy and dissiminated coagulopathy in vessels. It is reported that fibrinolytic system activation may play a role in vascular endothelial growth factor synthesis in the cases of dengue fever may be accountable for disease severity [17]. It is observed that D-dimer indicate the coagulation system activation due to the damage of cross-linked fibrin and shows clot formation and break down relate with severity of dengue[18].

We found that the value of coagulation factor X1 was high in cases of DHF II and IV. Factor XI was proposed to take part in initiating the coagulation, as a part of the contact system. It is hypothesized that increase value of factor XI is a source of thrombosis via continued production of thrombin, which prevent proteolysis of fibrin[19]. Other study reported that dengue patients with increase values of Factor XI, increased the chances of venous and arterial thrombosis. Data of study reported that a combined effect of host and viral factors may alter the balance of fibrinolysis and coagulation to bleeding in patients with dengue fever[20].

According to a study, D-dimer was weakly related with factor IX[21] (Cushman 2009). A genetic study prove that variation in the factor XI gene was associated with risk of deep vein thrombosis and pulmonary embolism[22]. A study reported that coagulation intrinsic pathway involve factor XI pathway and enhances values of -dimer are engaged in pathogenesis of coagulation disarray in DHF[23]. It is thought that the cause of this relationship is the increased formation of thrombin and stability of fibrin related to increased levels of factor [XI8]

Limitation: Our knowledge about the variability of coagulation factors within person is limited, so that levels estimated before a venous thromboembolism may not be related with the time of event. This could direct to underestimation of relationship and it may be possible that the relationship may be larger than we observed.

CONCLUSION

It is concluded that direct interrelationship of factor X1 and D-dimer may be a marker of deep venous thrombosis in dengue haemorrhagic fever. However more work is needed on the relationship of D-dimer and factor X1 in increasing the risk of deep vain thrombosis to reach a better conclusion.

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