

A Study of Incidence and Significance of Coagulopathy among Dengue Patients Admitted in a Tertiary Care Hospital at Tirunelveli, Tamil Nadu, India

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ABSTRACT

Introduction: Dengue fever, a vector borne disease has become endemic in India which creates a major health problem. Over 2.5 billion people (40% of world's population) are now at risk from dengue infection. It is a fatal infection with more mortality among children especially among infants. Major causes of mortality among dengue patients are shock and coagulopathy.

Aim: To know about the significance of coagulopathy in dengue patients and to emphasise its early correction to prevent mortality.

Materials and Methods: All dengue patients admitted during the study period of six months (March 2016 to August 2016) were included. These patients were graded into 4 categories according to the severity of clinical findings as per WHO guidelines. Blood

samples were collected for Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT) and platelet count. Coagulopathy was considered when APTT values were >41 sec.

Results: Out of 128 patients studied, 92 patients (71.88%) were classified as grade 1 and 2 dengue. Among them 18 patients (19.5%) had coagulopathy. Among 36 patients (28.2%) who were classified as grade 3 and 4 dengue, 31 patients (86.1%) had coagulopathy. This shows that coagulopathy was more among grade 3 and 4 dengue patients.

Conclusion: Early correction of coagulation abnormalities even before the child develops significant bleeding in Grade 3 and 4 dengue patients helps in preventing major bleeding and thus mortality in those children.

Keywords: Bleeding, Cytokine tsunami, Vascular damage

INTRODUCTION

Dengue fever is a vector borne disease. It is the most prevalent Arbovirus illness in the world; more than 100 million people are infected annually. Among them 2,50,000 cases result in dengue haemorrhagic fever causing approximately 25000 deaths annually [1]. Since 1990s, epidemics of dengue have become more frequent in India (Incidence 6.34/Million) [2]. Dengue is caused by 4 antigenically related but distinct viruses DEN1, DEN2, DEN3 and DEN4. Infection with an individual dengue virus serotype confers lifelong protection against that serotype. Since cross protection between serotypes is absent, multiple infections with different serotypes occur commonly [3]. In 1981, in Cuba, Dengue 2 virus infected a population previously exposed to Dengue 1 virus between 1977 and 1980 leading to an epidemic of more than 1,00,000 cases [4]. It can either be benign or fatal (Dengue haemorrhagic fever) characterised by increased capillary permeability leading to shock and abnormalities of coagulation leading to occult and overt bleeding, that leads to death. Shock could be identified early by a meticulous cardiopulmonary cerebral assessment of the patient [5]. But early coagulation abnormalities are not evident until the child develops any bleeding episode. In some dengue patients, by the time they manifest with significant bleeding they enter into an irreversible stage which results in mortality. Repeated laboratory investigations and careful monitoring is essential to trace the clinical progress of the disease. A study by Kannan A et al., showed a prevalence of 22.35% of coagulopathy in dengue patients, also proved a significant correlation between bleeding manifestations and abnormal APTT values [6]. It also showed that as platelet count decreases tendency for coagulopathy in turn is increased.

NS1 antigen can be detected from dengue patients in first 5 days of fever. About 80% of patients have detectable titers of IgM antibodies by day 5 of illness and 99% by day 10. IgG antibodies rise quickly

and peak at about two weeks post-infection and then decline slowly over 3 to 6 months [7]. Treatment is meticulous monitoring and fluid resuscitation. Drugs like NSAIDs and steroids have no role. In some patients, Intravenous immunoglobulin has been found to have some beneficial effects [8]. Present study was focused to find out the significance of coagulopathy and its outcome in dengue patients in Tirunelveli as there was no such region specific study.

MATERIALS AND METHODS

This study was designed as a cross-sectional study, done for a period of six months between March 2016 to August 2016 among the dengue patients admitted in Tirunelveli Medical College Hospital, Tirunelveli, Tamil Nadu, India. Proper clearance from Institutional Ethics Committee was obtained prior to the study (134/PAED/IEC/2016, dated: 17/02/2016). Children below 14 years (admitted in Paediatrics category) with dengue fever were included in this study after getting consent from their parents.

Inclusion Criteria

All dengue seropositive (Dengue NS1 ELISA panbiotech kits were used for finding sero reaction) admitted cases with less than 14 years of age; Sero-positive elsewhere and referred to our centre as well as found to be sero-positive while on management at our centre were included after getting consent from their parents.

Exclusion Criteria

All dengue sero-negative cases, children with liver disorders, children with history of congenital bleeding disorders.

Cases admitted during the study period were all included in the study. Upon admission, Clinical manifestations of bleeding like melena, haematemesis, epistaxis, ecchymosis patches etc., were looked for and Blood investigations-PT, APTT and Platelet count

were done on daily basis from day of admission till the child entered into the convalescence phase.

Samples were collected under strict aseptic precautions, blood samples were collected from peripheral veins and sent in Blue Citrate tubes and Lavendar EDTA tubes and analysed in Stago Coagulation analyser (PT, APTT) and SYSMEX cell counter (CBC- Platelet count), in case of low values, manual platelet counting was done. Based on the coagulopathy results, samples were grouped into 4 categories;

Grade 1- Thrombocytopenia, positive tourniquet test, absence of spontaneous bleeding;

Grade 2- Thrombocytopenia, positive tourniquet test, Presence of spontaneous bleeding (Mild);

Grade 3- Thrombocytopenia, positive tourniquet test, significant bleeding with circulatory failure;

Grade 4- Thrombocytopenia, positive tourniquet test, significant bleeding with profound shock and features of organ-hypo perfusion.

Coagulopathy was considered when APTT values were more than 41 seconds, as the commonest coagulation abnormality in dengue fever is increased APTT.

RESULTS

Out of 128 patients included in this study, 96 were having oral temperature greater than or equal to 102°F, 32 were having temperature range above 100°F but lesser than 102°F on admission. At the end of 3rd day of admission, 78 were having temperature greater than or equal to 102°F, 50 were having temperature range above 100°F but not more than 102°F. At the end of 5th day of admission, 104 were having temperature greater than or equal to 101.5°F, 24 were having temperature range above 100°F but not more than 101.5°F and at the end of 7th day of admission, 119 were having temperature greater than or equal to 99°F but lesser than 99.5°F, 09 were having temperature range above 98.5°F but not more than 99°F.

Children having only warning signs with no/minor bleeds were classified as Grade 1 and Grade 2 dengue patients. Among 92 (71.88%) patients graded as Grade 1 and Grade 2, 18 patients had coagulopathy (19.56%). Remaining 36 (28.2%) patients had evidence of circulatory collapse/significant haemorrhages and were classified as Grade 3 and Grade 4 dengue patients; among those 36 patients 31 of them (86.1%) had coagulopathy. This shows that prevalence of coagulopathy is more in Grade 3 and Grade 4 dengue patients.

Among the Grade 1 and Grade 2 dengue patients with prolonged APTT (18 patients), 11 patients were asymptomatic and remaining 7 patients had minor bleeding manifestations, which didn't require transfusion [Table/Fig-1].

Dengue patients grade 1 and 2	APTT <41 sec	APTT >41 sec	Total (92)
With bleeding	Nil	7 cases (38.9%)	07
Without bleeding	74 cases	11 cases (61.1%)	85

[Table/Fig-1]: Dengue patients grade 1 and grade 2 - APTT values.

Among the Grade 1 and Grade 2 dengue patients with abnormal PT (07 patients), 05 patients were asymptomatic and remaining 02 patients had minor bleeding manifestations, which didn't require transfusion. Abnormal PT values among Grade 1 and Grade 2 dengue patients were seen only around 7.5%, it gives an impression that PT prolongation doesn't correlate much with bleeding in these patients [Table/Fig-2].

Dengue patients grade 1 and 2	PT <12.5 sec	PT >12.5 sec	Total (92)
With bleeding	Nil	02 cases (2.17%)	02
Without bleeding	85 cases (92.3%)	05 cases (5.4%)	90

[Table/Fig-2]: Dengue patients grade 1 and 2-prothrombin time values.

Among the Grade 3 and Grade 4 dengue patients with coagulopathy (Prolonged APTT-31 patients), 29 patients (93.9%) had significant bleeding and was treated with blood products, other 2 patients were asymptomatic. Among the 29 patients, 2 patients who didn't have bleeding episodes in their early phase but with abnormal coagulation profile, had profound bleeding in the terminal phase of disease which couldn't be controlled with blood products and led to mortality. Prothrombin time values were prolonged in only 6 patients, among them only 2 had significant bleeding. Among the 28 patients who had significant bleeding PT values were normal [Table/Fig-3,4].

Dengue patients grade 3 and 4	APTT <41 sec	APTT >41 sec	Total (36)
With bleeding	1 Case (20%)	29 Cases (93.9%)	30
Without bleeding	4 Cases (80%)	2 Cases (6.45 %)	06

[Table/Fig-3]: Dengue patients grade 3 and grade 4- APTT values.

Dengue patients grade 3 and 4	PT <12.5 sec	PT >12.5 sec	Total (36)
With bleeding	28 cases (77.7%)	2 Cases (5.5%)	30
Without bleeding	2 cases (5.5%)	4 Cases (11.2%)	06

[Table/Fig-4]: Dengue patients grade 3 and 4- prothrombin time values.

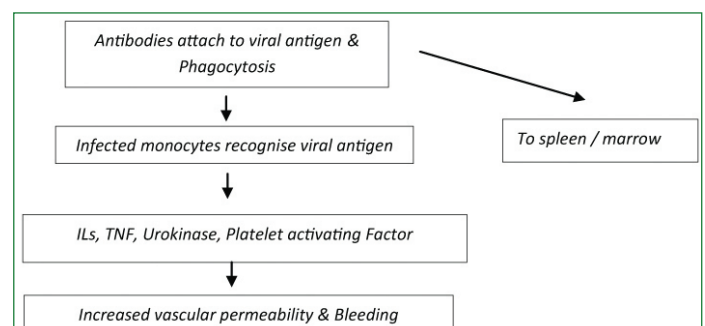
This indicates that coagulopathy that occurs in Grade 1 and 2 dengue patients is of less significance and coagulopathy in Grade 3 and 4 dengue patients have more impact and is fatal if not treated in time. The platelet count was less than 1.5 lac in 36 patients of grade 3 and 4 [Table/Fig-5]. This study shows that there was significant correlation between coagulopathy and bleeding manifestations especially in Grade 3 and 4 dengue patients.

Dengue patients	Platelet count <1.5 Lac	Platelet count >1.5 Lac
Grade 1 and 2	78 patients (84.7%)	14 patients (15.2%)
Grade 3 and 4	36 patients (100%)	Nil

[Table/Fig-5]: Platelet count in dengue patients.

DISCUSSION

The two major pathways for dengue haemorrhagic fever are vasculopathy and coagulopathy. Both of these are stimulated by the enhancement of immune activation of the patient. This leads to rush of cytokines and chemokines which is called as "CYTOKINE TSUNAMI", which leads to vasculopathy by enhancing the permeability of endothelial cells and producing anti-endothelial cell antibodies [9,10]. It also leads to coagulopathy by stimulating the blood clotting and fibrinolytic systems. The commonest coagulation abnormalities are increased APTT, decreased fibrinogen, increased FDP and D-dimer, enhanced fibrinolytic activity and release of heparan sulfate/chondroitin sulfate from the glycocalyx [Table/Fig-6].



[Table/Fig-6]: Mechanism of vasculopathy.

Raised APTT values and its correlation with dengue haemorrhagic fever is supported by Kannan A et al., Huang YH et al., Liu JW et al., Budastra N et al., Chuansumrit A et al., Chuang YC et al., Kulasinghe S et al., studies [6,11-16]. Studies further add indicate that prothrombin time can be a lesser reliable predictor. Also, as

platelet count decreases, the tendency for coagulopathy increases. Results in this study is contrary to findings by Hassan J et al., Wills BA et al., which showed no positive correlation between bleeding and coagulation abnormalities in dengue patients [17,18]. All these studies show only the incidence of coagulopathy among dengue patients. They do not specify their significance among the different grades of dengue fever. This study finds more incidence of coagulopathy in grade 3 and 4 dengue patients than in Grade 1 and 2 dengue patients. Hence early treatment of coagulation abnormalities in Grade 3 and 4 dengue patients will reduce the mortality among them.

Limitation(s)

The major limitation of study was the small sample size and cases of each grade cannot be further categorised due to limited availability of history and clinical data.

CONCLUSION(S)

Dengue haemorrhagic fever has become an endemic disease and mortality due to this viral infection is high especially when there is delay in treatment. The major causes for mortality such as shock and bleeding has to be addressed promptly. Some patients present with coagulation abnormalities (Lab), but without significant bleeding manifestations. They start to bleed at terminal stages of the disease and by that time it becomes refractory to all modalities of treatment. Such cases pose a great threat to the treating physician. This study shows the significance of coagulation abnormalities in Grade 3 and 4 dengue patients and the importance of early correction of coagulation abnormalities even before the child develops significant bleeding. This helps in preventing major bleeding and thus mortality in children admitted with dengue infection.

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