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Original Research Article

Clinical profile of dengue fever with severe thrombocytopenia and its complications: a retrospective study at a tertiary care hospital in South India

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ABSTRACT

Background: Dengue haemorrhagic fever is a potentially lethal illness that is universally prevalent in the tropics and has become a major health concern globally in recent decades. The clinical manifestation of dengue infection varies from asymptomatic to severe life threatening illness in the form of DHF/DSS. Dengue haemorrhagic fever or DSS may be fatal in 40% to 50% of untreated patients. A hallmark of dengue infection is severe thrombocytopenia which causes concern for the patients and treating doctors. The objective of this study was to correlate clinical profile during the evolution of dengue fever with severe thrombocytopenia (platelets <10,000/mm^3), and comparing frequencies between the different clinical forms in order to predict the severity of the disease. The present study includes 40 individuals who were found to be seropositive with the detection of NS1Ag, IgM and IgG antibodies for dengue infection with severe thrombocytopenia. Early diagnosis and monitoring is largely dependent on haematological parameters. As no specific antiviral therapy is available, supportive therapy is of utmost importance.
Methods: This is an observational, descriptive and retrospective study of 40 patients with clinical and serological diagnosis of dengue fever with severe thrombocytopenia (platelets<10,000/mm3), in the period from August 2015 to September 2016, who were admitted in a tertiary care hospital in South India. ELISA was performed for the detection of dengue NS1, Ig M and Ig G, haematological parameters by automated analyzer and peripheral smear, coagulation profile analysis were done.
Results: Out of 40 cases with severe thrombocytopenia, 50% of the patients had classical dengue fever, 30% cases had DHF with bleeding manifests and 20% cases with DHF plasma leakage signs and 5% lead to DSS. There was lack of association studied between severe thrombocytopenia and bleeding manifestations as p value<0.065 was insignificant. However, the risk of complications increased with decreasing platelet counts in the present study.
Conclusions: Thrombocytopenia was most predominant haematological discrepancy. There was no predilection for any age group or gender for thrombocytopenia or bleeding among the dengue patients. The results were relevant in assessing the severity of infection and can help by enabling the adaptation of the therapeutic conduct to the needs of individual patients.

Keywords: Bleeding, Dengue, Dengue hemorrhagic fever, Platelet count, Seropositive, Thrombocytopenia

INTRODUCTION

Dengue viral infection is currently amongst the most critical arthropod-borne infections from the public health view point. Concerning the incidence of dengue all over the world, the graph has risen up noticeably in recent decades and over 40% of the world's population is now at risk from dengue. It has been estimated that there may be 50 to 100 million dengue infections globally per year (World Health Organization (WHO), 2013).[1,2]

Four distinct serotypes of dengue virus are known to cause the disease (DEN-1, DEN-2, DEN-3 and DEN-4) and Aedes aegypti mosquito is the primary vector. Dengue fever is a severe, flu-like sickness in which high grade fever (104°F) is accompanied by severe headache, retrorbital pain, joint pains, vomiting and rashes on body, but is rarely fatal. However, severe dengue (previously referred as Dengue Haemorrhagic Fever) is a potentially lethal complication characterized by plasma leaking, fluid accumulation, severe bleeding, or organ impairment (WHO, 2013).[1]

Severe dengue infection is characterized by a 'leakage phase' (or critical phase) usually lasting 48 hours following an initial febrile phase. During the leakage phase, an increase in capillary permeability leads to extravasation of fluid and haemo-concentration. During the latter stages of febrile phase and early leakage phase (or even later), there is a steady drop in platelet count. At occasions, it can drop as low as 3000/µl in previously healthy individuals (normal platelet count in a healthy adult: 150,000-400,000/ µl).[3] The exact mechanism of this drop is unclear but presumed to be immunological.[4] The low platelet count leaves the patient at a significant risk of spontaneous bleeding. Thrombocytopenia in dengue infection raises concerns about bleeding risk.

WHO classification is defined as follows: Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS). The classical DF defined by the presence of acute febrile illness and ⩾2 of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia, rash. DHF was defined as fever with thrombocytopenia, any hemorrhagic manifestation e.g., positive tourniquet test, petechiae; purpura/ecchymosis; gum bleeding; or vaginal bleeding and evidence of DHF with plasma leakage (⩾20% hematocrit or by the presence of pleural or abdominal effusion or hypoalbuminemia). DSS was defined by rapid and weak pulse with narrow pulse pressure (<20mm Hg), hypotension and respiratory distress.[1]

Patients with dengue with warning signs should be managed with normal saline, at the rate 5-7 ml/kg/h for first 1-2 hours, 2-3 ml/kg/hours according to the clinical response. Treatment of hemorrhagic complications includes whole blood or packed cell transfusions. Platelet or fresh frozen plasma infusions should be given only if bleeding is not being controlled by whole blood transfusions.[5]

During the early stages of the disease, virus isolation, nucleic acid, or antigen detection can be used to diagnose the infection. Antibody response to infection differs according to the immune status of the host.[4]

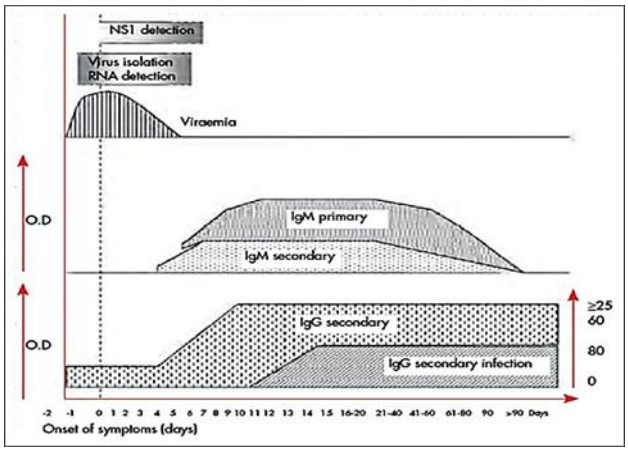

Figure 1: Timeline of primary and secondary infection and detection with diagnostic methods.

The decreasing platelet counts have found to predict the severity of the disease. There is need to study and know its adverse outcomes with increasing severity of low platelet count in this rapidly spreading disease that can be controlled to a great extent. In addition, the bleeding severity has not been well studied in India, especially in relation to platelet function. Not much work has been done on this parameter as well as non-hemorrhagic manifestations with low platelet count related to dengue fever. Hence, objective of the study, conducted to assess the severity of thrombocytopenia in seropositive dengue patients and to evaluate association of low platelet count with hemorrhagic and non-hemorrhagic manifestations which can be of great help in limiting morbidity and mortality associated with dengue fever. Thereby, this study also includes the effect of leukopenia on complications of dengue cases with severe thrombocytopenia.

METHODS

The present study was conducted in tertiary care hospital, Vijayawada, from the period of August 2015 till September 2016. Evaluation of Blood samples collected from 40 patients with NS 1 Antigen, IgM, IgG antibodies positivity experiencing febrile illness, clinically consistent with dengue infection was done in all these cases. Clinical findings and laboratory tests (including hematocrit and platelets counts) were registered. The association between severe thrombocytopenia and the presence of complications, such as hemorrhagic manifestations (positive tourniquet test, petechiae, ecchymoses, bleeding from gums, epistaxis, hematemesis, hematuria and menorrhagia) and signs of

plasma leakage (pleural effusions and haemoconcentration), were evaluated. Samples were processed within 6 hours of the initial sample collection and Platelet counts were performed on whole blood of those individuals who were found seropositive for dengue infection.

Statistical analysis

The data was entered and analyzed by using Frequency and percentages were calculated for qualitative variables like IgM positivity, age group, low platelets counts with hemorrhagic and non-hemorrhagic complications were expressed. The relationship between the frequencies of the clinical parameter and complications was analysed after constructing a 2x2 table and applying the statistical test of significance. Chi square tests were used to observe the association between qualitative variables. A p-value ≤ 0.05 was considered as statistical significant.

RESULTS

A total of 40 patients, diagnosed as dengue based on NS1, IgM and IgG positivity and haematological parameters with LFT and coagulation profile were done. Amongst them 65% (26) were males and 35% (14) were females with ratio of 1.8:1. The mean age obtained was 40.47 years and with maximum 65 years and minimum 20 years. The cases in the age group of (20-40) were 20 patients; (40-60) were 18 and (>60) were 2 patients.

On classifying dengue cases by WHO criteria, 50% (20 cases) had classical dengue fever with polyarthralgia, dengue hemorrhagic fever with bleeding manifestations were 30% (12 cases), and DHF with signs of plasma leakage were 20% (8 patients) and 5% (2 cases) complicated into dengue shock syndrome. Of 40 seropositive patients, 35% (14 cases) had severely low platelet count i.e. <5000 cells/mm^3, and 37.5% (15 cases) had leucopenia too.

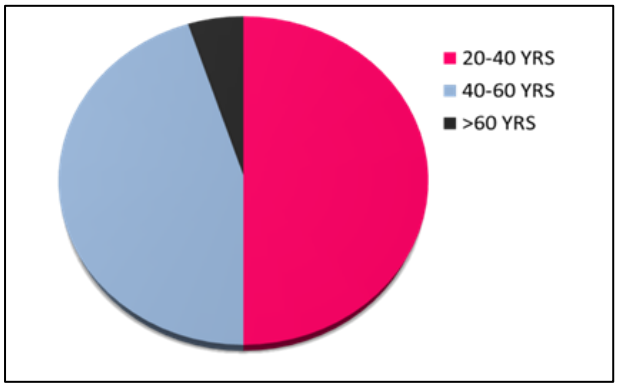

Figure 3: Frequency distribution of age.

Bleeding manifestations were equally common in all age groups. Severe thrombocytopenia association with hemorrhagic manifestations (Chi square = 3.3956; p <0.0654) and signs of plasma leakage were statistically insignificant. Thereby, the study implies that the increasing severity of thrombocytopenia is unrelated to both hemorrhagic and non-hemorrhagic manifestations of dengue.

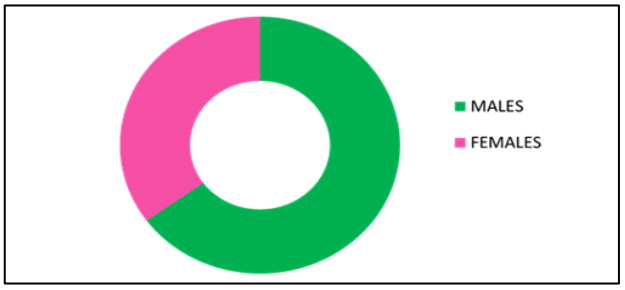

Figure 4: Frequency distribution of sex.

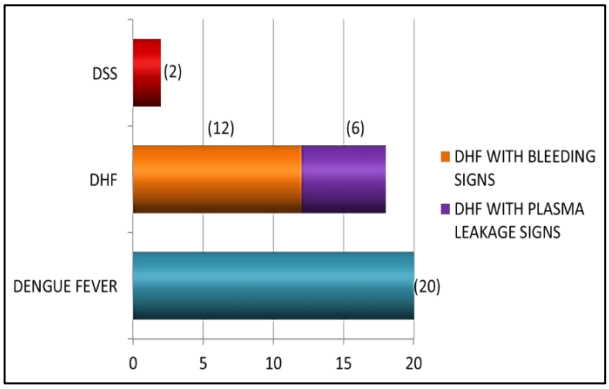

Figure 5: Frequency distribution of dengue fever classification.

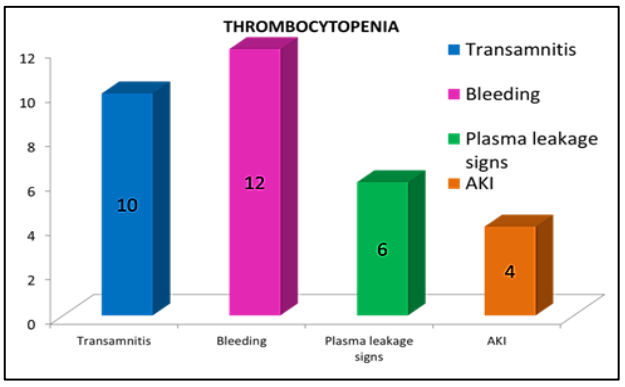

Figure 6: Frequency distribution of severe thrombocytopenia with risk of complications.

In our study, 15 patients had leukopenia and the correlation between leucopenia and complications of dengue fever with severe thrombocytopenia were studied. Leukopenia with thrombocytopenia showed a positive correlation but was not statistically significant (Chi square 0.1238; p< 0.312). This suggests that leucopenia may not have any relation with clinical outcomes of dengue fever with severe thrombocytopenia.

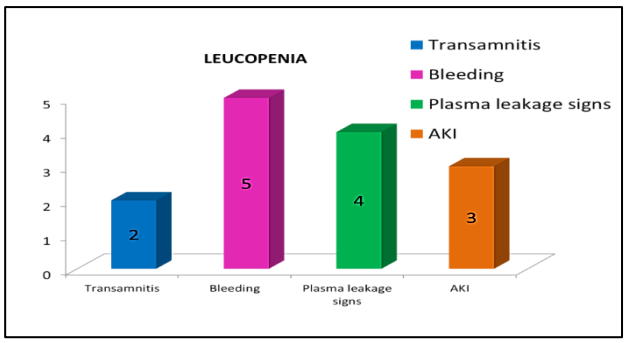

Figure 7: Frequency distribution of leucopenia with risk of complications.

In this study, varied complications were known to occur in patients having dengue with thrombocytopenia during its clinical course. Of the 40 patients in this study, 25% (10 cases) had transaminitis, 30% (12 cases) had hemorrhagic manifestations, signs of plasma leakage observed in 15% (6 cases), acute kidney injury in 10% (4 cases). The associations between severe thrombocytopenia and the complications of dengue were confirmed where there was a negative correlation between platelet count and complications rate (Chi square = 7.3632; $p < 0.025$). This indicates that lower the platelet count, more are the complications. There was no predilection for any gender among the patients who developed complications.

Table 1: Risks of complication rate in classified criteria of dengue fever.

No. of complications (AKI, bleeding, transaminitis, plasma leakage)	Classical dengue fever (20 cases)	DHF with bleeding manifestations (12 cases)	DHF with signs of plasma leakage (8 cases)
0 (nil)	4	0	0
1	13	10	2
2	3	2	6

DISCUSSION

Dengue fever (DF) with its severe manifestations such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) has emerged as a major public health problem of international concern.

Of the total 40 cases in our study, the age group of (20-40) were 50% ; (40-60) were 45% and (>60) were 5% with males 65% and females 35% with ratio of 1.8:1.These findings were comparable with a study conducted by Qiu FX et al, in which 81% patients more than 20 years with 70 (70%) patients were male and 30 (30%) were females with a male to female ratio of 2:1.[6] These findings were comparable with a study conducted by Agarwal et al in which male to female ratio was 1.9:1.[7] WHO defined severe dengue as presence of one or more of the following:

- Plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or
- Severe bleeding, and/or
- Severe organ impairment such as renal failure or hepatitis.[4] Our studies were similar to Vibha V. Gajera et al, study which had 70% cases of classical DF and 28% cases of DHF and 2% had DSS with fatal outcome.[8]

Relationship between platelet count and bleeding manifestations has been extensively evaluated. Some studies showed a high prevalence of bleeding in 50%, but our study showed patients having platelet count lower than 10000/µl with bleeding manifestations prevalence was only 30%.[9] Present results were similar to Raikar et al.[9] who reported that bleeding manifestations are not related to platelet count. There were also studies showing role of activation of fibrinolytic system responsible for bleeding manifestations in dengue fever in addition to the thrombocytopenia and APTT prolongation.[10] But this was not assessed in our study because of lack of infrastructure facilities and also the high cost of investigations.

In present study, out of 40 patients, 15% patients had non-hemorrhagic complications. The relationship between platelet count and non-hemorrhagic complications were less studied in the previous literatures and the present study found no significant association (p value<0.054) between them.

Leukopenia was observed in 37.5% in present study. Neutropenia may be due to marked degeneration of mature neutrophils and "shift to left during febrile phases of illness.[11] A study by Ahmed et al, leukopenia was observed in 43%.[12] A study by Dhooria et al, hepatic dysfunction was seen in 14.8%, leucopenia in 26% cases and two patients in his study had organ impairment.[13] Prathyusha et al, in her study at eluru showed that with increasing severity of leukopenia there is increased the incidence of hemorrhagic manifestations (P value 0.023).[14] However, she found no significant association of leukopenia with significant bleeding manifestations.[14] In present study also, there was no statistically significant correlation between leukopenia and complications rate in patients with dengue with thrombocytopenia. Patient with lower platelet count was found to have higher chances of

developing complications. In our study, this was statistically significant (p value<0.025) with positive correlation between platelet count and complications. As the platelet counts decreased, complications risk increased in the clinical outcome of dengue fever.

The lack of correlation between low platelet counts and bleeding manifestations has been noted in our dengue patients when compared to the previous studies.[11] However, there was statistically significant difference in severe thrombocytopenia with complications, which is contrary to previous studies.

CONCLUSION

Dengue is a life-threatening illness affecting thousands of patients during epidemics. Our study showed no significant correlation between hemorrhagic and non-hemorrhagic manifestations with low platelet count which was existent in previous literature. Platelet count can be used to predict complication rate in a patient admitted with dengue fever. Though leukopenia was seen early in the disease there was no significant correlation to risk of complications. Our experience with such patient stresses that careful monitoring and planning of management ahead of projected changes in platelet counts can be lifesaving. Dengue fever does not have specific medical therapy hence clinical recovery monitoring is largely dependent on haematological complications. However, more such studies are required with more sample size so that these findings could be confirmed.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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