Research Paper

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Clinical Profile and Outcome of Thrombocytopenia in Patients Affected with Dengue Fever in Goa

Medical Science

KEYWORDS : Dengue, thrombocytopenia, platelet transfusion, raised liver enzymes.

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ABSTRACT

Background: Dengue can have a significant economic and health toll on the community and is on the rise. Thrombocytopenia is one of the main reasons for the hospital admissions in these cases.

Objectives: To study the clinical profile and the outcome in thrombocytopenia due to dengue disease in Goa.

Methods: A retrospective descriptive study of a total of 73 patients, over one year, with confirmed diagnosis of dengue by the IgM MAC Elisa test. The data was collected from the case sheets, from the Medical Records Department and Microbiology Department.

Results: A total of 73 patients were included in the study, out of which 54 were males (73.9%) and 19 were females (26.2%). Most of the patients belonged to the age group of 20 – 29 years (39.7%). A total of 47.9% patients presented with fever on 4th day and 89.0% had thrombocytopenia on admission; while 38.3% had counts between 20000 to 50000, with a maximum drop observed on 4th to 6thday of fever. Only 6.8% of patients had severe hemorrhage. It was observed that only 11 patients received platelet transfusion. Mortality was seen in 2 patients and not directly related to the thrombocytopenia. Deranged AST was observed in 95.8% of patients and deranged ALT in 83.6% of patients. An association was observed with raised liver enzymes and thrombocytopenia in all the patients.

Conclusion: The study showed that prevalence of thrombocytopenia is high in dengue, but the resultant need for platelet transfusion is negligible. Platelet counts usually decreased by 4th to 6th day and then rose thereafter. Thrombocytopenia by itself did not increase mortality in dengue.

Introduction

Dengue is a mosquito-borne viral disease and is transmitted by female mosquitoes mainly of the species Aedes aegypti and to a lesser extent A. albopictus. Dengue virus is a single-stranded RNA enveloped virus that comprises of four serotypes (DENV 1, 2, 3 and 4) that belong to family Flaviviridae and genus Flavivirus.[1] They produce a spectrum of clinical illnesses ranging from a classical dengue fever (DF) to severe and potentially fatal complications known as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[2] Clinically it can manifest as an acute febrile illness, classical dengue fever, dengue hemorrhagic fever and dengue with shock. Thrombocytopenia has always been one of the criteria used by WHO as a potential indicator of severity. Thrombocytopenia may not manifest clinically and many patients do not have bleeding manifestations. Thrombocytopenia is associated with alterations in megakaryopoiesis by the infection of human hemopoetic cell and impaired progenitor cell growth, resulting in platelet destruction increased consumption or dysfunction or DIC. The mechanisms involved in thrombocytopenia and bleeding during infection are not fully understood. A number of hypotheses have been suggested to understand thrombocytopenia. In this context, the virus could directly or indirectly affect bone marrow progenitor cells by inhibiting their function[3] and to reduce the proliferative capacity of hematopoietic cells.[4] There is evidence that dengue virus can induce bone marrow hypoplasia during the acute phase of the disease[5]. Besides platelet counts, the functional disruption affects the plasma kinin system and the immunopathogenesis of dengue.[6] Platelet destruction occurs due to increased apoptosis, lysis by the complement system and by the involvement of antiplatelet antibodies.[7] Here, the relevance of platelets count in relationship to the clinical picture and outcome in dengue patients is being discussed. The objectives of the study include the following.

1. To study the proportion of thrombocytopenia among the dengue patients at Goa Medical College.
2. To study the clinical outcome among these patients with thrombocytopenia.

Materials and methods

This study was conducted at a tertiary care teaching hospital in Goa. This was a record based descriptive study and 73 of the patients admitted with dengue from June 2014 to July 2015 were included. The data on clinical presentations, biochemical parameters and the outcome were collected. All patients included in this study came with acute febrile illness and a diagnosis of dengue was made based on the report of the NSI antigen test or the rapid kit test of IgM antibodies for dengue at admission. All the cases were confirmed as dengue after the report of IgM MAC Elisa were positive. Only those cases which were confirmed by the IgM MAC Elisa test were included in the study, according to the NVBDCP guidelines for dengue.[8]

Laboratory parameters studied included platelet count at admission and at discharge, complete blood counts and liver function tests.

Inclusion criteria:

1. Acute febrile illness with clinical symptoms of dengue
2. Confirmed by MAC Elisa test.

Exclusion criteria:

1. Patients with other hematological conditions
2. Enteric fever
3. Malaria
4. Leptospirosis
5. Alcoholic liver disease patients

Statistical Analysis:

The data was collected and entered in Microsoft excel and analyzed with a hand held calculator**.** Burden of thrombocytopenia and other parameters among the dengue patients was expressed as percentage and averages.

Results

A total of 73 patients of dengue were retrospectively enrolled in the study. All patients enrolled were confirmed cases of dengue by the IgM MAC Elisa test. Table 1 shows the baseline characteristics of the patients. There was a clear preponderance of cases of dengue in males in this study, 73.9% v/s 26.0%. The age group studied was between 12 to 79 years of age. It was significantly

noted that dengue affects the young adults between the ages of 20-29 years of age (39.7%). The second most affected group was the one between the ages of 30-39 (24.6%). The least affected were those from 70-79 years (1.3%).

Patients were admitted irrespective of any complications usually on the 3rd or 4thday of fever. It is observed that 65 patients had platelet counts less than 1.5 lakhs indicating that 89.0% had thrombocytopenia on admission itself (Table 2). Eight patients had platelet counts between 1 to 1.49 lakhs (10.9%), 6 had between 80-89000 (8.2%) and 28 had platelet counts between 20-49000(38.3%). Seven patients had a platelet count less than 20000 (9.5%) while 28 patients in the study had platelet count between 20-49000 (38.3%). Therefore on an average, most patients in this study had a platelet count between 20000-49000. Sixty patients also had a WBC count less than 4000 (82.1%). As far as the duration of the fever was concerned, it was seen that the maximum fall in platelet count was between the 4th and 6th day of the fever, (47.9%) (Tables 3 and 4). Nearly 31.5 % of the patients had presented with fever of 1-3 days duration. It was seen that by the 7th day of the fever the platelet counts began to rise. Bleeding manifestations seen in the form of petechiae or purpura (34.2%) was the commonest presentation of thrombocytopenia (Table 5). This was the most wide spread sign of thrombocytopenia and seen on the ankles and the torso and back. Three patients had epistaxis (4.0%). Only 5 patients (6.8%) had severe bleeding, these patients had hematemesis, menorrhagia and hematuria. In these patients who had significant bleeding like hematemesis, hematuria, or menorrhagia the level of platelet count was studied and shown in Table 6. It was seen that the 2 patients who had hematemesis had a count between 20-49000 and the other one had a count greater than 50000. Similar observation was noted for menorrhagia. The patients with hematuria had a count of less than 20000, showing in the present study, that only 1 person had significant bleeding whose count was less than 20000.

Table 7 shows that platelet transfusions were given to 11 patients in the study (15.0%), the indications in 5 patients were due to significant bleeding manifestations and in 6, it was given prophylactically as their counts were less than 20000. Table 8 shows the abnormalities in liver function tests found .It was seen that raised liver enzymes were seen in all the cases. A large percentage of patients, i.e. 95.8% had AST raised and 83.5% had ALT raised. The range was mostly between 41-100 IU. Only 3 patients i.e. 4.1% had marginally raised bilirubin not exceeding 3mg.

Discussion

Dengue is an infectious disease which has a clinical profile ranging from a mild febrile illness to devastating complications of bleeding, multi-organ failure and death. In general, dengue is a self-limiting acute febrile illness followed by a phase of critical defervescence, in which patients may improve or progress to a severe form. Severe illness is characterized by hemodynamic disturbances, increased vascular permeability, hypovolemia, hypotension and shock. Thrombocytopenia and platelet dysfunction are common in both cases and are related to the clinical outcome.[9] The demographic profile of dengue has been described in studies in Delhi[10], Bangalore and Mangalore.[11] Although Goa has its fair share of dengue which manifests during the monsoon season and extends till February, no studies have been conducted to study the clinical pattern of dengue in the state.

In this retrospective descriptive study, 73 patients who were confirmed dengue by the IgM MAC Elisa test were studied. The Centre for Disease Control describes MAC Elisa having a specificity of 98% and sensitivity of 90.3%. In the current study 73.9 % were males and 26.0% were females. This preponderance in males was also seen in a study done by Muhammad A et al.[12] The reasons cited was more outdoor exposure to mosquito bites and males visiting health centers or seeking medical help more than females. The maximum number of patients, who were reported with dengue in the present study, was in the age group from 20-29 years (39.72%). A study done by Nishat et al in Delhi also observed most cases were in the age group of 21-30 years, thus showing a prominent infection in the younger adults.[10] This was also confirmed in other studies by Dar et al.[13] In mid-1990s most of the reported cases belonged to age group of 5-20 years, while in 2003, maximum number of positive cases were in the age group of 21-30 years.[13, 14]

It was observed that in the present study about 89.4% of dengue patients had thrombocytopenia. It is a common manifestation of dengue.[15] Pervin et al[16] also observed the incidence of 84.8% with low platelet count in these cases. Chairulfatha et al[17] found 83% of patients had thrombocytopenia on admission with significant bleeding seen only in those whose count was less than 15000. In the present study, significant bleeding was present in only 6.8% of patients; however not all had a count of less than 20,000. All these patients had duration of fever from 3 to 4 days on admission and maximum number of patients had the lowest platelet count on the 4th day of fever. In a study by Elzinandes et al,[9] it was also observed that platelet counts decreased from the 3rd until 7th day and then started picking up. In this study, platelet count was seen to improve by 7th day of the fever. Several explanations have been described on the mechanism of thrombocytopenia in dengue. Hemophagocytosis or bone marrow suppression may be possible explanations, and that endothelial sequestration of platelets could be the dominant mechanism of thrombocytopenia in patients with severe dengue.[18] Increased vWF expression may result in increased expression on endothelial surfaces of ultra-large (uncleaved) Vwf multimers, which avidly entrap platelets. This sequence would lead to platelet plugs in the microcirculation and low platelet counts in peripheral blood. Microcirculatory platelet plugs within an organ can contribute to organ failure.

The major clinical manifestations seen in the present study were purpura and petechiae. This was noted in 34.2% of the patients. Two persons had gum bleeds (2.7% and three had mild epistaxis (4%). Significant bleeding was found in only 5 patients. It is to be noted here that 36.5% did not have any clinical signs of thrombocytopenia and were asymptomatic which may indicate that there may be no clinical evidence of thrombocytopenia in dengue and it may just be a laboratory finding. In contrast a study by Muhammad et al[19] enrolling 245 dengue patients showed clinical bleeding related to platelet count and 80% had significant bleeding if counts less than 25,000. In another study by Chaudhary et al,[20] it was observed that bleeding occurred more often in patients with platelet counts below $20 \times 10^9 L^{-1}$. Makroo,[21] after studying 225 dengue patients found 88.4% with platelets less than 1 lakh on admission and 9.7% showed manifestations of bleeding. There was no correlation between clinical bleeding and platelet count unless counts were below 20000. A study by Muhammad et al[19] in Lahore found bleeding significantly related to thrombocytopenia and 23% bleeding in those with platelet count less than 25000, only making it just 4.4% of the cases. In the present study, 11 patients received platelet transfusions as shown in table 7. Thrombocytopenia was self-limiting and in those who received platelet transfusions, the platelet count improved subsequently. A case report by Prashanth et al[22] and Balla et al[23] showed improvement of platelet counts with steroids or intravenous immunoblobulins (IVIG). No patients received steroids or IVIG in our study. Mortality in our study was only 2.7% and cause of death was due to shock and multi organ failure and not due to thrombocytopenia as counts in both the deaths did not drop below 70000. Death and mortality in dengue has been attributed to the capillary leak causing loss of plasma volume, progressive organ derangement and DIC. There was no difference in the clinical presentations and outcome in males or females patients.

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It was noticed that all the cases of dengue included in this study showed deranged liver enzymes seen from admission, which improved was seen at discharge. Patients did not have any icterus or tender hepatomegaly and the rise was seen more in liver enzymes AST as compared to ALT. Abnormal liver function tests have been reported in several studies and our study showed a similar pattern. A study by Garcia et al[24] showed deranged liver enzymes in 47% of the patients. Increase in Liver enzymes has been described, where the possible rise in AST was contributed by non-hepatic sources like skeletal muscles. Given the prominence of musculoskeletal symptoms among adults with dengue, skeletal muscle injury could contribute to the elevation in AST levels. The plasma half-life of AST is shorter than that of ALT, but it is possible that the slower improvement in ALT levels simply reflects slower evolution of the hepatic disease than of the musculoskeletal problems. Rigato et al[25]also observed increasing liver enzymes although not exceeding 300-400IU/L. In study by Dinhet et al,[26] AST and ALT levels began to increase slightly in the early febrile period; median (90% range) of 43 IU/L (18–314 IU/L) for AST levels and 40 IU/L (14–236 IU/L) for ALT levels. No significant differences in level of thrombocytopenia was seen in males v/s females and similar pattern was seen as far as liver enzymes were concerned, suggesting that the disease follows similar pattern in males and females affected with dengue.

When dengue first emerged in India during 1950–60s, the disease was mild despite circulation of all four serotypes. The circulation of serotypes in different parts of the country and changes in the circulating serotypes in consecutive years has been reviewed recently. The Indian isolates obtained over a span of 50 years by NIV were sequenced and analyzed with global data.[27,28] The phylogenetic analysis of the E gene sequence revealed that the Indian viruses formed clusters that were temporally distinct. For all four serotypes, the viruses circulating in India in the 1950s and causing mild disease were either replaced or evolved into lineages/genotypes with greater virulence and/or transmissibility.

Conclusion

In this study, we examined 73 proved patients of dengue and highlighted the thrombocytopenic manifestations of the illness. It has been seen that the concern, apprehension in dengue is due to these manifestations which may result in mortality and hence the importance of the study. The study reinforced the evidence that thrombocytopenia is indeed a common presentation in dengue; it follows a particular pattern and with all patients kept under observation, the clinical impact and translation into life threatening thrombocytopenia was negligible. Low platelet count may only increase the duration of hospital stay but does not translate into increased mortality or morbidity. The need for platelet transfusions was seen in only 11 patients. Although a wide spectrum of dengue ranging from hepatic encephalopathy, glomerulonephritis, encephalitis, myocarditis is described, these were not common in Goa.

Limitations of the study:

Study was a record based study, so in depth history and special proforma charts were not available. Follow up reports after discharge could not be done. Due to MAC Elisa kits being available only at sentinel sites, less number of confirmed cases v/s the overall suspected cases could be taken.

Table 1: AGE AND SEX WISE DISTRIBUTION OF DENGUE POSITIVE PATIENTS

Age	Male percentage	Female percentage	total
12-19	5	1	6
20-29	24	5	29
30-39	14	4	18
40-49	4	3	7
50-59	5	3	8
60-69	1	3	4
70-79	1	-	1
total	54	19	73
percentage	73.97%	26.02%	100%

Table 2: PLATELET COUNTS IN THE 73 STUDIED PATIENTS

Platelet count	No of cases	Percentage
>1.5 lakh	8	10.9
1-1.49	8	10.9
80-99000	6	8.2
50-79000	16	21.9
20-49000	28	38.3
<20000	7	9.5

Table 3: DURATION OF FEVER AT TIME OF ADMISSION

Duration of fever	No of patients	Percentage
1-3 days	23	31.5%
4-6 days	35	47.9%
6-10 days	15	20.5%

Table 4: PLATELET COUNT IN RELATION TO THE DURATION OF FEVER

Platelet count	1-3days fever	4-6 days fever	7-10 days fever
<20000	1	5	1
20000-49000	7	16	5
50000-79000	5	10	1
80000-99000	4	2	-
1-1.5 lakhs	3	2	3
>1.5lakhs	3	01	5

Table 5: BLEEDING MANIFESTATIONS SEEN IN DENGUE PATIENTS IN THE STUDY

Manifestation	No of patients	Percentage
Petechiae/Purpura	25	34.2%
Ecchymosis	0	-
Sub conjunctival bleed	1	1.3%
Oral bleeds	2	2.7%
Epistaxis	3	4.1%
Hemetemesis	2	2.7%
Bleeding PR	0	-
Hematuria	1	1.35%
Menorrhagia	2	2.7%
ICbleed	0	-

Table 6: LEVEL OF PLATELETS IN RELATION TO BLEEDING

Platelet count	epistaxis	hematemesis	hematuria	menorrhagia
>1.5	-	-	-	-
1-1.50000	-	-	-	-
80-99000	-	-	-	-
50-79000	1	-	-	-
20-49000	-	2	-	2
<200000	2	-	1	-

Table 7: NUMBER OF PATIENTS WHO RECEIVED PLATELET TRANSFUSIONS.

Platelet counts	Platelet transfusions	Indications Severe hemorrhage	Indications Prophylaxis
20-49000	4	4	-
<20000	7	1	6
Total	11	5	6

Table 8: ABNORMALITIES IN LIVER FUNCTION TESTS

Liver enzymes	0-40	41-100	101-200	201-300	>300	total	percentage
AST	3	24	19	15	12	70	95.8
ALT	12	31	17	13	0	61	83.5

Serum bilirubin	No of patients	percentage
1-3mg	3	4.11
normal	70	95.8

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