Evaluation of Platelets as Predictive Parameters in Dengue Fever

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Abstract Dengue is an arboviral disease and occurs in tropical countries where over 2.5 billion people are at risk of infection. Each year an estimated 100 million cases of dengue fever (DF) occur and between 2.5 and 5 lakh cases of dengue hemorrhagic fever (DHF) are reported to WHO. Severe thrombocytopenia and increased vascular permeability are two major characteristics of DHF. A study was conducted to note the relationship between the platelet counts and severity of the disease in pediatric cases of dengue fever. Platelet counts were found to be predictive as well as recovery parameter of DF/DHF/DSS.

Keywords Dengue · Dengue haemorrhagic syndrome · Dengue shock syndrome · Platelet count · Thrombocytopenia

Introduction

Dengue is an arboviral disease and occurs in tropical countries where over 2.5 billion people are at risk of infection. Dengue fever (DF) is characterized by biphasic fever, myalgia, headache, rash, leukopenia and various degrees of thrombocytopenia. The incidence of dengue fever is estimated to have increased to 30 fold in the past 50 years [1]. Dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) are life threatening reversible vascular complications of DF and are associated with severe thrombocytopenia and increased vascular permeability [2]. The incidence of these complications are found

to be increasing [1]. The decreasing platelet counts have found to predict the severity of the disease and is associated with increased hematocrit, increased liver enzymes, altered coagulation profile [3]. The objective of the present study was to note the relationship between the platelet counts and the severity of the disease in pediatric cases of DF.

Material and Methods

Children below 15 years with seropositivity for DF admitted to JSS University Hospital, a tertiary care center between 1st May and 15th August 2009 were evaluated for platelet count and severity of the disease. The reference criteria for diagnosis of DF/DHF/DSS was as stated in the Table 1.

Statistical Analysis

Descriptive statistics, Chi square test and contingency coefficient analysis were employed using SPSS (version 16) for Windows.

Results

During the study period there were 414 pediatric cases admitted with fever. Of these 105 were found to be seropositive for dengue. Of these seropositive cases 70% had thrombocytopenia (<1L) while the remaining 30% had normal platelet counts (Fig. 1).

Majority of the dengue cases were noted in the age group of 6–10 years and in the same age group there was a male predominance. The next majority of cases were noted among 2–5 years followed by 11–15 years. The least number of cases were seen in the age group of 0–1 years

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Table 1 Criteria for diagnosis of DF/DHF/DSS*Clinical case definition for dengue fever*

Classical dengue fever or break bone fever is an acute febrile viral disease frequently presenting with headaches, bone or joint pain, muscular pains, rash, and leucopenia

Clinical case definition for dengue hemorrhagic fever

Necessary Criteria

1. Fever, or recent history of acute fever
2. Hemorrhagic manifestations
3. Low platelet count ($100,000/\text{mm}^3$ or less)
4. Objective evidence of “leaky capillaries:”
 - Elevated hematocrit (20% or more over baseline)
 - Low albumin
 - Pleural or other effusions

Clinical case definition for dengue shock syndrome

- 4 criteria for DHF +
- Evidence of circulatory failure manifested indirectly by all of the following
 - Rapid and weak pulse
 - Narrow pulse pressure (≤ 20 mm Hg) OR
 - Hypotension for age
 - Cold, clammy skin and altered mental status
 - Frank shock is direct evidence of circulatory failure

Fig. 1 Distribution of pediatric fever cases**Table 2** Age and sex wise distribution of dengue seropositive cases

Sex	Age groups				
	0–1	2–5	6–10	11–15	Total
Male	9	12	33	7	61
	14.8%	19.7%	54.1%	11.5%	100.0%
Female	3	13	17	11	44
	6.8%	29.5%	38.6%	25.0%	100.0%
Total	12	25	50	18	105
	11.4%	23.8%	47.6%	17.1%	100.0%

($P < 0.001$). However, the distribution of male and female across the different age groups was statistically same ($P > 0.05$) (Table 2).

Table 3 Platelet counts and age wise distribution of cases

Age groups	Platelet counts				Total
	<20,000	21–50,000	51–1 lakh	>1 lakh	
0–1	1	3	4	4	12
	8.3%	25.0%	33.3%	33.3%	100.0%
2–5	0	7	7	11	25
	0%	28.0%	28.0%	44.0%	100.0%
6–10	6	16	20	8	50
	12.0%	32.0%	40.0%	16.0%	100.0%
11–15	0	5	5	8	18
	0%	27.8%	27.8%	44.4%	100.0%
Total	7	31	36	31	105
	6.7%	29.5%	34.3%	29.5%	100.0%

Table 4 Platelet counts compared with severity of disease at admission

Categories of dengue				
Platelet counts	DF	DHF	DSS	Total
<20,000	0	5	2	7
	0%	71.4%	28.6%	100.0%
21–50,000	15	13	3	31
	48.4%	41.9%	9.7%	100.0%
51–1 lakh	21	10	5	36
	58.3%	27.8%	13.9%	100.0%
>1 lakh	22	9	0	31
	71.0%	29.0%	0%	100.0%
	58	37	10	105
	55.2%	35.2%	9.5%	100.0%

Of the patients with thrombocytopenia (platelet count <1 lakh), 36 patients (48.64%) had platelet counts between 51,000 and 1 lakh (mild thrombocytopenia), 31 patients (41.89%) had platelet counts between 21,000 and 50,000 (moderate thrombocytopenia) while the remaining 7 patients (9.45%) had platelet counts $<20,000$ (severe thrombocytopenia). A significant association was observed between the severity of thrombocytopenia and the age groups. Thrombocytopenia was found to be more severe in age groups of 6–10 years than in the older age group and this difference was significant ($P < 0.05$) (Table 3).

The seropositive patients were followed clinically for the symptoms of DHF/DSS and they were correlated with the respective platelet counts. At the time of admission features of DHF/DSS were noted in 47 patients and these comprised 38 patients of dengue with thrombocytopenia and 9 patients of dengue without thrombocytopenia. Further among the cases with thrombocytopenia it was noted that 41.66% of cases (15/36 patients) with mild thrombocytopenia, 51.61% of cases (16/31 patients) with moderate

thrombocytopenia and 100% of cases (7/7 patients) with severe thrombocytopenia presented with DHF/DSS (Table 4). A significant association was observed between the severity of thrombocytopenia and the clinical presentation of DHF/DSS ($P < 0.05$). All cases with severe thrombocytopenia and greater percentage of patients with moderate thrombocytopenia presented with DHF/DSS when compared to those with mild thrombocytopenia. A significant drop in platelet counts was noted as the patient presented with symptoms of DHF/DSS.

Following the patients with necessary treatment, all cases of only DF, irrespective of their varying platelet counts (58 cases), patients with DHF/DSS without thrombocytopenia (9 cases) and with mild thrombocytopenia (15 cases) showed complete recovery. Of the 16 DHF/DSS patients with moderate thrombocytopenia, 11 (68.75%) showed complete recovery, 4 (25%) had persistent thrombocytopenia but showed clinical improvement, while the remaining 1 (6.25%) showed a further fall in platelet count and succumbed in spite of treatment. In the last group of 7 patients with DHF/DSS who had severe thrombocytopenia, 2 (28.57%) recovered completely and of the remaining, 3 (42.85%) though they had persistent thrombocytopenia showed clinical improvement while 2 (28.57%) succumbed with further fall in platelet counts (Table 5). This accounts for the 95 cases (90.5%) who showed a significant improvement after treatment of both the clinical status and platelet counts. 7 cases (7%) showed features of DHF with moderate and severe thrombocytopenia while only 3 cases (2.85%) despite treatment succumbed with further fall in their platelet counts which is significant ($P < 0.01$). Thus, there was a significant association noted between the clinical improvement or deterioration of DF cases and their platelet counts ($P < 0.05$). Patients with only DF had higher platelet counts compared to the lower counts observed in patients with DHF/DSS. Following treatment, significantly the maximum number of cases showed clinical improvement with elevation in their platelet counts, few cases with features of DHF had moderate to severe

thrombocytopenia while the cases of severe thrombocytopenia presented with DSS and succumbed ($P < 0.05$).

Discussion

DF and DHF are caused by one of the four closely related but antigenically distinct virus serotypes (DEN1, DEN2, DEN3 and DEN4) of the genus flavivirus. Infection with one of these serotypes does not provide cross immunity, so persons living in a dengue endemic area can have four different dengue infections during their life time [4].

In the present study DF was more common in males (58%) and among the pediatric age group the largest proportion was seen in the age group of 6–10 years. This is in accordance with the study at Belgium [5]. Other workers, have noted that most patients with serological and virological confirmation were in the age group of 5–9 years [6, 7]. Although DF is a self limited febrile illness, DHF is characterized by prominent haemorrhagic manifestations associated with thrombocytopenia and an increased vascular permeability [8]. The clinical diagnosis of DHF especially in the early phase of illness, is not easy. Laboratory findings such as thrombocytopenia and a rising hematocrit in DHF cases are usually observed by day 3 or 4 of the illness. Thrombocytopenia may be occasionally observed in DF but is a constant feature and one of the diagnostic criteria of DHF [9]. Though dengue virus induced bone marrow suppression decreased platelet synthesis, an immune mechanism of thrombocytopenia caused by increased platelet destruction appears to be operative in patients with DHF [2]. The present study showed DHF/DSS was more common in patients of DF with thrombocytopenia and this is supported by Mourao MP who has observed that patients with DHF had lower platelet counts than patients with only DF [10].

Several studies on DF have revealed a variable prevalence of thrombocytopenia. Sumaro has found a prevalence of 81% in the department of child health, Cipto Mangunkusumo National Hospital, Jakarta, Indonesia. 10 years later, a prevalence of 59% was observed in the same department [6]. In the study at Belgium, thrombocytopenia was found in 58% of confirmed cases of DF at admission and in 83% during hospitalization [5]. In the present study 80% of cases of DHF/DSS had thrombocytopenia.

The diagnosis of DF/DHF/DSS was based on the criteria stated in the Table 1, whereas in the study of de Castro et al. [2] the diagnosis of DHF was confirmed by the presence of haemorrhagic signs such as petechiae with purpura, epistaxis, menorrhagia or a positive tourniquet test. DSS was confirmed with a pulse pressure ≤ 20 mmHg. The clinical presentation and relevance of thrombocytopenia is still poorly described in the literature [10]. The

Table 5 Platelet counts and dengue patients after treatment

Category of dengue	Platelet counts				Total
	<20000	21–50,000	51–1 lakh	>1 lakh	
DF	0	25	28	42	95
	0%	26.3%	29.5%	44.2%	100.0%
DHF	3	4	0	0	7
	42.9%	57.1%	0%	0%	100.0%
DSS	2	1	0	0	3
	66.7%	33.3%	0%	0%	100.0%
Total	5	30	28	42	105
	4.8%	28.6%	26.7%	40.0%	100.0%

need for better classification of the severity of dengue infection has been proposed in order to classify different entities of dengue infections [1].

The major pathophysiologic hallmark that determine disease severity and distinguish DHF from DF and other viral haemorrhagic fevers are plasma leakage due to increased vascular permeability and abnormal hemostasis. Hypovolemic shock occurs as a consequence of and subsequent to, critical plasma volume loss [11]. Abnormal hemostasis including increased capillary fragility, thrombocytopenia, impaired platelet function, consumptive coagulopathy and in the most severe form disseminated intravascular coagulation (DIC) contribute to varying degree of hemorrhagic manifestations [12].

The clinical outcome and platelet counts recorded during the course of hospitalization have shown that a recovery from thrombocytopenia was associated with clinical improvement while further fall in platelet counts was associated with fatality. This is in par with the findings of the study by Mourao [10]. The severe fall in platelet count inspite of treatment was associated with fatality which accounted for 2.8% of cases as against a fatality rate of 1% noted in the study at Belgium.

Conclusion

Platelet count is thus a predictive as well as a recovery parameter of DF/DHF/DSS.

References

1. Chen RF, Yang KD, Wang L, Liu JW, Chiu CC, Cheng JT (2007) Different clinical and laboratory manifestations between dengue haemorrhagic fever and dengue fever with bleeding tendency. *Trans R Soc Trop Med Hyg* 101(11):1106–1113
2. de Castro RA, de Castro JA, Barez MY, Frias MV, Dixit J, Genereux M (2007) Thrombocytopenia associated with dengue hemorrhagic fever responds to intravenous administration of anti-D (Rh(o)-D) immune globulin. *Am J Trop Med Hyg* 76(4): 737–742
3. Phuong CXT, Nhan NT, Kneen R, Thuy PTT, Thien CV, Nga NTT et al (2004) Clinical diagnosis and assessment of severity of confirmed dengue infections in vietnamese children: is the world health organization classification system helpful? *Am J Trop Med Hyg* 70(2):172–179
4. Gubler DJ, Clark GG 1996. Dengue/dengue hemorrhagic fever: the emergence of a global health problem. *Emerg Infect Dis*. 1(2). Available at <http://www.cdc.gov/ncidod/eid/vol.no.2/gubler.htm>
5. Chairulfatah A, Setiabudi D, Agoes R, Colebunders R (2003) Thrombocytopenia and platelet transfusions in dengue haemorrhagic fever and dengue shock syndrome. *Dengue Bull* 27: 141–143
6. Harun SR (1990) Clinical aspects of dengue haemorrhagic fever in children. In: proceedings of the seminar and workshop on dengue haemorrhagic fever and its control, Jakarta, pp 62–68
7. Samsi TK, Sugianto D (1990) Evaluation of concentrated platelet transfusion in severe dengue haemorrhagic fever. In: Proceedings of the National Conference of Indonesian Paediatrics Association, Ujung Pandang, pp 138–139
8. Saito M, Oishi K, Inoue S, Dimaano EM, Alera MT, Robles AM et al (2004) Association of increased platelet associated immunoglobulins with thrombocytopenia and the severity of disease in secondary dengue virus infections. *Clin Exp Immunol* 138: 299–303
9. World Health Organization (1997) Dengue haemorrhagic fever: diagnosis, treatment and control, 2nd edn. WHO, Geneva
10. Mourao MP, Lacerda MV, Macedo VO, Santo JB (2007) Thrombocytopenia in patients with dengue virus infection in Brazilian Amazon. *Platelets* 18(8):605–612
11. Srichaikul T, Nimmannitya S (2000) Haematology in dengue and dengue hemorrhagic fever. *Bailieres Best Pract Res Clin Haematol* 13(2):261–276
12. Nimmannitya S (1999) Dengue hemorrhagic fever: disorders of hemostasis. IX congress of the International Society of Haematology Asia-Pacific Division, Bangkok. pp.184–187. <http://www.ishapd.org/1999/50.pdf>