Original Research Article

Clinical profile of thrombocytopenia in tropical infectious diseases

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ABSTRACT

Background: In an infant or child thrombocytopenia can occur due to large spectrum of illness ranging from tropical infection to malignancy or bone marrow failure. Management is decided by the severity of thrombocytopenia, associated risk factors and underlying illness. Children with thrombocytopenia may be asymptomatic – detected by complete blood count for some other clinical issue or symptomatic-presenting with mucosal and/or cutaneous bleeding and rarely central nervous system bleed. Aim of this research is to study the distribution of patients with thrombocytopenia, their grading according to platelet counts and etiology with special focus to infective causes, other complications in these infections and recovery from thrombocytopenia.
Methods: This is an observational analytical retrospective study. 100 randomly selected pediatric patients (6 months to 12 years) admitted in pediatric ward with documented thrombocytopenia (platelet count <150,000/ul) on admission or at any point of time during hospitalisation are enrolled and analyzed.
Results: 91% patients have thrombocytopenia associated with infective causes, of which 44% have dengue. 7 patients in study have bleeding manifestations and 3 required platelet transfusion. 50% patients with dengue with thrombocytopenia have leucopenia and 2% have pancytopenia. 57.1% patients with enteric fever with thrombocytopenia show elevated alanine aminotransferase (ALT) levels. Mean platelet recovery time is 2 to 4 days for various infections.
Conclusions: Majority of patients do not have bleeding manifestations, and they are mainly seen with severe thrombocytopenia associated with infections. Requirement of platelet transfusion is not common and is seen only in patients with severe thrombocytopenia with significant bleeding manifestation.

Keywords: Thrombocytopenia, Dengue, Bleeding

INTRODUCTION

Thrombocytopenia is a common presentation of many febrile and few non-febrile illnesses in children.[1] The common febrile illness in children like dengue, viral fever, malaria and enteric fever are associated with thrombocytopenia.

Normal platelet count is ≥150,000/uL.[2] Thrombocytopenia is defined as a platelet count of less than 150,000/µl. It is clinically suspected when there is a history of easy bruising or bleeding in a child.[3] Pseudo-thrombocytopneia can occur due to use of excessive ethylenediaminetetraacetic acid (EDTA) while sampling.[4]

In an infant or child thrombocytopenia can occur due to large spectrum of illness ranging from tropical infection to malignancy or bone marrow failure. Management is decided by the severity of thrombocytopenia, associated risk factors and underlying illness.

In general, the risk of bleeding does not increase until the platelet count falls significantly below 100,000/µl. For example, surgical bleeding solely due to a decreased

platelet count typically does not occur until the platelet count is less than 50,000/µl. Whereas, spontaneous bleeding does not occur until the platelet count is less than 20,000/µl.[2] Younger circulating platelets are larger and more hemostatically active.[5] Hence patients with immune thrombocytopenic purpura (ITP) have less severe bleeding symptoms compared to patients with same degree of thrombocytopenia due to bone marrow failure from leukemia, whose platelets tend to be older and less active.

Detailed history and clinical examination provide clues to the underlying etiology. Laboratory evaluation in form of complete blood count, peripheral blood smear, bone marrow examination and other tests like a direct Coomb's test, D-dimer and fibrinogen levels, and lactic acid dehydrogenase (LDH) help to establish the diagnosis and its severity.

The aim and objectives of present study is to evaluate the distribution of patients with thrombocytopenia, their grading according to platelet counts and etiology with special focus to infective causes, frequency of bleeding manifestations and requirement of platelet transfusion and other complications in these infections and recovery from thrombocytopenia.

METHODS

Study area and duration

An observational analytical retrospective study conducted over 2 years - from August 2016 to July 2018, in the pediatric department of NHL medical college and VS hospital in Ahmedabad, Gujarat, India.

Inclusion criteria

Children in the age group of 6 months to 12 years admitted in pediatrics ward with thrombocytopenia were included in the study.

Exclusion criteria

Children <6 months and >12 years, children with any underlying chronic illness, and patients with suspected malignancy or marrow infiltration were excluded from the study.

Sample size

100 randomly selected children meeting inclusion criteria with parents giving valid consent were included in the study.

Study tool

Data is collected from case report files and laboratory investigation and proformas are filled.

Data analysis

The data was analyzed using statistical package for social sciences (SPSS) trial version and Microsoft excel 2013. Descriptive statistics were performed for various variables. The chi-square test for association was used and $p < 0.05$ was considered as statistically significant.

RESULTS

Out of 100 cases studied, 8 (8%) are between 6 months to <1 year age, 35 (35%) were 1 year to <5 years age and 57 (57%) were 5 years to 12 years age.

Out of 100 patients studied, 49 (49%) were males and 51 (51%) were females.

Out of 100 patients, 39 (39%) patients had mild thrombocytopenia, 26 (26%) patients moderate thrombocytopenia, and 35 (35%) had severe thrombocytopenia.

6 patients with severe thrombocytopenia and 1 with moderate thrombocytopenia showed bleeding manifestations. Of these 7 patients with bleeding manifestations, 3 had dengue illnesses, 3 had malaria and 1 had ITP; of which 3 patients required platelet transfusion (Table 1).

Table 1: Grades of thrombocytopenia and bleeding manifestations.

Thrombocytopenia	Total patients	Bleeding manifestations
Mild	39	0
Moderate	26	1
Severe	35	6
Total	100	7

Out of 100, 44 (44%) patients have dengue illnesses, followed by malaria – 16 (16%) and other viral illnesses – 16 (16%), enteric fever – 7 (7%), infective hepatitis – 5 (5%), severe acute malnutrition – 4 (4%), pneumonia – 2 (2%), transient bone marrow edema (TBME) – 1 (1%). Out of 16 malaria cases, 15 (94%) were with *Plasmodium vivax* (*P. vivax*) and 1 (6%) was with *P. falciparum*.

Mean platelet count in different infections are - malaria – 60175/µl, dengue illnesses – 72263/µl, pneumonia – 89550/µl, other viral illnesses – 89900/µl, enteric fever – 91200/µl and infective hepatitis – 99520/µl.

9 (9%) patients had thrombocytopenia due to other non-infective causes (Table 2).

Out of 44 dengue patients, 16 (36%) had mild thrombocytopenia, 13 (30%) had moderate thrombocytopenia and 15 (34%) had severe thrombocytopenia. It is to be noted that patients of dengue

illnesses with platelet counts more than 150000/µl were not included in study.

Table 2: Case distribution and mean platelet counts.

Diagnosis	Number of patients	Mean platelet count
Dengue illnesses	44	75263
Malaria	16	60175
Other viral illness	16	89900
Enteric fever	7	91200
Infective hepatitis	5	99520
Pneumonia	2	89550
TBME	1	112000
Others	9	NA

Out of 16 malaria patients, 3 (19%) patients had mild thrombocytopenia, 4 (25%) had moderate thrombocytopenia and 9 (56%) had severe thrombocytopenia.

Out of 7 patients with enteric fever, 3 (43%) had mild thrombocytopenia and 4 (57%) had moderate thrombocytopenia.

Out of 5 patients with infective hepatitis, 3 (60%) had mild thrombocytopenia, 1 (20%) had moderate thrombocytopenia and 1 (20%) had severe thrombocytopenia.

Out of 16 patients with other viral illnesses, 6 (38%) had mild thrombocytopenia, 5 (31%) had moderate thrombocytopenia and 5 (31%) had severe thrombocytopenia.

3 (18.8%) out of 16 malaria patients and 16 (36.4%) of 44 dengue patients showed elevated alanine aminotransferase (ALT) levels. 4 (57.1%) out of 7 patients with enteric fever showed elevated ALT levels. P value is 1.67 (>0.05), hence is statistically significant (Table 3).

Out of 44 patients of dengue, 22 (50%) had leucopenia, 1 (2%) had pancytopenia and others – 21 (48%) had isolated thrombocytopenia. The mean leucocyte count in dengue patients with leucopenia was 2964/µl. The lowest leucocyte count noted was 1300/µl (Table 4).

Out of 3 patients with mild thrombocytopenia, 1 had leucopenia, and out of 4 patients with moderate thrombocytopenia, 2 had pancytopenia including leucopenia (Table 5).

Of 12 malaria cases, 1 case with mild thrombocytopenia had mild anemia, of 3 cases with moderate thrombocytopenia, 2 had mild anemia and 1 had moderate anemia, and of 8 patients with severe thrombocytopenia 3 had mild anemia and 5 had moderate anemia. Thus, there is no significant relation between the severity of thrombocytopenia and anemia in malaria (Table 6).

Table 3: Infections and grades of thrombocytopenia.

Infection	Dengue	Malaria	Enteric fever	Infective hepatitis	Other viral illnesses
Grade of thrombocytopenia	N (%)	N (%)	N (%)	N (%)	N (%)
Mild thrombocytopenia	16 (36)	3 (19)	3 (43)	3 (60)	6 (38)
Moderate thrombocytopenia	13 (30)	4 (25)	4 (57)	1 (20)	5 (31)
Severe thrombocytopenia	15 (34)	9 (56)	0 (0)	1 (20)	5 (31)
Total	44 (100)	16 (100)	7 (100)	5 (100)	16 (100)

Table 4: Dengue and depression of other cell lines.

Dengue	Leucopenia	Pancytopenia	Isolated thrombocytopenia	Total patients
No. of patients	22	1	21	44
Percentage	50	2	48	100

Table 5: Enteric fever and depression of cell lines.

Enteric fever	Leucopenia	Pancytopenia
Mild thrombocytopenia	1	0
Moderate thrombocytopenia	2	2
Severe thrombocytopenia	0	0
Total	3	2

Table 6: Anemia and thrombocytopenia in malaria.

Malaria	Mild anemia	Moderate anemia	Severe anemia	Total
Mild thrombocytopenia	1	0	0	1
Moderate thrombocytopenia	2	1	0	3
Severe thrombocytopenia	3	5	0	8
Total	6	6	0	12

Table 7 shows the mean platelet recovery time, to reach platelet count beyond 50000/µl for different infections.

Table 7: Platelet recovery time.

Diagnosis	Mean platelet recovery time (days)	Number of patients
Infective hepatitis	4	1
Dengue	3.7	15
Malaria	3.1	9
Other viral illnesses	2.8	5
Pneumonia	2	1

DISCUSSION

In present study, 57% patients are between 5 to 12 years age. Thrombocytopenia is statistically significant in age group of >5 years as majority of cases studied comprise cases of dengue illnesses, malaria, enteric fever and other viral illnesses in patients >5 years age.

Male: female ratio was 0.96, which is not statistically significant. Thus, no gender discrimination is seen in the study.

Present study shows mild thrombocytopenia in 39%, moderate thrombocytopenia in 26% and severe thrombocytopenia in 35%. The study by Gutthi et al showed mild thrombocytopenia in 22%, moderate thrombocytopenia in 39% and severe thrombocytopenia in 39%.[6] Thus, the percentage of patients with mild to moderate thrombocytopenia – 61% is comparable to the present study – 65% (p value=0.55 which is >0.05, hence not statistically significant). In another study by Nair et al, 53.9% patients had mild to moderate thrombocytopenia and 46.1% had severe thrombocytopenia.[7]

Bleeding manifestations are seen in 7 patients, of which 6 had severe thrombocytopenia; out of these only 3 patients required platelet transfusion. None of the patients with mild thrombocytopenia showed bleeding manifestations.

Table 2 shows the etiological distribution of patients with thrombocytopenia. 91% of the cases in present study show infective cause of thrombocytopenia, with mean platelet counts in the range of moderate thrombocytopenia. A study done at Delhi demonstrated the commonest causes of thrombocytopenia was viral fever (other than dengue and chikungunya) 27.78%, followed by dengue 22.2%,

enteric fever 12.22%, chikungunya 11.11% and malaria 8.33%; in contrast to our results which shows dengue (44.4%) is the commonest cause.[7] Kumaran also found viral fever to be the commonest cause in 50.3% cases.[8,9] In another study done by Gandhi malaria was found to be the major cause in 41.07%.[10] Similarly, Lakum, also found malaria as the most common cause of febrile thrombocytopenia in 46.8% of the cases.[11] These differences could be possibly explained by the seasonal variations. Another study done by Bhalara, showed dengue (60.8%) as the main aetiology.[12]

Table 3 shows distribution of patients according to the grades of thrombocytopenia in different infections. Out of 44 dengue patients, 16 (36%) had mild thrombocytopenia, 13 (30%) had moderate thrombocytopenia and 15 (34%) had severe thrombocytopenia. Thus, the number of patients with severe thrombocytopenia is nearly half of that with mild to moderate thrombocytopenia. In the study by Gutthi et al, mild to moderate thrombocytopenia was seen in 56% and severe thrombocytopenia in 44% cases of dengue presenting with thrombocytopenia, as compared to present study showing mild to moderate thrombobocytopenia in 66% and severe thrombocytopenia in 34%.[6] Statistical analysis reveals p value 0.14 (>0.05), which is not statistically significant. Thus, both studies show comparable results.

Whereas in malaria cases with thrombocytopenia, the study by Gutthi et al shows mild to moderate thrombocytopenia in 62% and severe thrombocytopenia in 28%, in contrast to present study showing mild to moderate thrombocytopenia in 44% and severe thrombocytopenia in 56% cases.[6] Severe thrombocytopenia is not seen in enteric fever in present study.

Elevated ALT levels are seen in 57.1% patients with enteric fever as compared to 18.8% patients with malaria and 36.4% patients with dengue illnesses. P value is 1.67 (>0.05), hence is statistically significant. The elevated ALT seen in significant number of patients in enteric fever compared to dengue illnesses and malaria is due to underlying pathophysiology of respective illnesses.

50% of dengue patients had leucopenia, 2% had pancytopenia and rest 48% had isolated thrombocytopenia. Gutthi et al noted 73% leucopenia in patients of dengue with thrombocytopenia, as compared to 50% in present study. Depression of other cell lines is also noted in enteric fever; 3 (42.8%) patients show leucopenia and 2 (28.5%) show pancytopenia out of 7 patients with

enteric fever.[6] Table 6 shows the distribution of malaria patients with different grades of thrombocytopenia along with the grades of anemia. Thus, there is no significant relation between the severity of thrombocytopenia and anemia in malaria. The anemia suggests underlying nutritional status rather than hemolysis. The mean platelet recovery time for different infections as shown in Table 7, ranges from 2 to 4 days.

Limitations

The present study does not include cases with thrombocytopenia associated with suspected malignancy and marrow infiltration. Also, a detailed analysis of thrombocytopenia associated with non-infective causes like immune thrombocytopenia, nutritional deficiencies, metabolic disorders or syndromes is not included in the present study.

CONCLUSION

Thrombocytopenia is seen as an associated finding in many tropical infections. No gender predisposition is seen. Bleeding manifestations are not common and seen only in few patients with severe thrombocytopenia. Requirement of platelet transfusions is rare. Severe thrombocytopenia is generally not seen in cases of enteric fever and infective hepatitis, whereas severe thrombocytopenia is common in malaria, but bleeding manifestations are rare. Dengue and other viral illnesses present with varied grades of thrombocytopenia. Enteric fever frequently alters hepatic function compared to other infections like malaria and dengue. Depression of other cell lines resulting in leucopenia and pancytopenia is also noted in dengue illnesses and enteric fever. There is no significant relation between the severity of thrombocytopenia and anemia in malaria.

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