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Original Research Article

A study of clinical and laboratory profile of febrile children presenting with thrombocytopenia

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ABSTRACT

Background: A large number of acute febrile illnesses have an infectious aetiology and many of them are associated with thrombocytopenia. The objective was to study the clinical and laboratory profile of febrile children with thrombocytopenia, associated clinical complications and assess the relationship between platelet levels and severity of disease.
Methods: The study was carried out in 180 children up to the age of 18 years, seen in Out Patient Department as well as those admitted in the wards of Department of Paediatrics of a 999 bedded hospital in North India from July 2016 to June 2017.
Results: The commonest causes of thrombocytopenia in our study were Viral Fever (other than dengue and chikungunya) 27.78% (50), followed by Dengue 22.2% (40), enteric fever 12.22% (22), chikungunya 11.11% (20), malaria 8.33% (15), septicaemia 5.55% (10), ITP 5.55% (10), haematological malignancy 1.67% (03) and megaloblastic anaemia 1.11%(2). Bleeding manifestations were present in 19.45 % of patients and the commonest sites were skin and mucous membranes. Bleeding manifestations were seen most commonly in children with a platelet count less than <20,000/µl.
Conclusions: Viral fevers (non-specific) followed by dengue and chikungunya were the most common causes of fever with thrombocytopenia.

Keywords: Dengue, Fever, Malaria, Malignancy, Platelet count, Septicaemia, Viral fever

INTRODUCTION

In a tropical country like India, a large number of acute febrile illnesses have an infectious aetiology and many of them are associated with thrombocytopenia. Malaria, dengue, enteric fever and most viral infections are commonly associated with thrombocytopenia. Besides these, nutritional anaemia like megaloblastic anaemia is also associated with thrombocytopenia.

We come across a large number of cases, both as inpatients and outpatients presenting with fever with thrombocytopenia.[1] Thrombocytopenia is defined as a platelet count less than normal range usually below 1,50,000 per micro-litre.[2] Reduced platelet count caused by EDTA is a common laboratory phenomenon and leads to pseudo thrombocytopenia.[3] Sometimes non-infectious causes such as primary haematological disorders may also present with febrile thrombocytopenia.[4]

Patients of fever with thrombocytopenia can initially present with just simple fever and may in due course of time lead to adverse unpredictable outcomes including death. Therefore, in our study we analysed the clinical profile of patients of fever with thrombocytopenia. This helped in an early diagnosis and appropriate intervention which prevented adverse outcomes and helped saving many lives.

The objective was to study the clinical and laboratory profile of febrile children with thrombocytopenia, associated clinical complications and assess the relationship between platelet levels and severity of disease.

METHODS

The study was conducted in Department of Paediatrics of a 999-bedded hospital in North India. It was a cross sectional time bound hospital based study from 1st Jul 2016 to 30th June 2017. The study was carried out on total of 180 children from 01-18 years of age, seen in Out Patient Department as well as those admitted in the Pediatric wards.

Inclusion criteria

Children of both sexes aged 1-18 years, who presented with fever (rectal temperature ≥38°C /100.4°F) and had thrombocytopenia (platelet count <1.5 lakhs/mm^3) (with or without clinical bleeding).[5]

Exclusion criteria

Children with fever but no thrombocytopenia and also those with thrombocytopenia but no fever were excluded. Previously diagnosed conditions which can lead to thrombocytopenia such as ITP, cirrhosis, chronic liver disease, malignancy, patients on drugs (amino salicylic acid, linezolid, amiodarone carbamazepine, captopril, methyldopa, anti-cancer drugs) causing thrombocytopenia were excluded.

Collection of data

Study was done on 180 febrile children presenting with thrombocytopenia in OPD or admitted to paediatric ward. After recording a careful history, detailed general physical examination and systemic examination was done. Routine investigations were done in all cases. Specific investigations were done as indicated case wise.

All the patients were subjected to routine haematological investigations like haemoglobin, total leukocyte count, platelet count, peripheral smear study for blood cells and malarial parasites, red cell indices - MCV (mean corpuscular volume), dengue NS1antigen, dengue IgM and IgG, prothrombin time with INR, activated partial thromboplastin time, renal function test and liver function test.

Baseline platelet counts were done on the day of presentation. Repeat platelet counts were done in subjects with marked thrombocytopenia until normal or near-normal values were reached. Other investigations as necessary were done to achieve diagnosis such as bone marrow trephine biopsy, serological study for HIV infection, TSH, Serum widal, D-Dimer, Serum vitamin B12 level, Anti-Nuclear Antibody (ANA). Once the specific diagnosis was reached, patients were treated for it specifically and symptomatically. For platelet count, two methods were used. Primarily, an automated cell counter was used with features of counting RBC's, WBC's, platelets and haemoglobin estimation along with blood indices all together. If thrombocytopenia was documented, then direct visualization was done in which 0.02 ml EDTA blood was diluted with 2ml of diluting fluid followed by charging the Neubaur's chamber with the fluid and number of platelets was counted.

Statistical analysis

Statistical analysis was done using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Chi-square test was done for qualitative variables and t-test was used for quantitative variables. P<0.05 was considered as statistically significant.

RESULTS

The present study was conducted in age group 1-18 years. Incidence of thrombocytopenia was more in male children (52.22%) as compared to female children (47.78%) (Table 1). Febrile thrombocytopenia was found commonest between the months of July to September affecting 83 (46.11%) patients, 44 (24.44%) patients were affected between October to December 28 (15.55%) from January to March and 25 (13.89%) from April to June (Table 1).

Table 1: Detailed data on the study.

Study data profile	
Total number of cases	180
Male: Female	94:86
Age range	01-18
Month-wise prevalence	**No of patients (%)**
January to March	28 (15.55%)
April to June	25 (13.89%)
July to September	83 (46.11%)
October to December	44 (24.44%)
Platelet count distribution	
< 10,000/ mm^3	24 (13.33%)
10,000 – 20,000 / mm^3	30 (16.67%)
20,000 – 50,000 / mm^3	43 (23.89%)
>50,001/ mm^3	83 (46.11%)

The commonest cause of thrombocytopenia in our study were viral fever (other than dengue and chikungunya) 27.78% (50), followed by dengue 22.2% (40), enteric fever 12.22% (22), chikungunya 11.11% (20), malaria 8.33% (15), septicaemia 5.55% (10), ITP 5.55% (10), haematologic malignancy 1.67% (03) and megaloblastic anaemia 1.11%(02) (Table 2 and Figure 1).

Table 2: Correlation of aetiology with platelet count.

Etiology	N (%)	Platelet Count			
		<10,000/µl	10,000-20,000µl	20,000-50,000µl	>50,000µl
Dengue	40 (22.22)	10	10	12	8
P. Falciparum Malaria	05 (2.78)	0	1	2	2
P.Vivax Malaria	10 (5.55)	0	1	3	6
Enteric fever	22 (12.22)	0	2	5	15
Chikungunya	20 (11.11)	1	2	4	13
Viral fever other than dengue and chikungunya	50 (27.78)	2	4	10	34
ITP	10 (5.55)	5	4	1	0
Megaloblastic anemia	02 (1.11)	0	1	1	0
Septicemia	10 (5.55)	5	4	1	0
Hematologic Malignancy	03 (1.67)	1	1	1	0
Cirrhosis of Liver	02 (1.11)	0	0	1	1
Pulmonary tuberculosis	01 (0.55)	0	0	0	1
Kala-azar	02 (1.11)	0	0	1	1
HIV	01 (0.55)	0	0	0	1
Thalassemia/ Hypersplenism	02 (1.11)	0	0	1	1
Total	180	24	30	43	83

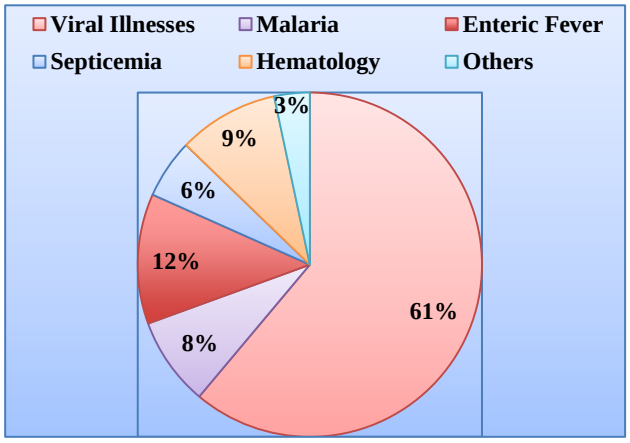

Figure 1: Aetiology of fever with thrombocytopenia.

There were no differences in aetiology in both sex which was statistically significant (Figure 2).

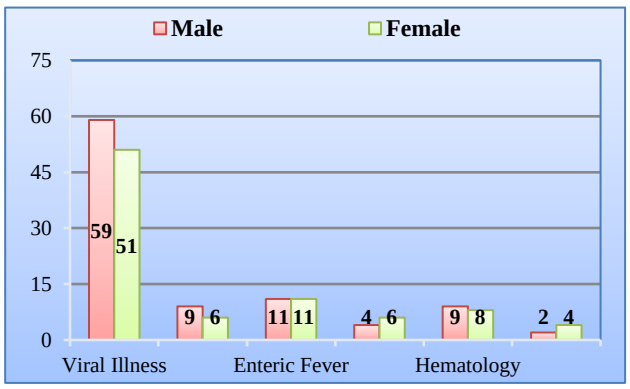

Figure 2: Bar diagram showing aetiology in both sexes.

Out of the 180 thrombocytopenic patients, 35 (19.45%) patients were symptomatic and showed bleeding manifestations. Skin and mucosal bleeds were seen in 15 patients as a major bleeding manifestation followed by 8 patients having gum bleeding.

Haematemesis, melena and epistaxis was seen in 2 patients each, haematuria, subconjunctival haemorrhage and intracranial haemorrhage was seen in 1 patient each. The platelet count at which each of these manifestations was seen is shown in Table 3.

In present study platelet count range of >50000/mm^3 was found in 83 (46.11%) patients, while 43 (23.89%) had platelet count in range of 20000- 50000/ mm^3, 54(30%) patients had count <20000/ mm^3. In present study, aetiologically there were 10(5.55%) cases of dengue fever, 5 (2.78%) cases each of ITP and septicaemia, 2(1.11%) cases of viral fever and 1 (0.55%) case of haematological malignancy had severe thrombocytopenia (Table 2).

Thirty five (19.45%) cases of thrombocytopenia were symptomatic and had bleeding manifestations. Majority of patients with bleeding manifestations (77.14%) were having platelet count <20,000/ mm^3. Only seven patients (3.89%) with count between 20,000-50,000/ mm^3 and one case suffering from dengue with platelet count more than 50,000, demonstrated bleeding manifestation (Table 3).

Eight patients presented with platelet count <10,000/ µl but had no hemorrhagic manifestations. Ten patients having bleeding manifestations required platelet transfusions irrespective of their platelet count.

Remaining patients were given disease specific treatment only. The diagnosis of 3 cases of haematological malignancy and 2 cases of megaloblastic anaemia were confirmed by bone marrow aspiration study.

Table 3: Hemorrhagic manifestations associated with thrombocytopenia.

		Platelet Count			
	Total No of patients (n=180)	**<10,000/µl**	**10,000-20,000µl**	**20,000-50,000µl**	**>50,000µl**
Asymptomatic	145 (80.55)	8	19	36	82
Symptomatic	35 (19.45)	16	11	7	1
Site of bleeding	**Total no. of patients (n=35) n%**				
Skin and mucous membrane (Petechia, ecchymosis, purpura)	15 (44.12)	6	5	3	1
Gum Bleeding	9 (25.71)	3	3	2	0
Hematemesis	2 (5.89)	0	1	1	0
Hematuria	1 (2.94)	2	0	0	0
Melena	2 (5.89)	1	1	0	0
Bleeding per rectum	2 (5.89)	2	0	0	0
Epistaxis	2 (5.89)	0	1	1	0
Sub conjunctival hemorrhage	1 (2.94)	1	0	0	0
Intracranial hemorrhage	1 (2.94)	1	0	0	0

Initial clinical presentation in the hospital in majority of the patients was fever, headache, body ache and joint pain followed by gastrointestinal symptoms like abdominal pain and vomiting (Table 4). Only 10 patients (5.55%) presented with cough and dyspnoea. We had 2 mortality in the study group and both were due to dengue.

Table 4: Clinical presentation of cases of fever with thrombocytopenia.

Feature	Number	%
Fever	180	100
Headache	110	61.11
Body ache	120	66.67
Joint pain	92	51.11
Petechial rashes	15	8.33
Abdominal pain	29	16.11
Vomiting	34	18.89
Loose motion	8	4.44
GI bleed	6	3.33
Cough and dyspnea	10	5.55
Hematuria	1	0.55
Abnormal RFT	30	16.67
Abnormal LFT	45	25
Hypotension	23	12.78
Tachycardia	63	35

DISCUSSION

Fever is the presenting complaint in many illnesses especially the infectious causes. Peripheral smear of many of these illnesses show thrombocytopenia. Transient thrombocytopenia occurs with many systemic infections. It is also a very common manifestation in tropical infections like malaria especially the falciparum type, dengue, chikungunya, a variety of viral infections and enteric fever. Thrombocytopenia usually occurs in 50- 75% with bacterial or with fungal infections. It occurs in 50% cases of gram negative bacterial infections and also in sepsis. It is even seen in other viral infections including HIV.[6]

The commonest causes of thrombocytopenia in our study were viral fever (other than dengue and chikungunya) 27.78% (50), followed by Dengue 22.2% (40), enteric fever 12.22% (22), chikungunya 11.11% (20) and malaria 8.33% (15). However in other studies like that done by Nair in New Delhi, septicemia (26.6%) was the major cause of febrile thrombocytopenia.[7] In another study done by Gandhi malaria was found to be the major cause in 41.07%.[8] Similarly, Lakum, also found malaria as the most common cause of febrile thrombocytopenia in 46.8% of the cases.[9] Another study done by Bhalara, showed dengue (60.8%) as the main aetiology.[10]

In present study, viral infections were the commonest cause due to the higher prevalence of these infections during the rainy season. This difference could have been due to seasonal and regional variation. Similar to present study, Kumaran also found viral fever to be the commonest cause in 50.3% cases.[11]

Early diagnosis of viral infections remain a challenge to all clinicians. In a study by Ho, they calculated several parameters to predict early diagnosis of laboratory

confirmed dengue and other viral infections.[12] No single laboratory test was good enough in terms of positive predictive value for acute dengue infection. In cases where all the available investigations were negative, we labelled them as probably viral fever (27.78%).

Nair labelled them as unknown aetiology in his study.[7] Serological diagnosis of viral infections is expensive, cumbersome and not easily available. Owing to limited resources and laboratory facilities, the diagnosis of fever could not be made in 71 (47%) cases. Hence labelled as undiagnosed fever.

In present study, spontaneous bleeding was seen in 57.14% while petechiae was seen only in 42.86%. In a study by Nair et al spontaneous bleeding was seen in 77.78% as a major manifestation followed by petechiae/purpura seen in 22.22%.[7] However, in a study done by Patil petechiae was the major manifestation in 73.9% followed by spontaneous bleeding only in 26.9%.[13] While in another study by Lohitashwa et al, purpura (63%) was the commonest bleeding manifestations followed by spontaneous bleeding (37%).[14]

In present study, other than fever most patients had headache (61.11%), body ache (66.67%) and joint pains (51.11%). The reason for these clinical features may have been because majority of our patients were of viral illness, dengue and chikungunya. Similar results were seen in Khan's study, which showed chills and rigors in 80%, myalgia in 70%, vomiting in 60%, headache in 50% and rash in 25%.[15]

Unusual clinical feature was pharyngitis in 7% of patients. Murthy's study and Kochar showed deranged renal parameters in 24.68% and 6.25% cases respectively.[16,17] In the present study, renal function tests were deranged in 16.67% cases of fever with thrombocytopenia.

Firstly, present study was applicable only to the pediatric age group and hence, we do not know whether the same results can be extrapolated to the general population as well. Secondly, many acute febrile cases may have been treated in the peripheral clinics and hospitals without any complete blood count being done at all. Hence, our hospital based model might not reflect all the cases of fever with thrombocytopenia in the given locality or population. Lastly, our study did not do an in-depth correlation with other clinical manifestations.

CONCLUSION

Febrile thrombocytopenia is a commonly observed haematological entity commonly caused by infections like viral illnesses, dengue, malaria, enteric fever etc. It commonly manifests with clinical features of underlying disease condition and sometimes with bleeding manifestation also. There is no relation between platelet count and bleeding manifestations. Thrombocytopenia also has no correlation to mortality and morbidity. Mortality in febrile thrombocytopenia is not directly associated with degree of thrombocytopenia.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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