

Original Research Article

Clinical profile, laboratory parameters and severity predictors in children with fever and thrombocytopenia- experience of a tertiary care centreKhodaija Mahvish¹, Md Rizwan Akhtar^{2*}, Girijanand Jha³, Binod Kumar Singh⁴¹Senior Resident, Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India²Assistant Professor, Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India³Senior Resident, Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India⁴Professor and HOD, Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India

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Abstract

Background and Objectives. Fever with thrombocytopenia is a common clinical entity that refers to reduction in platelet count below age and sex reference values in a febrile child. With early recognition, risk stratification and prompt treatment, morbidity and mortality can be limited. However, undue anxiety in parents or treating doctors may prompt one to do unnecessary platelet transfusions. In this study, we intended to study clinical profile, laboratory parameters and severity predictors in children with fever and thrombocytopenia. **Methodology:** We conducted this prospective observational study over 1 year from April 2019 to March 2020 at department of Pediatrics, NMCH, Patna, Bihar including children of 1-14 years of age with fever and platelet count below 150000/mm³ with or without bleeding. **Results:** Over the study period, we enrolled 120 children with febrile thrombocytopenia. Mean age was 6.9 years and most of the affected children were in 5-10 years age group (43.3%). Incidence of febrile thrombocytopenia was highest between months of July & September (44.2%). Other presenting features were body ache (60.8%), headache (55.8%) and joint pain (48.8%) etc. Common etiologies were dengue fever (25.8%), unspecified viral illness (17.5%), septicemia (10%), ITP (7.5%), enteric fever (6.67%) etc. Only 26 (21.7%) suffered from bleeding manifestations. Skin bleeds were the commonest bleeding manifestation (34.6%) followed by gum bleeding (23.1%), hematemesis (7.7%), hematuria (7.7%) etc. Duration of fever >5 days, hemodynamic instability, hepatomegaly, platelets count <10,000/cu mm, abnormal KFT and elevated liver enzymes were associated with a significant higher risk of bleeding. **Conclusion:** Febrile thrombocytopenia is most frequently caused by infections: viral diseases (dengue, chikungunya and other viruses), malaria, enteric fever etc. Clinical features are reflective of the primary disease/condition as well as bleeding manifestations. Late presentation to hospital, prolonged fever and end organ damage influence outcome in these children.

Keywords: bleeding, dengue, fever, infection, malaria, platelet count, thrombocytopenia.

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Introduction

The most common reason for which Pediatrician's consultation is sought is evaluation of a febrile child. It is therefore of utmost importance to assess carefully every febrile child to find an etiology[1]. Fever with thrombocytopenia is a distinct clinical entity that refers to reduction in platelet count below age and sex reference values[2] (usually taken as 150×10⁹/L) in a child with fever. Reduced platelet count caused by EDTA is a common laboratory phenomenon and leads to pseudo thrombocytopenia[3]. In tropical countries such as India, most of acute febrile illnesses have an infectious aetiology and many of them are associated with thrombocytopenia[4]. The basic mechanism of thrombocytopenia is related to decreased production or increased destruction (immune or non-immune) or increased sequestration in spleen. Nevertheless, in day to day pediatric practice, the common conditions associated with fever and thrombocytopenia in children are infections like malaria, dengue, scrub typhus & other rickettsial infections, meningococemia, leptospirosis, other viral illnesses and septicemia. It is important to remember that sometimes non-infectious causes such as primary hematological disorders/ malignancy may also present as febrile thrombocytopenia.

Clinical features of this condition is quite variable. Many a times

thrombocytopenia is discovered incidentally in an asymptomatic child being evaluated for other conditions and is usually transient[5,6]. However, some may experience bleeding manifestations like petechiae, epistaxis, gum bleeding, hematuria or gastrointestinal hemorrhage. Sometimes, there may be life threatening events like intracranial hemorrhage or massive GI bleeding, usually at lower platelet counts[7]. Infact, thrombocytopenia is the most common cause of bleeding in children. In Indian scenario, fever with thrombo-cytopenia is commonly seen in hospital setting during monsoon and peri monsoon period. It is believed that the climatic conditions during these periods of year are favorable for transmission of most of these infections [8]. Occasionally, some of these children may go on to develop a stormy course with multi-organ dysfunction requiring intensive care unit admission which is associated with significant morbidity and mortality[9].

Unpredictable course of this condition leads to serious anxiety in parents of these children as well as treating doctors which may prompt one to do unnecessary "prophylactic" platelet transfusions. However, with early recognition, risk stratification and prompt initiation of treatment, disease related morbidity and mortality can be limited[10]. With there being an increasing number of cases all over India, studies focusing on this condition has become important. Based on this background we intended to study the clinical profile, laboratory parameters, short term outcome and prognostic factors in children with fever and thrombocytopenia at our tertiary care center.

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Aim and Objectives

Aim: To study the profile of fever with thrombocytopenia in children.

Objectives: 1. To study the common causes of febrile thrombocytopenia in children.

2. To study the clinical and laboratory parameters in these children.

3. To study the severity of thrombocytopenia and factors predicting bleeding in these children

Methodology

Study setting: OPD and I.P.D of deptt of Pediatrics N.M.C.H Patna, Bihar, India

Study duration: 1 year, from June 2019 to May 2020.

Study design: prospective observational study.

Inclusion criteria: In the present study we included children between 1-14 years of age with fever (axillary temperature >38 deg C) and platelet count below 150000/mm³ with or without bleeding.

Exclusion criteria: Infants with febrile thrombocytopenia and children with thrombocytopenia without fever and previously diagnosed cases of platelet disorder/dysfunction were excluded from the present study. Previously diagnosed conditions/diseases which could lead to thrombocytopenia such as ITP, cirrhosis, malignancy and children receiving antiplatelet drugs or drugs known to cause thrombocytopenia were also excluded as their clinical or laboratory parameters could mimic or influence the parameters being studied in the present study.

Study technique: After obtaining informed consent from either parent, we enrolled participants in the present study. Information regarding baseline characteristics were entered in a structured proforma. All children were subjected to focused history taking and thorough clinical examination. Special emphasis was given on obtaining data related to type and duration of fever and bleeding manifestations present at the time of presentation to our hospital or

later during the course of their hospital stay. Investigations sent included CBC, peripheral blood smear and CRP in all cases. Rapid diagnostic test for malarial parasites, blood culture, Widal test, ELISA tests for dengue virus, IgM against rickettsial infection etc were done as per clinical suspicion of the primary disease. Coagulation studies, L.F.T, R.F.T, C.S.F analysis, bone marrow aspiration, serum B12 level and radiological investigations were done as needed in select cases. Platelet count was repeated every other day in children with platelet count between 50000-15000/cu mm and daily in children with platelet count <50000/cu mm until normal or near normal values were reached. Every incidence of low platelet count detected by automated analyzer was confirmed by doing a manual platelet count. Once a specific diagnosis was reached, children were treated accordingly.

Statistical analysis: Data so collected was recorded, tabulated and entered in Microsoft excel sheet, and then analyzed by using statistical software "SPSS ver.21®". Variables were expressed as mean, standard deviation, proportions and percentiles as appropriate. Dichotomous variables were compared using Chi-square test whereas continuous variables were compared using Student t-test. P-value <0.05 was taken as significant.

Observation and results

Over the study period, we enrolled 120 children with febrile thrombocytopenia. Mean age of the study group was 6.9 years. Most of the affected children were in 5-10 years age group (n=52, 43.3%). Mean weight of the study population was 19.34 Kg. Males (69) outnumbered females (51) with a male: female ratio of 1.35:1. Incidence of febrile thrombocytopenia was highest between the months of July to September (n=53, 44.2% of total cases) followed by October to December (n= 27, 22.5% of total cases) and therest (n=40, 33.3% of total cases) from January to June. Table 1 depicts general characteristics of the study population.

Table 1: General characteristics of the study population

Parameter	Value
Age in years, mean ± SD	6.9 ± 2.7
Weight in Kg, mean ± SD	19.3 ± 3.8
Male gender, n (%)	69 (57.5%)
Rural area inhabitant, n (%)	73 (60.8%)
Urban area inhabitant, n (%)	47 (39.2%)
Platelets count	
<10,000/cu mm, n (%)	16 (13.3%)
10,000-50,000/cu mm, n (%)	39 (32.5%)
50,000-1,00,000/cu mm, n (%)	46 (38.3%)
1,00,000-1,50,000/cu mm, n (%)	19 (15.8%)

We also studied the clinical features of these 120 children in our study. The most common presenting feature after fever was bodyache (60.8%), headache (55.8%) and joint pain (48.8%). Table 2 depicts the clinical features of these children in relation to gender. There was no statistically significant difference in presentations in relation to gender of these children.

Table 2: Presenting features of the 120 children studied

Presenting feature	Total no. of children (n=100)	Male gender (n=69)	Female gender (n=51)
Fever	120 (100%)	69 (100%)	51 (100%)
Body ache	73 (60.8%)	40 (58.0%)	33 (64.7%)
Headache	67 (55.8)	36 (52.2%)	31 (60.8%)
Joint pain	58 (48.3%)	30 (43.5%)	28 (54.9%)
Petechial skin rash	12 (10%)	7 (10.1%)	5 (9.80%)
G.I bleed	5 (4.2%)	3 (4.35%)	2 (3.92%)
Hematuria	2 (1.7%)	1 (1.45%)	1 (1.96%)
Loose stools	7 (5.8%)	4 (5.80%)	3 (5.88%)
Vomiting	29 (24.2%)	16 (23.2%)	13 (25.5%)
Abdominal pain	19 (15.8%)	11 (15.9%)	8 (15.7%)
Breathing difficulty	12 (10%)	7(10.1%)	5 (9.80%)
Hypotension	16 (13.3%)	9 (13.1%)	7 (13.7%)
Tachycardia	35 (29.2%)	19 (27.5%)	16 (31.4%)
Deranged LFT	27 (22.5%)	15 (21.7%)	12 (23.5%)
Deranged KFT	14 (11.7%)	7 (10.1%)	7 (13.7%)

Common causes of thrombocytopenia in our study were dengue fever (25.8%) followed by unspecified viral illness (17.5%), septicemia (10%), ITP (7.5%), enteric fever (6.67%), Chikungunya (6.67%) and others. Fig 3 shows distribution of platelet count in different causes of febrile thrombocytopenia.

Table 3: Variation of platelet counts in relation to aetiology

	No. of children	<10,000/mm ³	10,000-50,000/mm ³	50,000-1,00,000/mm ³	1,00,000-1,50,000/mm ³
Dengue fever	31 (25.8%)	3	13	10	5
Chikungunya	8 (6.67%)	1	2	3	2
P. falciparum malaria	6 (5.00%)	1	3	1	1
P. vivax malaria	4 (3.33%)	1	1	2	0
Enteric fever	8 (6.67%)	0	2	4	2
Other viral illnesses	21 (17.5%)	3	5	9	4
Septicemia	12 (10.0%)	3	4	4	1
Pulmonary TB	1 (0.83%)	0	0	1	0
Kala-azar	3 (2.50%)	0	1	2	0
HIV	3 (2.50%)	0	1	1	1
ITP	9 (7.50%)	2	4	3	0
Megaloblastic anemia	3 (2.50%)	0	0	2	1
Hematological malignancy	5 (4.17%)	1	2	1	1
Chronic liver disease	4 (3.33%)	0	1	2	1
Hypersplenism	2 (1.67%)	1	0	1	0
Total	120 (100%)	16	39	46	19

Bleeding manifestations

Out of the 120 thrombocytopenic children, only 26 (21.7%) were symptomatic and suffered from bleeding manifestations, whereas majority of the children (78.3%) were asymptomatic. Skin bleeds were the commonest bleeding manifestation as seen in 9 (34.6%) children. This was followed by gum bleeding in 6 (23.1%), hematemesisis 2 (7.7%), hematuria in 2 (7.7%), melena in 2 (7.7%) and epistaxis in 2 (7.7%) children. Subconjunctival hemorrhage, hematochezia and intracranial hemorrhage was seen in 1 child each. Platelet count at each of these manifestations is shown in Table 4. Majority of the patients with bleeding manifestations (38.5%) had

platelet count <10,000/mm³. Only seven patients (26.9%) with platelet count >50,000/mm³ had bleeding manifestation. However, 6 children had platelet count <10,000/mm³ but didn't suffer from any hemorrhagic manifestations. Only 8 (30.8%) children with bleeding manifestations required platelet transfusions and this was independent of their platelet count. Remaining children improved with supportive and disease specific treatment only. 16 children unfortunately succumbed (13.3%). Common causes of death were MODS, pulmonary edema, shock and respiratory failure which were more reflective of the primary disease under evaluation.

Table 4: Bleeding manifestations in relation to platelet count

	No. of children	<10,000/mm ³	10,000-50,000/mm ³	50,000-1,00,000/mm ³	1,00,000-1,50,000/mm ³
Asymptomatic	94(78.3%)	6	30	40	18
Symptomatic	26(21.7%)	10	9	6	1
Site of bleeding (Total no.=26)					
Skin(Petechiae,ecchymosis, purpura)	9(34.6%)	2	3	3	1
Gum bleeding	6(23.1%)	2	3	1	0
Hematemesisis	2 (7.7%)	1	1	0	0
Hematuria	2 (7.7%)	1	0	1	0
Melena	2 (7.7%)	1	0	1	0
Hematochezia	1 (3.8%)	1	0	0	0
Epistaxis	2 (7.7%)	1	1	0	0
Subconjunctival hemorrhage	1 (3.8%)	0	1	0	0
Intracranial hemorrhage	1 (3.8%)	1	0	0	0

We also studied influence of various parameters on occurrence of bleeding in these patients as shown in table 5. We observed that in univariate analysis, following parameters were associated with a significant higher risk of bleeding: duration of fever >5 days, hemodynamic instability, hepatomegaly, platelets count <10,000/cu mm, abnormal KFT and elevated liver enzymes.

Table 5: Factors associated with a higher risk of bleeding

	No bleeding, n= 94	Bleeding, n= 26	P value
Duration of fever>5 days, n (%)	13	9	0.01
Hemodynamic instability, n (%)	7	9	<0.001
Warning signs, n (%)	9	6	0.07
Hepatomegaly, n (%)	17	15	<0.001
Leukopenia, n (%)	51	13	0.70
Platelets count <10,000/cu mm, n (%)	6	10	<0.001
Abnormal KFT, n (%)	6	8	<0.001
Elevated liver enzymes, n (%)	14	13	<0.001

Discussion

In the present study we intended to study the pattern and profile of thrombocytopenia in febrile children. Thrombocytopenia is said to

occur when platelet count falls below 1,50,000/cu mm. Such low platelet counts are suspected when there is a history of easy bruising or bleeding, or it may be detected as an incidental finding during

investigations done for other reasons. Fortunately, unlike in adults, the overwhelming majority of pediatric thrombocytopenia cases are reactive, i.e., secondary and mostly benign. Fever is the presenting feature in many childhood diseases, especially in infectious conditions. Blood investigations in such children frequently reveals thrombocytopenia. In the present study, we enrolled 120 children with febrile thrombocytopenia. Most of the affected children were in 5-10 years age group (n=52, 43.3%). Incidence of febrile thrombocytopenia was highest between the months of July to September, followed by October to December. Similar findings were reported by Nair et al[11] which probably reflects the higher incidence of infectious diseases, particularly Dengue fever, during this period. The most common causes of thrombocytopenia in our study was dengue fever (25.8%) followed by unspecified viral illness (17.5%). Our findings are comparable to study done by Bhalara et al[12] who showed dengue (60.8%) as the commonest cause of thrombocytopenia in febrile children. However, Nair et al[13] in their study in Delhi found septicemia as the major cause (26.6%) of febrile thrombocytopenia and Gandhi et al[14] found malaria to be the major cause in 41.07% cases. This difference can be attributed to seasonal and regional variation of the common infections. In the present study, common symptomatology apart from fever were body ache (60.8%), headache (55.8%), and joint pains (48.3%). Such high incidence of these constitutional symptoms can be attributed to the fact that the most common etiology in our study was related to viral illness (dengue, chikungunya and other viral illnesses). Similar findings were reported by Khan et al[15] who showed that there were chills and rigors in 80%, myalgia in 70%, vomiting in 60%, headache in 50% and rash in 25% cases. Murthy et al reported a relatively higher occurrence of renal impairment in 24.68% cases[16]. However, they had included only children with malaria in their study on fever with thrombocytopenia in children. Nevertheless, in our study too we found deranged renal function tests in 11.7% and deranged LFT in 22.5% of such unfortunate children with fever and thrombocytopenia. Out of the 120 thrombocytopenic children, only 26 (21.7%) were symptomatic and suffered from bleeding manifestations, whereas majority of the children (78.3%) were asymptomatic. Skin bleeds were the commonest bleeding manifestation as seen in 34.6% of children with bleeding. Similar to our findings, Nair et al[11] also reported petechiae/purpura in 22.22% and spontaneous bleeding in 77.78% of such children. However, Patil et al[17] reported petechiae as the commonest manifestation in 73.9% followed by spontaneous bleeding only in 26.9%. While in another study by Saini et al[18] petechiae/purpura (91.40%) was the commonest bleeding manifestation followed by spontaneous bleeding (57%). These probably reflect the heterogeneity in etiological parameters and risk of bleeding. (platelets level, severity of primary disease, end organ involvement)

We also studied the factors associated with a higher risk of bleeding. We observed that in univariate analysis, following parameters were associated with a significant higher risk of bleeding: duration of fever >5 days, hemodynamic instability, hepatomegaly, platelets count <10,000/cu mm, abnormal KFT and elevated liver enzymes. These probably represent the sub group of children with a more severe disease as well as end organ damage. In their study Gowd et al[19] found that late visit to hospital with prolonged fever and warning symptoms influenced poor outcome in these children. They also found that children presenting with hepatomegaly, platelet count less than 1 lakh, elevated hematocrit, abnormal renal function test, elevated liver enzymes and abnormal coagulation profile at the time of admission had poor outcome. This reiterates that early diagnosis and proper treatment of the primary condition is the most important parameter influencing outcome in such children.

Conclusion

Febrile thrombocytopenia, a commonly observed problem is most frequently caused by infections: viral diseases (dengue, chikungunya, and other viruses), malaria, enteric fever etc. The clinical features of

this condition are reflective of the primary disease/condition as well as bleeding manifestations. Bleeding occurs usually but not always with a more severe thrombocytopenia. Late presentation to the hospital, prolonged fever and end organ damage influence outcome in these children.

Limitations

First limitation is that ours is a single centre study and so our findings cannot be extrapolated to the general population. Secondly, many acute febrile cases recover soon and so blood counts are not done in all cases. Hence, our hospital based model might not be reflective of all cases of fever with thrombocytopenia in the given locality or population. Third limitation is that we didn't do long term follow up of these patients to look for incomplete recovery or recurrence of thrombocytopenia.

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