A Prospective Study of Clinical Profile in Febrile Illness with Thrombocytopenia in Children Aged 1 to 12 Years Admitted in a Tertiary Care Centre in Telangana

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ABSTRACT

BACKGROUND

Fever with thrombocytopenia is a common clinical problem in paediatric wards. Significant number of acute febrile illnesses have an infectious aetiology and are often associated with thrombocytopenia. The objective of the study was to determine the clinico-etiological profile and outcome of children admitted with febrile thrombocytopenia, especially in those with infective aetiology.

METHODS

The study design is a prospective observational study. It was conducted from September 2017 to August 2019 in the Department of Paediatrics, Niloufer Institute of Women and Child Health, Hyderabad. A total of hundred (100) children in the age group of 1 year to 12 years presented with fever, and thrombocytopenia were included in the study. Newborns, infants, children with febrile thrombocytopenia, known ITP (idiopathic thrombocytopenic purpura), already diagnosed haematological malignancy and children on antiplatelet drugs like aspirin were excluded from the study. After informed written consent, detailed history was elicited, clinical examination and necessary laboratory investigations were carried out, and the data was captured in a pre-structured proforma. Study parameters were analysed using Statistical Package for Social Sciences (SPSS) version 16 software.

RESULTS

The study included 100 children. A ratio of 1.4 : 1 was observed in male to female ratio. As of the clinical features, gastrointestinal (GI) symptoms such as nausea, vomiting and pain abdomen were more common, followed by headache and myalgia. On examination, two-thirds of the children had hepatomegaly, and one-third had splenomegaly. Among 100 children with febrile thrombocytopenia, 38 children had bleeding manifestations (cutaneous bleeds > GI bleeds > other bleeds) in those with moderate to severe thrombocytopenia. In the etiological profile, dengue fever was more common, followed by undiagnosed fever, enteric fever, ALL (acute lymphoblastic leukemia), scrub typhus, malaria and leptospira, respectively. Out of 100 children, 94 were discharged, and 6 children with ALL were referred to the haemato-oncology center for further management.

CONCLUSIONS

Clinical presentation of cases with febrile thrombocytopenia is varied. Common causes of febrile thrombocytopenia observed in this study were dengue fever followed by un diagnosed fever and enteric fever.

KEYWORDS

Fever, Thrombocytopenia, Platelet count, Bleeding

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BACKGROUND

Parents often seek medical attention whenever the child looks sick or develops fever. Among children, fever and upper respiratory symptoms are the common cause of visit to a medical professional or hospital visit. In recent years, fever with thrombocytopenia is a common clinical presentation which required hospitalization, as it is associated with significant morbidity. Evaluation of these children for the aetiology will facilitate in management, as some of them may present with shock with hemodynamic instability and bleeding manifestations.[1] The aetiology may differ based on the geographical location and the seasonal variation. Fever is the most common symptom requiring a visit to a medical professional during the monsoon and pre monsoon season, wherein viral and mosquito borne infections are more prevalent.

A platelet count of below 1,50,000/mm^3 is defined as thrombocytopenia, which is the lower limit of normal range as is supported by the National health and nutrition examination survey.[2] Thrombocytopenia can result from either increased destruction, decreased production or increased consumption. Mild to moderate thrombocytopenia do not require any treatment and may present as asymptomatic to mild bleeding manifestations respectively. Those with severe thrombocytopenia will mostly be sick looking at presentation and have bleeding manifestations or hemodynamic instability. The aetiology can be varied from infections, idiopathic to bone marrow infiltration. In spite of advancements in technology, a thorough history, physical examination and endemicity of infections in a particular area may guide in differential diagnosis of fever with thrombocytopenia. In a developing country like India, infections may be the common cause of thrombocytopenia such as seen in malaria, typhoid, dengue fever, septicaemia, etc.

An early diagnosis of the aetiology of fever with thrombocytopenia will facilitate in the management of the children with better outcome.

Aims and Objectives

1. To determine the clinical, etiological profile, laboratory parameters of children with acute febrile illness associated with thrombocytopenia.
2. To assess the disease outcome of children with acute febrile illness associated with thrombocytopenia.

METHODS

This is a prospective observational study conducted at the Department of Paediatrics, Niloufer hospital, Osmania Medical College, Hyderabad, Telangana state, over a period of 2 years from September 2017 to August 2019, among children aged 1 year to 12 years. Institutional Ethical Committee clearance was taken from the Institute with IEC No ECR / 300 / Inst / AP / 2013 / RR - 16. All children admitted with fever and thrombocytopenia were enrolled in the study. At the time of admission, a few children already had the complete blood picture (CBP) report showing thrombocytopenia. Among others who were admitted with fever, whose investigation revealed thrombocytopenia were also included in the study. Neonates, infants and children with afebrile thrombocytopenia, previously diagnosed with malignancies with thrombocytopenia, on antiplatelet medications like aspirin, clopidogrel were excluded from the study. The parents/guardians of the children were counselled and a written informed consent was taken before inclusion in the study. Details of age, gender, presenting complaints i.e., duration of fever, headache, myalgias, gastro intestinal symptoms, cutaneous or gastro intestinal or other bleeds like gum bleeds, epistaxis and hematuria, seizures, oedema were noted.

A detailed clinical examination was done and the findings were noted. Laboratory investigations including complete blood picture, peripheral smear for malarial parasite, renal and liver function tests were done. Depending upon the differential diagnosis, blood culture, other relevant investigations such as Widal test, leptospiral IgM antibody test, dengue serology, NS1 antigen test, scrub typhus IgM enzyme linked immunosorbent assay (ELISA), etc were done accordingly. For those with suspected hematologic malignancy, bone marrow aspiration was done. The children were monitored for early diagnosis of organ dysfunction, bleeding manifestations, and for signs of shock. They were treated as and when the complications occurred. In hemodynamically stable children, platelet count was done on alternate days. For hemodynamically unstable children and for those with bleeding manifestations, it was monitored on a daily basis till the count reached 1,00,000/mm.[3] Any need for blood product transfusion was documented. In children with fever and thrombocytopenia, where the clinical examination and routine investigations did not yield any conclusive result, a diagnosis of undiagnosed fever was made which possibly can be of viral aetiology. The final outcome was noted as either discharge, referral or death.

Statistical Analysis

Data was analysed using Statistical Package for Social Sciences (SPSS software version 16). Simple calculations such as proportion, percentages, mean values and standard deviation were derived.

RESULTS

A total of 100 children were included in the study, i.e., n = 100. Demographic data which included age, gender was analyzed using proportions as for statistical purpose. As the total number is 100, the numbers and corresponding percentages tally numerically. Among the 100 children, gender distribution revealed 59 % male and 41 % female with a male female ratio of 1.4 : 1. Children were categorized into less than five years and more than five years age group. Out of 100 children, 51 were less than 5 years, 49 were more than 5 years of age. The most common clinical presentation in all children was fever (100 %), followed by 58 % with gastro intestinal (GI) symptoms like nausea, vomiting and

pain abdomen. 40 % had headache, while arthralgia and myalgia were noted in 25 % and 35 % respectively. Seizures were observed in 6 % of cases whereas 8 % presented with altered sensorium (Table 1).

Symptoms	n (%)
Fever (n = 100)	100 (100 %)
Arthralgia (n = 100)	25 (25 %)
Myalgia (n = 100)	35 (35 %)
Headache (n = 100)	40 (40 %)
GI symptoms [nausea, vomiting, pain abdomen] (n = 100)	58 (58 %)
Abdominal distention (n = 100)	20 (20 %)
Altered sensorium (n = 100)	08 (8 %)
Seizures (n = 100)	06 (6 %)

Table 1. Clinical Presentation of Cases of Fever with Thrombocytopenia

On general examination of children at admission, out of 100 children, majority had pallor (43 %) and hepatomegaly was the common clinical finding on palpation (80 %) followed by splenomegaly (30 %). Abdominal distension was noted in 20 % of cases and jaundice was not so uncommon presentation seen in 12 % of them. (Table 2).

Sign	Frequency/Percent
Pallor (n = 100)	43 (43 %)
Jaundice (n = 100)	12 (12 %)
Oedema (n = 100)	20 (20 %)
Cutaneous bleed (n = 100)	18 (18 %)
Hepatomegaly (n = 100)	80 (80 %)
Splenomegaly (n = 100)	30 (30 %)
Abdominal distension (n = 100)	20 (20 %)

Table 2. Clinical signs at Admission

The mean and standard deviations of various laboratory parameters of the included children were shown in Table 3. The mean haemoglobin level suggested a normal to below normal range suggestive of anaemia. It corelates with the finding of pallor noted in the clinical examination. The liver enzymes ranged from normal to increased values. Similarly, the platelet count at admission was found to be less than 1.5 lakh/cumm.

Lab Parameters	Mean $\pm$ Standard Deviation
HB (haemoglobin) gm/dl	9.5 ± .76
WBC (cells per cu.mm)	7300 ± 5200
Platelet count [At admission] (cells = per cu.mm)	89000 ± 35000
Platelet count lowest (cells per cu.mm)	76000 ± 26000
SGOT U/L	99 ± 79
SGPT U/L	90 ± 77
TSB (total serum bilirubin) mg/dl	0.64 ± 0.54

Table 3. Laboratory Parameters and Statistical Values

Dengue was the common cause of fever with thrombocytopenia in 56 % of children, enteric fever in 8 % and acute lymphocytic leukemia in 6 % of the cases (Table 4). Malaria and leptospira accounted to 4 % each and scrub typhus 5 % respectively.

Diagnosis	Frequency/Percentage
Dengue fever	56 (56 %)
Enteric fever	08 (8 %)
Malaria	04 (4 %)
Scrub typhus	05 (5 %)
Leptospira	04 (4 %)
ALL (acute lymphoid leukemia)	06 (6 %)
Undiagnosed fever	17 (17 %)

Table 4. Aetiology of Febrile Thrombocytopenia

Severity of thrombocytopenia was graded, based on the platelet count as, mild between 1,00,000 to 1,50,000 cells/mm^3, moderate between 50,000 to 1,00,000 cells/mm^3 and severe below 50,000 cells/mm^3. Of the total cases, moderate and severe thrombocytopenia was noted in 48 % and 34 % respectively. Dengue was the most common cause of thrombocytopenia (56 %) followed by undiagnosed fever and enteric fever. Among all the 56 children affected with dengue fever, 85.7 % of them had moderate to severe thrombocytopenia. In enteric fever, out of 8 cases, 6 had moderate, and 2 had mild thrombocytopenia. In children with malaria, all 4 had moderate thrombocytopenia. In those with scrub typhus, out of 5, 1 had severe, 2 moderate and 2 children had mild thrombocytopenia. In children diagnosed with leptospira, out of the total 4 cases, 1 case had severe, 2 moderate and 1 case had mild thrombocytopenia. In all 6 children with ALL, severe thrombocytopenia was noted (Table 5).

Aetiology	Mild Thrombo-cytopenia	Moderate Thrombo-cytopenia	Severe Thrombo-cytopenia
Dengue fever	8 (14.3 %)	26 (46.4 %)	22 (39.3 %)
Enteric fever	2 (25 %)	6 (75 %)	0
Malaria	0	4 (100 %)	0
Scrub typhus	2 (40 %)	2 (40 %)	1 (20 %)
Leptospira	1 (25 %)	2 (50 %)	1 (25 %)
ALL (acute)	0	0	6 (100 %)
Undiagnosed fever	5 (29.4 %)	8 (47.1 %)	4 (23.5 %)

Table 5. Grades of Thrombocytopenia in Specific Aetiology

In children with thrombocytopenia, cutaneous bleeds presenting as petechiae were the commonest bleeding manifestation in 18 % followed by gastrointestinal bleeds in 12 % of them. In 8 % of children, there were mucosal bleeds in the form of epistaxis, gum bleeds or as hematuria (Table 6).

Bleeding Manifestations	Frequency/ Percent (n - 38)	Moderate Thrombo-cytopenia	Severe Thrombo-cytopenia
Cutaneous bleeds	18	8 (44.4 %)	10 (55.6 %)
GI bleeds	12	4 (33.3 %)	8 (66.7 %)
Other bleeds- epistaxis, hematuria, gum bleeds	8	2 (25 %)	6 (75 %)

Table 6. Site of Bleeding Manifestations

The bleeding manifestations were commonly seen in those with moderate and severe thrombocytopenia, while none had in those with mild severity.

Outcome

Among the total 100 children, 94 children improved with appropriate treatment and 6 children were referred to the attached MNJ Cancer hospital, Hyderabad, Telangana for evaluation and management of haematological malignancy.

DISCUSSION

Fever with thrombocytopenia has varied clinical presentations and is of diverse aetiology. It is caused by infectious and non-infectious conditions. A prospective

observational study was conducted over a period of 2 years among children in the age group of 1 to 12 years. The study focuses on common clinical presentation and aetiology of febrile thrombocytopenia which may facilitate in early identification of the disease-related complications and management. Demographic data of age showed a male preponderance with the male : female ratio being 1.4 : 1 which is comparable with studies done in children as well as study in adults by Kumar Praveen et al.[3] in which the male : female ratio was 1.2 : 1. Majority of the children in the study group were between 3 to 8 years of age, which is comparable to study by Shah G.S et al.[4] In a study by Subramanian et al.[5] majority of the children were below 5 years of age. This is the common age group wherein children prefer outdoor play activity, that may increase the risk of exposure to mosquito bites.

During the pre-monsoon and monsoon period, water collection in and around residential homes will be the breeding ground for mosquitoes. This will increase the incidence of mosquito borne diseases with seasonal variation. Dengue infection shows a bimodal peak for age groups of less than 1 year and between 5 to 7 years. Dengue is the most common aetiology of febrile thrombocytopenia among children in many of the studies. In areas endemic for malaria, thrombocytopenia was found to be more commonly associated infection with plasmodium falciparum and vivax. In the present study, majority of children had dengue as the cause for thrombocytopenia, and majority had gastro intestinal symptoms like nausea, vomiting, and pain abdomen. In a study by Subramanian et al.[5] and Sujatha et al.[6] in dengue symptoms related to gastrointestinal system were the commonest. In contrast, Nikalje Anand et al.[7] noted headache as the most common symptom.

In our study, all children were febrile at admission. Shah G. S et al.[4] study revealed hepatomegaly in three fourth of children, splenomegaly in one-fourth of children, and petechiae in half the study group. This study results are comparable with the present study wherein hepatomegaly was noted in 80 %, and splenomegaly in 30 % of children. In contrast, in a study by Karthik raj et al.[8] splenomegaly was noted in 4.5 % and hepatomegaly were found in 45 % respectively. Splenomegaly was a common finding in children diagnosed with malaria, enteric fever, and dengue fever. Pallor was more common, cause could be multi-factorial like nutritional anaemia, recurrent infections, unbalanced diet, etc. It was noted in 43 % of children in the present study, abdominal distension was commonly observed in dengue fever, possibly due to ascites and increased capillary leak or vascular permeability.

Out of the 100 children, majority (82 %) had moderate to severe thrombocytopenia, which may be due to the fact that more children being referred to in the later stage of their illness. In a study by Karthik raj et al.[8] severe thrombocytopenia was noted in 33 % of children, whereas in our study it was noted in 34 % of the children which is comparable. Pankaj et al.[9] study revealed severe thrombocytopenia in 60 %, moderate thrombocytopenia in 27 % and mild thrombocytopenia in 13 % of children respectively. In contrast, in our study moderate thrombocytopenia was seen in 48 % of cases, whereas in a study by Mohan et al.[10] 48 % had mild thrombocytopenia, 35 % moderate and 17 % severe thrombocytopenia. These are comparable to our study. There is a need to correlate the clinical manifestations with the laboratory investigations particularly with respect to platelet count as thrombocytopenia can sometimes be due to sampling error.

In our study, cutaneous bleeds presenting as petechiae was the commonest bleeding manifestation observed in 18 %, followed by GI bleeds in 12 % and other mucosal bleeds such as epistaxis and gum bleeds seen in 8 %. In the study done by Agarwal et al.[11] study results showed petechiae in 42 % of the study group. In the study by Prithvi Raj et al.[12] and Amitha et al.[13] petechiae was the commonest bleeding manifestation followed by mucosal bleeds, which are comparable with our study. It was observed that bleeding manifestations were more common in children with severe and moderate thrombocytopenia, while there were none among those with mild thrombocytopenia. Gastrointestinal bleeds were commonly seen in dengue fever, which were either overt or occult, and are often associated with shock and metabolic acidosis. Cutaneous bleeds were more common in scrub typhus, leptospira, ALL, and undiagnosed fever. In scrub typhus, bleeding was considered to be infection-induced immune-complex vasculitis, perivasculitis and consumptive thrombocytopenia. In undiagnosed fever, bleeding manifestations were due to immune-mediated platelet destruction by viral aetiology and associated platelet consumption. In contrast, Shah G. S et al.[4] and Mohan et al.[10] study results revealed GI bleeds were more common than petechiae and other bleeds. In study by Prithvi Raj et al.[12] bleeding manifestations were more common with a platelet count of fewer than 50,000 cells/cumm. In contrast many of the studies[7,10,11] revealed that there was no correlation between platelet count and bleeding manifestations.

In the present study, infections were the common cause of febrile thrombocytopenia. Among the infections, dengue fever was the most common cause with about half of the study group affected by it and was comparable to many other studies. Undiagnosed fever was the second most common cause followed by enteric fever in the present study. Other conditions detected were malaria, leptospira, scrub typhus, haematological malignancy. In studies by Nikhalje Anand et al.[7] Prithvi Raj et al.[12] and Rekha et al.[14] showed undiagnosed fever as the commonest aetiology followed by dengue fever and enteric fever. In a study by Raikar et al.[15] revealed that dengue fever was the commonest aetiology followed by malaria and sepsis. These studies were comparable with the present study in reference to diagnosable aetiology. In contrast, studies by Amita et al.[13] and Suresh et al.[16] showed malaria as the commonest cause followed by dengue and undiagnosed fever. As the common cause being vector borne diseases like dengue, malaria, rickettsial infections etc, precautionary measures have to be taken to prevent bites and to prevent collections of water which are breeding places for mosquitoes. Proper storage of water and garbage disposal along with maintenance of ponds and lakes will go a long way in the prevention of vector borne diseases.

The children were followed up during the hospital stay and the final outcome of them was noted. 94 % of children improved clinically and got discharged after effective and specific treatment, while 6 % of children diagnosed with acute lymphoblastic leukemia were referred for haemato-oncological consultation and specific management to MNJ Cancer Hospital, Hyderabad. In the study by Sujatha et al.[6] the mortality was 0.7 % and was found in children with severe dengue. Though majority of these children with acute illness with low platelet count recover in the course of time, caution to be exercised in those with bicytopenia. Though leucopenia may be associated in viral infections, presence of anaemia with thrombocytopenia, a careful examination and follow up to be done so as not to miss malignancy. The low platelet count in most of the cases will be transient and recover completely and when prolonged, look out for other causes. The study was conducted to know the clinical profile and aetiology among children presenting with febrile thrombocytopenia. The common cause of febrile thrombocytopenia in most of the studies were infections, and majority were of viral aetiology. As bleeding manifestations were more commonly observed in moderate to severe thrombocytopenia, their presence will caution us to be more vigilant about the possible bleeding. This helps us in managing and monitoring the children with better outcomes. Diagnosis of the cause of febrile thrombocytopenia will help the treating paediatrician in counseling the parents and also in management of the child.

CONCLUSIONS

Clinical presentation of children with febrile thrombocytopenia is varied. The common cause of febrile thrombocytopenia was mostly infections followed by haematological malignancies. Children with acute febrile illness should be investigated with frequent CBP and platelet count, even in the absence of bleeding manifestations, apart from the routine laboratory investigations as guided by the clinical presentation.

Limitations of This Study

The study was conducted as an observational prospective study in a tertiary care center. Hence, there is a possibility of missing milder forms of infections and this study may not reflect the actual distribution of the cases at the population level. More studies are needed at the community level to know different aetiologies in different geographical regions.

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