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Original Research Article

Etiological profile of febrile thrombocytopenia in children aged <12 years in a tertiary care centre

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ABSTRACT

Background: Febrile thrombocytopenia is platelet count <1,50,000/mm^3 associated with fever irrespective of age and gender. There is an increasing trend in the incidence of febrile thrombocytopenia with varied etiology. Though infections are the most common cause in tropical countries like India, sometimes non-infectious conditions like primary haematological disorders and malignancies can also present as febrile thrombocytopenia. Hence it is essential for the treating physicians to be fully aware of etiological factors for febrile thrombocytopenia and how to approach to the condition.
Methods: A hospital based observational study done at Kamineni Institute of Medical Sciences during the study period October 2020 to December 2021 by collecting and analysing details of 100 patients between 1 month-12 years of age who presented with fever and thrombocytopenia at admission. Patients on drugs causing thrombocytopenia were excluded from the study.
Results: Majority of the cases (51%) belonged to the age group of 1-6 years. Out of 100 subjects, 60% of them had dengue fever, 12% of cases had malaria and 10% of cases had enteric fever. Bleeding manifestations were seen in 12% of cases and blood product transfusion was done in 30% of the cases. 98% of cases had recovered and 2 deaths were reported.
Conclusions: Febrile thrombocytopenia is a common clinical presentation in children. Majority of the dengue cases responded well to treatment given as per WHO guidelines. In most of the other infections, thrombocytopenia was transient and asymptomatic with lesser severity and resolved with the treatment of underlying condition.

Keywords: Febrile, Thrombocytopenia, Dengue, Etiology

INTRODUCTION

Febrile thrombocytopenia is the thrombocytopenia associated with fever irrespective of age and gender.[1] Thrombocytopenia is defined as platelet count less than 1,50,000 /mm^3.[2] Fever is an acute phase response which is one of the most common manifestations of an infection/inflammation.[3] Fever is produced due to production of substance called pyrogen. Thrombocytopenia is due to decreased production, increased destruction (immunological and non-immunological) or increased sequestration in spleen.[4] There is an increasing trend in the incidence of fever with thrombocytopenia especially in the pediatric age group.[4] The presence of thrombocytopenia in a child with fever acts as an etiological clue which can aid in early diagnosis and treatment. Although thrombocytopenia has a varied etiology, infectious conditions are more common in tropical countries like India.[3] Viral haemorrhagic fevers (dengue, chikungunya), malaria, enteric fever,

leptospirosis, rickettsial infections are some of the common conditions associated with febrile thrombocytopenia.[1,4] Sometimes non-infectious conditions such as primary haematological disorders, malignancies can also present as febrile thrombocytopenia.[1,3] Drugs which can cause thrombocytopenia are acetaminophen, amiodarone, ceftriaxone, penicillin, diazepam, ranitidine and phenytoin.[5] Although these patients can present with simple fever, the clinical condition of the child can deteriorate rapidly (depending on the etiological factors) if not diagnosed and treated in time.[6] Hence it is essential for the treating physicians to be fully aware of all the etiological factors for febrile thrombocytopenia and have a clear knowledge as to how to approach the condition.[6]

Aim and objectives

Aim

The aim was to study the etiological profile of febrile thrombocytopenia in children aged between 1 month to 12 years admitted to the pediatric department.

Objectives

The objectives were to study the clinical and demographic profile of children presenting with fever with thrombocytopenia and to establish possible etiology for children with fever and thrombocytopenia.

METHODS

The present study was a hospital based observational study done in the department of Pediatrics at Kamineni Institute of Medical Sciences, Narketpally, Nalgonda between October 2020 to November 2021. Patients between 1 month to 12 years of age who presented with fever in whom complete blood picture showed thrombocytopenia (platelet count <1,50,000 /mm^3) at the time of hospitalization were taken up for the study. Patients less than 1 month and greater than 12 years of age and patients on drugs known to cause thrombocytopenia were excluded from the study. A total of 572 cases were admitted during the study period, of which 420 cases had febrile illness. Among 420 cases with fever, 108 cases had fever with thrombocytopenia. 100 children satisfying the inclusion criteria for febrile thrombocytopenia were taken up for the study. Ethical clearance from the institutional ethics committee was obtained. All the details regarding cases having fever and thrombocytopenia were taken from the medical records. History, clinical examination and details of the investigations pertaining to the clinical condition were noted on a predesigned proforma. The data from the fully filled questionnaire were analysed using Microsoft excel as statistical tool and represented below as proportions. Investigations such as hemogram with peripheral smear, C-reactive protein, renal function test, liver function test, complete urine examination, malarial parasite smear, coagulation profile, blood culture sensitivity, serological tests to detect dengue, leptospira, rickettsia, enteric fever, ultrasonography of chest and abdomen, chest X-ray, COVID antibodies were done based on the clinical condition of the patient. At admission, a blood sample of 1 ml for hemogram was collected in sterile EDTA (ethylenediaminetetraacetic acid) bulbs by venepuncture after taking all aseptic precautions and immediately transferred to laboratory and results were obtained by an automated haematology analyser. Platelet counts were obtained by machine count and whenever there was low platelet count it was rechecked by manual method. For cases with bleeding manifestations, 1.8 ml of venous blood was collected in a bottle containing 0.2 ml of 3.8% sodium citrate. PT, APTT, INR were obtained by automated coagulation analyser. A platelet count of <1,50,000 /mm^3 is defined as thrombocytopenia irrespective of age and gender. Thrombocytopenia has been arbitrarily classified as below. The patients are classified into these grades based on the lowest level of platelet count during the hospital stay.

Mild thrombocytopenia is when the platelet count is 1,00,000 to <1,50,000 /mm^3.

Moderate thrombocytopenia is when the platelet count is 50,000 to <1,00,000 /mm^3.

Severe thrombocytopenia is when the platelet count is <50,000 /mm^3.

RESULTS

A total of 100 children with fever and thrombocytopenia were taken up for the study. Majority of the cases (51%) belong to the age group 1-6 years, and (47%) belong to the age group of 7-12 years. Among these cases females (57%) are more common than males (43%) (Figure 1). The most common etiology of fever with thrombocytopenia was dengue fever (60%), followed by malaria (12%), enteric fever (10%), other undifferentiated viral fevers (10%) and MIS-C (multisystem inflammatory syndrome in children) (4%), immune thrombocytopenic purpura (2%), leukaemia (1%) and hepatitis A (1%) (Figure 2). Among the patients with severe thrombocytopenia, 12 patients had bleeding manifestations and deranged coagulation profile and were given fresh frozen plasma. Among the 50 subjects with severe thrombocytopenia, 15 patients had platelet levels <15,000 and were given platelet transfusion (Figure 3). Among the total dengue cases (n=60), severe thrombocytopenia was seen in 38 children of which 15 patients required blood products transfusion (Figure 4). Duration of hospital stay in majority of cases (67%) was prolonged to due to bleeding manifestations and associated complications. (Figure 5).

Most of the children presented with vomiting (61%), headache (45%), myalgia (43%), along with other gastrointestinal symptoms like pain abdomen (23%),

loose stools (13%), followed by anorexia (19%), rash (8%) and bleeding manifestations (12%). Most common clinical signs included hepatomegaly (53%), abdominal distension (26%), splenomegaly (23%), decreased air entry on respiratory system examination (18%). In present study anaemia is present in (52%) of cases, liver enzymes were significantly elevated in (66%) of cases and ultrasonography of chest and abdomen showed features of serositis in (20%) of cases. Majority of them were successfully treated and discharged (98%), there were 2 deaths in present study (2%) due to dengue shock syndrome.

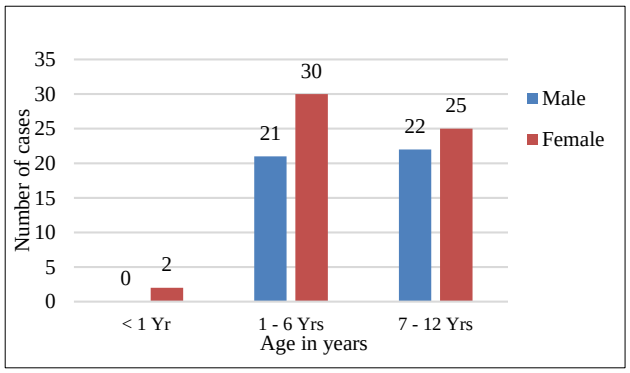

Figure 1: Age and gender wise distribution of febrile thrombocytopenia.

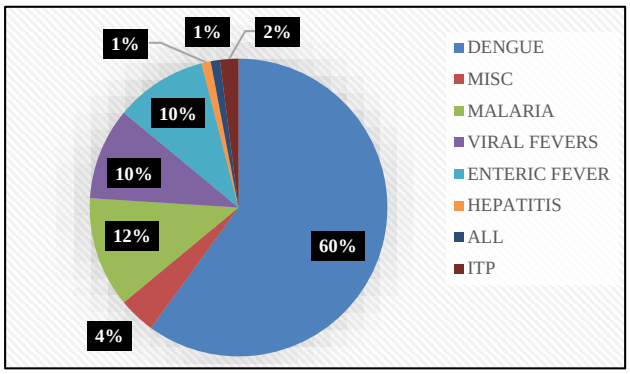

Figure 2: Etiological distribution of febrile thrombocytopenia.

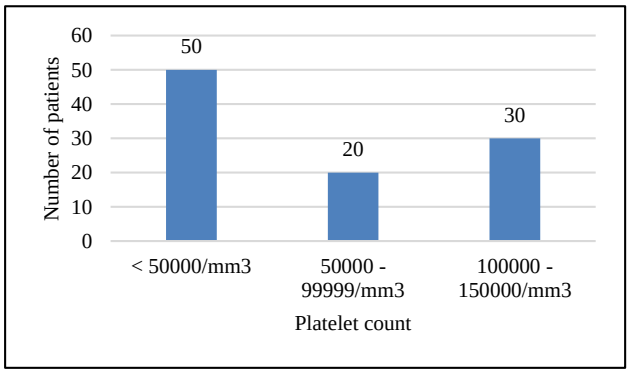

Figure 3: Distribution of cases based on severity of thrombocytopenia.

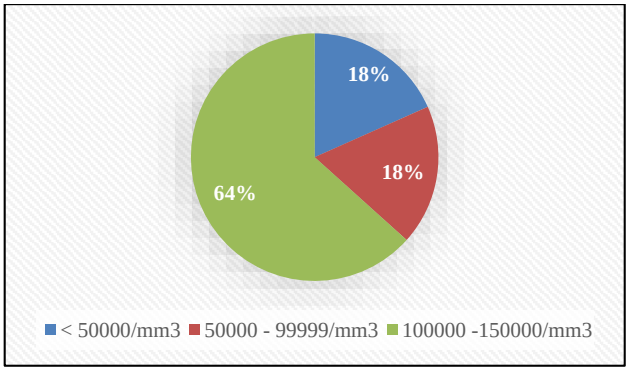

Figure 4: Distribution of dengue cases based on severity of thrombocytopenia (n=60).

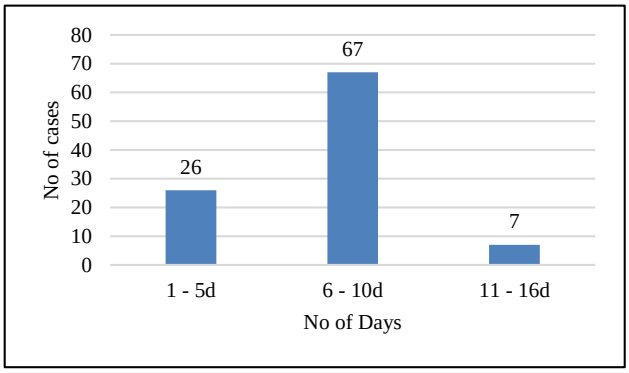

Figure 5: Distribution of children with febrile thrombocytopenia based on duration of hospital stay.

DISCUSSION

Fever is one of the most common presenting symptoms for most of the hospital visits in children. Thrombocytopenia may be an important laboratory finding in a febrile child as it needs further evaluation regarding the etiology. The varied etiological profile and unpredictable clinical outcome often poses a diagnostic as well as therapeutic challenge to clinicians. This study had been undertaken with a view to assess the clinical and etiological profile of patients with febrile thrombocytopenia and to assess the complications associated with it. In the present study, out of total fever cases (420) admitted during the study period, 100 subjects fitting into inclusion criteria were taken up for the study. Few cases had normal platelet counts at admission but developed thrombocytopenia during the hospital stay and were not included in the study. Majority of the patients (60%) included in the study had positive dengue serology. It may be due to reason that the incidence of dengue has increased due to geographical expansion of the virus. Though it occurs in seasonal epidemics many areas have also become endemic to dengue virus resulting in cases throughout the year.[1] The most common age group affected was 1-6 years, which indicated that most of them were in the pre-school age group and were indulged in the increased outdoor activity and which ultimately causing them prone to more

infections. The most common clinical presentation other than fever in the present study were vomiting (61%), headache (45%), myalgia (43%). This could be possibly explained by the fact that most of the illnesses in the present study were of viral etiology. This finding was similar to the study done by Subramanian et al in which the most common clinical presentation was fever followed by headache (68.1%), body ache (70.60%) and joint pains (61.13%).[2] The other clinical presentation included gastrointestinal symptoms like pain abdomen (23%), loose stools (13%), anorexia (19%), bleeding manifestations (12%) and rash (8%). The most common clinical signs included hepatomegaly (53%), abdominal distension (26%), splenomegaly (23%), decreased air entry on respiratory system examination (18%). These findings were similar to the study done by Guthi et al.[4] Among the dengue cases, mild thrombocytopenia was seen in 18% of cases, moderate thrombocytopenia was seen in 18% of cases and severe thrombocytopenia in 64% of cases. Bleeding manifestations were noted predominantly in cases with platelet counts (<20,000 /mm^3), during the phase of defervescence with melena being the most common bleeding manifestation, followed by epistaxis, gum bleeding and cutaneous bleeding. Fresh frozen plasma was given for 12 patients with bleeding manifestation and deranged coagulation profile. This was similar to the findings by Nair et al where he noticed a predominance of bleeding manifestation in children with platelet count less than 10,000 /mm^3.[3] Single donor platelet transfusion was given for 15 patients with platelet count less than 15,000 /mm^3. Some patients required more than one platelet transfusion during the hospital stay. Few patients were given both fresh frozen plasma and platelet transfusion. Deterioration in the clinical condition of the patient, at the time of defervescence was an important clue towards dengue fever. It was also observed that sick patients had significant rise in the transaminases, haematocrit and a deranged coagulation profile. A sudden fall in platelet count with increasing haematocrit values heralds the onset of capillary leak. Patients with severe thrombocytopenia (platelet count <50,000 /mm^3) had evidence of fluid overload or multisystem organ involvement like pleural effusion, pericardial effusion, hepatitis and shock within the first 24-48 hours of admission. The pathogenesis of thrombocytopenia in dengue fever was not clearly understood. Increased peripheral destruction of antibody coated platelets was strongly suspected as the possible mechanism.[4] The second most common cause of febrile thrombocytopenia in our study was malaria (12%). This was in contrary to the findings of the study done by Guthi et al and Morales et al in which malaria was the most common etiology of febrile thrombocytopenia.[4,8] Finding of thrombocytopenia with anaemia was an important clue to the diagnosis of malaria in patients with acute febrile illness.[3] Although malaria was the second most common cause of febrile thrombocytopenia, bleeding manifestations were infrequent even with severe thrombocytopenia. Definitive increase in platelet count was noted after institution of anti-malarial therapy among these cases.[3] The other causes of febrile thrombocytopenia like enteric fever (10%), undifferentiated viral fevers (10%) were associated with mild to moderate thrombocytopenia and did not show any evidence of bleeding manifestations. Multi-system inflammatory syndrome as a cause of febrile thrombocytopenia was seen in 4% of cases. In the era of COVID-pandemic, as a complication of COVID-19 infection multi-system inflammatory syndrome in children was seen in few cases. Bleeding manifestations were seen in cases with multi-system inflammatory syndrome and required both fresh frozen plasma as well as packed red blood cell transfusion. The duration of hospital stay was prolonged (6-10 days) in majority of cases (67%) due to bleeding manifestations and associated complications like pleural effusion, pericardial effusion and ascites. The mortality rate in our study was (2%) which was due to severe dengue with disseminated intravascular coagulation. In a study done by Karthik et al recovery rate was (98.6%) and death rate was (1.3%).[1] In another study done by Morales et al discharge rate was (98.4%) and death rate was (1.6%).[8]

Comparison of present study with various studies

In a study done by Karthik et al predominant age group was 6-10 years (34%), followed by 11-15 years (29%) and 1-5 years (25%).[1] Male to female ratio was almost equal 1:1. The most common symptomatology at presentation was high grade fever. Constitutional symptoms and warning symptoms were the next common symptoms at presentation. The predominant diagnosis was dengue fever in children (69%) which was similar to present study, followed by other viral haemorrhagic fever (8%), scrub typhus fever (5%), malaria (1%), leukaemia (2%), sepsis with disseminated intravascular coagulation (2%), haemolytic uremic syndrome (1.3%) and leptospirosis (1%). 5 deaths were reported. In another study done by Subramanian et al there was equal distribution of children with thrombocytopenia in the age group 1 to 5 years and 5 to 10 years with both being around 30% of the total cases.[2] There was a male predominance with nearly 54% cases being males. Most of the cases were due to infectious etiology. Among the infective causes for thrombocytopenia, predominant children were affected by viral fevers including dengue (78%) which was similar to present study followed by malaria, enteric fever, chikungunya and other haematological and connective tissue disorders. Around 33% of those children with thrombocytopenia had bleeding manifestations. Bleeding manifestations were seen more among those with platelet counts <20,000 /mm^3. Cutaneous bleeds were the most common presentation of bleeds. In a study done by Nair et al commonest cause 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%.[9] Bleeding manifestations were seen in 57.7% of children and nearly 42% had cutaneous bleeds. Another study done by Bhalara et al

showed dengue (60.8%) as the main etiology which was similar to the present study.[10] There was a predominance of male children compared to female children. The commonest age group affected was 5 to 10 years accounting for nearly 30% of all cases. Children between 1 to 5 years and 1 month to 1 year contributed to 59% of all cases. In another study done by Morales et al peak incidence of febrile thrombocytopenia was seen in the age group of 3.5-3.9 years.[8] Major etiology for febrile thrombocytopenia was found to be *Plasmodium vivax* infection in 59% of cases. In another study done by Sujatha et al most common age group was above 10 years with a male predominance of 60%.[7] The most common etiology was dengue fever (83%).

Limitations

The limitations of present study were the children admitted with fever and who developed thrombocytopenia during the course of hospital stay were not included in the study. The exact etiology of other viral haemorrhagic fevers was not identified. As this study was done at rural tertiary centre, the major etiological cause of febrile thrombocytopenia was dengue fever, results would be different with varied conclusions if the study was done at an urban care centre.

CONCLUSION

Febrile thrombocytopenia is a common clinical presentation in children, majority of cases in the study group were in the age group 1-6 years (51%), implying the increased outdoor activity and thereby increased risk of exposure to mosquito vectors. The most common etiology in this study is dengue fever (60%). Other infections like malaria (12%), enteric fever (10%), undifferentiated viral fevers (10%), MIS-C (4%) also contribute to etiology of febrile thrombocytopenia but in lesser numbers. Majority of the dengue cases responded well to fluid resuscitation done as per WHO guidelines. In most of the other infections, thrombocytopenia was transient and asymptomatic usually in the mild to moderate range and resolved with treatment of underlying condition. Rarely diseases like leukaemia, idiopathic thrombocytopenic purpura or sepsis may also present as febrile thrombocytopenia but a proper peripheral smear, bone marrow examination or serial hemograms will help in arriving at a proper diagnosis. The average duration of hospital stay observed was (6-10 days) in 65% of cases. Few cases (7%) required hospital stay for a longer duration due to bleeding manifestations, blood product transfusions and associated complications.

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

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