

A Study of Clinical and Lab Profile of Fever with Thrombocytopenia

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ABSTRACT

Introduction: India is a tropical country and is home to a variety of infectious diseases. In the recent years, a spurt in the number of cases of febrile thrombocytopenia has been noted, especially during the monsoon season. As febrile thrombocytopenia is the result of varied etiology, clinical course is often unpredictable. We undertook this study with an aim to analyze cases of febrile thrombocytopenia and identify etiology, clinical profile and complications associated with it. Objectives: To identify the etiology, clinical profile and assess the complications of febrile thrombocytopenia.

Material and Methods: In this prospective descriptive study, patients with fever and thrombocytopenia of age 1-18 yrs were enrolled and examined. Hemogram, smear for malarial parasite, blood culture, widal test, antibody titers for dengue virus, C-reactive protein and screening for viral hepatitis were sent for establishing the etiology. Coagulation studies, L.F.T (Liver Function Tests), R.F.T (Renal Function Tests), C.S.F (CerebroSpinal Fluid) analysis, bone marrow aspiration and other radiological investigations were done in selected cases. They were managed according to standard WHO (World Health Organization) protocols.

Results: There were 54 males and 46 females in the enrolled population. Most common etiology was malaria followed by dengue. In majority of them, thrombocytopenia was transient and asymptomatic where as bleeding manifestations were commonly seen in dengue cases. Most common symptoms associated were abdominal pain and melena. Irrespective of platelet transfusion, spontaneous recovery was noted in dengue patients.

Conclusions: Platelet transfusions do not influence the incidence of severe bleeding in dengue fever. Much more awareness, vigilance and research in the diagnostic modalities is further needed to avoid unnecessary panic and platelet transfusions.

Keywords: Platelet Count, Malaria, Dengue, Bleeding Manifestations

INTRODUCTION

Fever with thrombocytopenia is a distinct clinical entity and refers to a reduction in platelet count below $150 \times 10^9/L$ in association with fever. Thrombocytopenia is due to decreased production, increased destruction (immunogenic¹⁻⁴ and non immunogenic⁵⁻⁹) or increased sequestration in spleen and patients with thrombocytopenia may experience bleeding manifestations like petechiae, epistaxis, gum bleeding, hematuria, gastrointestinal hemorrhage or intracranial bleeding. It is the most common cause of bleeding in children.¹⁰ Febrile thrombocytopenia is often the result of infections like malaria, dengue fever, leptospirosis, enteric fever, septicemia, rickettsial infections and viral fever.¹¹⁻¹⁶ The climatic conditions in tropical countries like India are favorable for the transmission of most of these infections and every year, with onset of monsoons, a rising trend has been observed in the number of

cases admitted into wards and intensive care units with febrile thrombocytopenia with a variable clinical course and an unpredictable outcome.

The uncertain course is often a source of concern to the patients and treating doctors alike and results in unnecessary “prophylactic” platelet transfusions. This study has been undertaken to evaluate the clinical and etiological profile of febrile thrombocytopenia and to assess the complications associated with it.

MATERIAL AND METHODS

Prospective descriptive study from October 2012 to August 2014 in Department of Pediatrics, Maharajah’s Institute of Medical Sciences, Nellimarla, Vizianagaram after obtained from the ethics committee of the institute.

This study was undertaken in 100 pediatric patients in the age group of 1 to 18 years of age, who were admitted in MIMS hospital with the presentation of fever and thrombocytopenia (less than 1.5lak/cu.mm). Infants with febrile thrombocytopenia and patients with thrombocytopenia without fever were excluded from this study.

Informed consent was obtained and a detailed history was taken with special emphasis on the bleeding manifestations at the time of their admission and to those that presented during the course of their hospital stay. A thorough clinical examination was carried out in each and every case and work up was planned accordingly.

Investigations sent included hemogram, smear for malarial parasites, blood culture, widal, antibody titers for dengue virus, C-reactive protein and screening for viral hepatitis. Coagulation studies, L.F.T, R.F.T, C.S.F analysis, bone marrow aspiration and other radiological investigations were done as needed in select cases.

The platelet count was repeated from time to time and platelets were transfused if platelet count was $<10,000/cu.mm$ without hemorrhagic risk factors or $<20,000/cu.mm$ with hemorrhagic risk factors and in patients with dengue shock syndrome and septicemia with DIC (Disseminated Intravascular Coagulation). Patients were managed according to standard WHO protocols.

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STATISTICAL ANALYSIS

Data was recorded on tabulated sheets and analyzed statistically using descriptive statistics.

RESULTS

Out of 100 cases of fever with thrombocytopenia, 54 were males and 46 were females. The maximum number of cases was recorded in the age group of 6-10 years (41%). The percentage of cases noted in the age groups of 1-5 years, 11-15 years and 16-18 years are 32%, 22%, 5% respectively.

Etiology of thrombocytopenia

The most common cause was malaria in 35% of cases followed by dengue in 34% of cases, sickle cell anemia with sepsis in 7% of cases, enteric fever in 5% of cases and septicemia in 5% of cases. Other minor causes include scrub typhus in 3% of cases, ALL (Acute Lymphoblastic Leukemia) in 3% of cases, viral hepatitis in 2% of cases, undiagnosed in 6% of cases.

Among the malaria cases, falciparum malaria was detected in 63% (22) of cases and vivax malaria in 37%(13) of cases. Cases with dengue fever were classified according to 2011 WHO classification of dengue fever. Dengue fever without hemorrhage was noted in 15%(5) of cases, dengue haemorrhagic fever grade 1 in 23% (8) of cases, grade 2 in 26% (9) of cases, grade 3 (Dengue shock syndrome) in 18%(6) of cases and grade 4 (dengue shock syndrome- undetectable pulse and blood pressure) in 18%(6) of cases.

Severity of thrombocytopenia

Thrombocytopenia has been arbitrarily classified as:

- Severe - < 50,000cells/cu.mm
- Moderate - 50,000 - 1,00,000 cells /cu.mm
- Mild - 1,00,000 -1,50,000 cells/cu.mm

Out of these, mild (1,00,000 -1,50,000) thrombocytopenia was seen in 22% of cases, moderate (50,000-1,00,000) thrombocytopenia was seen in 39% of cases and severe (<50,000) thrombocytopenia was seen in 39% of cases. This classification is based on the lowest level of platelet counts seen during their hospital stay. Among the cases of malaria, mild thrombocytopenia was seen in 29% (10) of cases, moderate thrombocytopenia was seen in 43% (15) of cases and severe thrombocytopenia was seen in 28% (10) of cases.

Out of 34 cases of dengue, mild thrombocytopenia was seen in 18%(6) of cases, moderate in 38% (13) of cases and severe in 44% (15) of cases. Although, almost all cases of dengue fever had mild thrombocytopenia in the febrile phase, in patients who developed hemorrhagic manifestations, there was rapid decline in platelet count to <50,000 cells/cu.mm during the phase of defervescence along with a rise in hematocrit. The above classification is based on the least platelet count during hospital stay.

Bleeding manifestations

Bleeding manifestations were seen in 45 patients. Out of 45 patients with bleeding manifestations, GI (Gastrointestinal) bleeding and melena were found in 47% (21) of cases, petechiae and ecchymosis in 35% (16) of cases and epistaxis and gum bleeding in 18% (8) of cases. Bleeding manifestations associated with thrombocytopenia were commonly seen among dengue cases during the phase of defervescence, with melena being the most common bleeding manifestation among these cases. Other

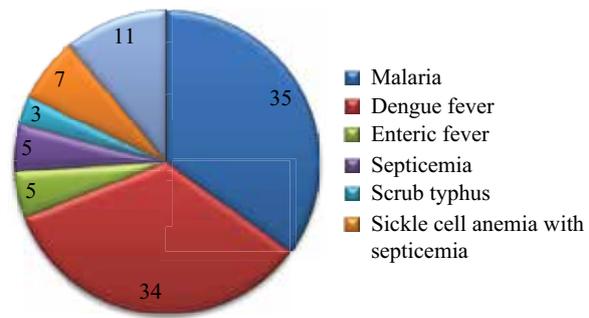


Figure-1: Pie chart showing the distribution of etiology in the study population

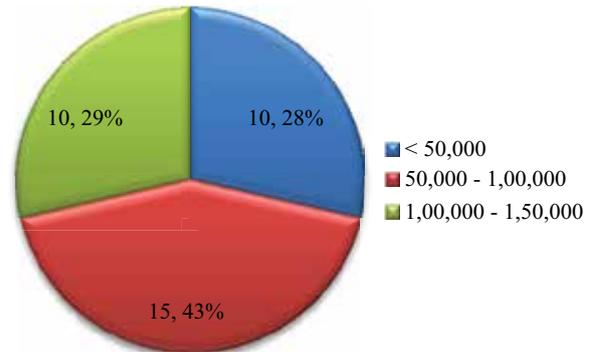


Figure-2: Pie chart showing the distribution of severity of thrombocytopenia in malaria cases

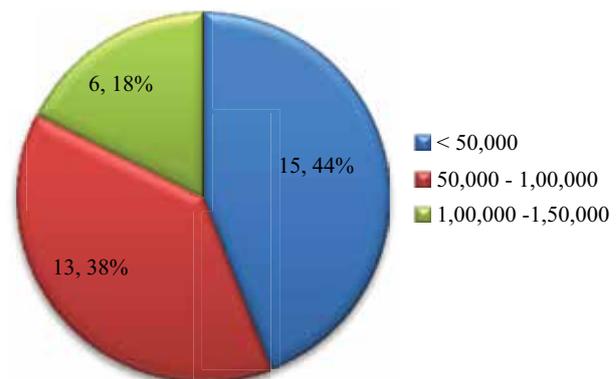


Figure-3: Pie chart showing the distribution of severity of thrombocytopenia in dengue cases

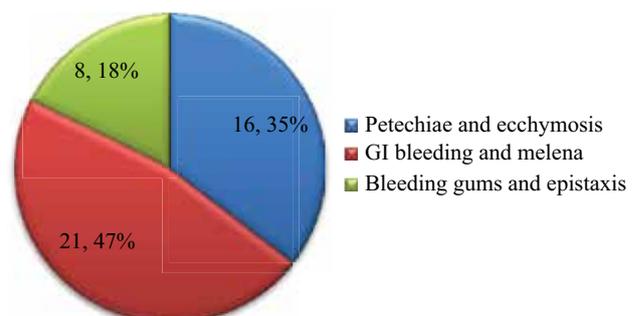


Figure-4: Pie chart showing various bleeding manifestations noted in the study population

conditions which presented with bleeding manifestations were septicemia and ALL.

Although malaria is the most common cause of febrile thrombocytopenia, bleeding manifestations were infrequent,

even with severe thrombocytopenia. Enteric fever, viral hepatitis, scrub typhus were associated with mild to moderate thrombocytopenia and did not show any evidence of bleeding. The most common associated symptom was abdominal pain in 43 cases and vomiting in 38 cases followed by headache, myalgia and jaundice. Among cases of dengue fever, abdominal pain was seen in 22 cases, vomiting in 10 cases, petechiae and purpura in 11 cases, GI bleeding and melena in 18 cases and epistaxis in 3 cases. Anemia was the commonest sign found in 69% (69) of the cases. Hepatomegaly was found in 41% (41) of cases, splenomegaly in 32% (32) of cases and hepatosplenomegaly in 55% (55) of cases. Lymphadenopathy was found in 5% (05) of cases.

Malaria cases were most commonly associated with hepatosplenomegaly or splenomegaly alone. Out of 34 cases of dengue, anemia was seen in 62% (21) of cases and leucopenia was seen in 73% (23) of cases. Dengue fever was commonly associated with tender hepatomegaly (increase in liver size) during the phase of defervescence.

Platelets were transfused in 20 patients, which included patients with platelet count <10,000, patients with dengue shock syndrome and in patients with septicemia. None of the malaria cases received platelet transfusions. There was spontaneous improvement in platelet count within 48 hours of institution of anti malarial treatment in malaria cases. Among dengue cases, the average time for platelet count recovery was within 2-8 days of illness, irrespective of whether they received platelet transfusion or not.

Outcome

Out of 100 patients, 94 of them had good recovery and 6 of them expired. In the 6 cases, 3 deaths (50%) were due to septicemia, 2 (33.3%) were due to complicated malaria and 1 (16.6%) was due to ALL.

DISCUSSION

Febrile thrombocytopenia is a distinct clinical entity, commonly encountered in infectious diseases. A number of infections such as malaria, dengue fever, scrub typhus, leptospirosis, chikungunya, enteric fever, bacterial and fungal sepsis as well as certain other viral infections result in thrombocytopenia. The varied etiological profile and unpredictable clinical outcome often poses a diagnostic as well as therapeutic challenge to clinicians. This study has 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 of 100 cases with febrile thrombocytopenia, 54% were males and 46% were females. 73% of the patients were under the age of 10 years. According to Badvi A. J. et al,¹⁷ male to female ratio was 64:36 and 77% of patients were in age group under 10 years. Similar sex distribution was seen in certain local and international studies.¹⁸⁻²⁰

Most common cause was malaria in 35% of cases. Finding of thrombocytopenia with anemia is an important clue to the diagnosis of malaria in patients with acute febrile illness.²¹⁻²³ Thrombocytopenia seen in complicated falciparum malaria is due to disseminated intravascular coagulation along with platelet endothelial activation, but the one seen in uncomplicated malaria like Plasmodium vivax has multifactorial etiology. Few

postulated mechanisms are macrophage activation leading to platelet destruction, increased levels of cytokines, immunological destruction due to antiplatelet IgG, oxidative stress, shortened platelet life span in peripheral blood, sequestration in nonsplenic areas and partly due to pseudothrombocytopenia due to clumping of platelets. Decreased thrombopoiesis has been ruled out, because platelet-forming megakaryocytes in the marrow are usually normal or increased.^{21,24-26}

The association of thrombocytopenia with malaria was reported to be higher than the present study in certain other studies done by Ansari et al,¹⁹ Jamal A et al,²⁷ Beale P et al¹² and Badvi A.J. et al¹⁷ who reported a prevalence of 69.18%, 72%, 85%, 50% respectively. The second most common cause was dengue fever, found in 34% of cases. It was found to be 11.11% and 17.1% in Jamal A et al²⁷ and Mahmood K et al²⁸ studies respectively. Sick cell anemia with septicemia, enteric fever, and septicemia constituted about 7%, 5% and 5% respectively. In Badvi A. J. et al study,¹⁷ enteric fever contributed to about 5% of cases of febrile thrombocytopenia which is similar to the present study.

Among the malaria cases, Plasmodium falciparum was the most common species responsible for thrombocytopenia in 63% of cases followed by Plasmodium vivax in 37% of cases. In Badvi A. J. et al study,¹⁷ Plasmodium falciparum was reported in 45% of cases of malaria, followed by mixed infection of Plasmodium falciparum and Plasmodium vivax in 30% and Plasmodium vivax in 25% of cases. In K.R.Meena et al study,²⁹ plasmodium vivax was identified in 70% of cases, Plasmodium falciparum in 20% and mixed infection in 10% of cases. In Guruprasada Shetty et al study,³⁰ Plasmodium vivax found in 66%, Plasmodium falciparum in 16% and mixed in 18% of cases. Ansari S et al¹⁹ has reported Plasmodium falciparum in 69.18% cases of malaria which is similar to the results of the present study. In contrast, Jamal A et al²⁷ reported 72% thrombocytopenia in cases of Plasmodium vivax and 11% with Plasmodium falciparum species. Another study conducted by Patel U et al³¹ reported Plasmodium falciparum in 47.5% and Plasmodium vivax in 52.5% of cases.

The pathogenesis of thrombocytopenia in dengue fever is not clearly understood. Increased peripheral destruction of antibody coated platelets is strongly suspected as the possible mechanism. Other modes include acute bone marrow suppression leading to amegakaryocytic condition, mild DIC like presentation and enhanced platelet destruction by the reticuloendothelial system.³²

In the present study, out of 34 cases of dengue, dengue fever without hemorrhage was noted 15% of cases, dengue hemorrhagic fever grade 1 in 23% of cases, grade 2 in 26% of cases, grade 3 (dengue shock syndrome) in 18% of cases and grade 4 (dengue shock syndrome- undetectable pulse and blood pressure) in 18% of cases. Ahmed S et al¹⁶ studied 35 patients and found dengue hemorrhagic fever (DHF) in 62% of children and majority had grade 2 severity.

In the present study, GI bleeding and melena were the commonest type of bleeding manifestations seen in 47% of cases, petechiae and ecchymosis were seen in 35% of cases, bleeding gums and epistaxis were seen in 18% of cases. In Badvi A. J. et al study,¹⁷ petechiae and ecchymosis were seen in 46% of cases, followed by epistaxis and gum bleeding in 34% of cases, subconjunctival hemorrhage in 14% of cases, hematuria in 8% of cases and

vaginal bleeding in 1.5% of cases. Signs of bleeding were reported in 24% children and in 23% adults by Kuhne T et al.¹⁸ In the present study, out of 34 cases of dengue, abdominal pain was the commonest associated symptom noted in 65% of cases followed by vomiting in 29% of cases. Contrary to other infections where these symptoms were noted early in the illness, in dengue fever, they were noted at the time of defervescence and constituted important warning symptoms to predict the risk of a patient developing complications. GI bleeding and melena were seen in 53% of cases, petechiae and purpura in 32% cases and epistaxis in 8% of cases. In Ahmed S et al study,¹⁶ frequently noted clinical features included fever (97%), vomiting (68%), abdominal pain (68%) and rashes (65%). Gastrointestinal bleeding (61%) and epistaxis (26%) were commonest haemorrhagic manifestations.

In the present study, anemia was found in 69% of cases, hepatomegaly in 41% of cases, splenomegaly in 32% of cases, combined hepatosplenomegaly in 55% of cases and lymphadenopathy in 5% of cases. In Badvi A. J. et al study,¹⁷ anemia was found in 71% of cases, where as splenomegaly was seen in 79.2%, hepatomegaly in 60.9% and lymphadenopathy in 39.1% of cases.

In the present study, there were 39% patients with severe thrombocytopenia, 39% patients with moderate thrombocytopenia and 22% patients with mild thrombocytopenia. In Badvi A. J. et al study,¹⁷ severe thrombocytopenia was seen in 60%, moderate thrombocytopenia in 20% and mild thrombocytopenia in 20% of cases.

In the present study, out of 35 cases of malaria, mild thrombocytopenia was seen in 29% of cases, moderate thrombocytopenia seen in 43% of cases, severe thrombocytopenia was seen in 28% of cases. K.R.Meena et al²⁹ reported 38.71% cases with mild, 20.4% cases with moderate and 40.8% cases with severe thrombocytopenia among malaria cases. Guruprasada Shetty et al³⁰ reported 31% cases with mild, 43% cases with moderate and 26% cases with severe thrombocytopenia among malaria cases. Finding of thrombocytopenia with anemia is an important clue to the diagnosis of malaria in patients with acute febrile illness. Definitive increase in platelet count was noted after institution of anti malarial therapy among these cases.

In the present study, out of 34 cases of dengue, anaemia was seen in 62% of cases and leucopenia in 73% of cases where as in comparison, anaemia was noted in 57% of cases and leucopenia in 43% of cases, in Ahmed S et al study.¹⁶ Finding of thrombocytopenia with leucopenia is an important clue to the diagnosis of dengue in patients with acute febrile illness.

CONCLUSION

Febrile thrombocytopenia is a challenging problem in clinical practice and is usually caused by infectious diseases. In this study, malaria is the most common cause of febrile thrombocytopenia closely followed by dengue fever, especially in epidemic scenarios. Other infections such as enteric fever, scrub typhus, chikungunya fever, viral hepatitis, leptospirosis and sepsis also contribute to cases of febrile thrombocytopenia but in lesser numbers.

Bleeding manifestations associated with thrombocytopenia were commonly seen among dengue cases. Deterioration in the clinical condition of the patient, at the time of defervescence is

a strong pointer towards dengue fever. Vomiting, pain abdomen and bleeding manifestations were the common warning symptoms noted in this series. A rapid decline in platelet count with rising hematocrit heralds the onset of capillary leak. Platelet transfusions were carried out as per WHO guidelines. In most DHF/DSS cases, platelet transfusions do not influence the incidence of severe bleeding. In the epidemic scenario, there is a widespread panic among the general public with a demand for platelet transfusions, which is sometimes perpetrated by ill-informed medical practitioners. There is a need to create public awareness campaigns as well as conduct workshops to update doctors regarding the latest management guidelines. Treatment costs for DHF/DSS cases could be reduced if these unnecessary platelet transfusions are avoided. In most other infections, thrombocytopenia was transient and asymptomatic, usually in the mild to moderate range and resolved with treatment of underlying condition.

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