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Clinical and laboratory profile in fever with thrombocytopenia: A clinical study

Dr. Siddu BN[1], Dr. Preveen Kumar Sindhur[2], Dr. Niveditha S Reddy[3*]
[1, 3] Post graduates, Department of Paediatrics, KVG Medical College, Sullia, RGUHS, Karnataka, India
[2] Professor, Department of Paediatrics, KVG Medical College, Sullia, RGUHS, Karnataka, India

Abstract
Objective: To identify the etiology, clinical profile and assess the complications of febrile thrombocytopenia.
Design: Prospective descriptive study
Setting: tertiary care hospital
Participants: This study was undertaken in 50 paediatric patients in the age group of 1 to 15 years of age, who were admitted in KVG medical college and hospital with the presentation of fever and thrombocytopenia (less than 1.5lakh/cu.mm).
Results*:* There were 26 males and 24 females in the enrolled population. Most common etiology was dengue followed by malaria and rickettsia. In majority o, thrombocytopenia was transient and asymptomatic whereas bleeding manifestations were commonly seen in dengue cases. Common symptoms associated were abdominal pain and petechial rash. 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 and research is further needed to avoid unnecessary panic and platelet transfusions.

Keywords: fever, thrombocytopenia, dengue, transfusion

Introduction
Fever is defined as an elevation of the body temperature above the normal circadian range, as the result of a change in the thermoregulatory centre located in the anterior hypothalamus. A morning temperature of more than 37.2°C (98.9 °F) or evening temperature of more than 37.7°C (99.9°F) would define fever. Thrombocytopenia is defined as platelet count less than 150,000 /µl. This is due to decreased production, increase destruction (immunogenic and non-immunogenic), and increased sequestration in spleen. Of these infections being the commonest cause of thrombocytopenia [1, 2].
Diseases which commonly present with fever and thrombocytopenia are malaria, leptospirosis, rickettsial infections, septicaemia, typhoid, borreliosis, arbovirus such as dengue or yellow fever, rodent-borne viruses such as Hanta and Lassa fever, human immunodeficiency virus (HIV), visceral leishmaniasis and TTP-HUS [3, 4].
The climatic conditions in tropical countries like India are favourable 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 a nun predictable 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.

Materials and Methods
Prospective descriptive study from October 2018 to July 2019 in Department of Paediatrics, KVG medical college and hospital, Sullia, D.K.
This study was undertaken in 50 paediatric patients in the age group of 1 to 15 years of age, who were admitted in KVGMCH with the presentation of fever and thrombocytopenia (less than 1.5lakh/cu.mm). Ethical committee clearance was obtained.

Inclusion Criteria
- All new patients below 15 years with fever (temperature >99.9°F).
- Thrombocytopenia (platelet count <1,50,000 cells/mm3).

Exclusion Criteria
- Patient presenting with thrombocytopenia without fever.
- Diagnosed case of immune thrombocytopenic purpura.
- Patient with thrombocytopenia already diagnosed to have haematological disorder on treatment with chemotherapy and other immunosuppressive agent.
- Diagnosed cases of platelet disorder and dysfunction.
- Patients on treatment with antiplatelet drugs and other drugs causing thrombocytopenia.
- Patients with cirrhosis and chronic liver disease.

Informed consent was obtained and a detailed history was taken with special emphasis on the bleeding manifestations at thetime of their admission and to those that presented during the course of their hospital stays. 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 titres 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 selected cases.

Results

Out of 50 cases of fever with thrombocytopenia, 26 were males and 24 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, 11-13 years and 14-15 years are 32%, 22%, 5% respectively.

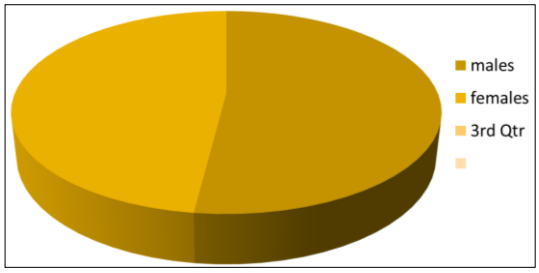

Fig 1

Etiology of thrombocytopenia

The most common cause was dengue in 35% (18) of cases followed by malaria in 34% (17) of cases, rickettsia in 7% (4) of cases, enteric fever in 5% (2) of cases and septicaemia in 5% (2) of cases. Other minor causes include viral hepatitis in 4% (2) of cases, ALL (Acute Lymphoblastic Leukaemia) in 3% (1) of cases, undiagnosed in 7% (4) of cases.

Table 1

Cause	No of cases	Percentage
Dengue	18	36
Malaria	17	34
Enteric fever	10	20
Rickettsia	5	10
Septicemia	4	8
Others	3	6

Among the malaria cases, falciparum malaria was detected in 63% (11) of cases and vivax malaria in 37% (6) of cases. Cases with dengue fever were classified according to 2014 WHO classification of dengue fever. Dengue without warning signs (54%), dengue with warning signs (25%), sever dengue (21%).

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

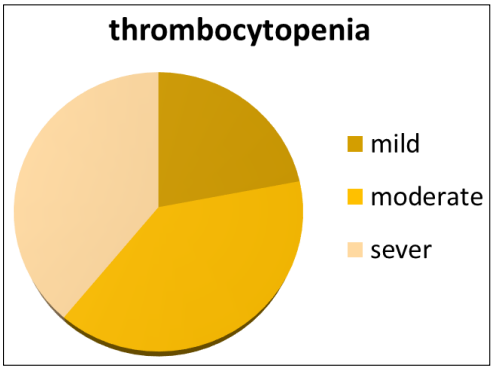

Fig 2

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.

Out of 18 cases of dengue, mild thrombocytopenia was seen in 18% (3) of cases, moderate in 39% (6) of cases and severe in 44% (9) of cases. Although, almost all cases of dengue fever had mild thrombocytopenia in the febrile phase, in patients who developed haemorrhagic manifestations, there was rapid decline in platelet count to <50,000 cells/cu.mm during the phase of defervesce along with a rise in haematocrit. The above classification is based on the least platelet count during hospital stay.

Bleeding manifestations

Bleeding manifestations were seen in 24 patients. Out of 24 patients with bleeding manifestations, GI (Gastrointestinal) bleeding and melena were found in 48% (12) of cases, petechiae and ecchymosis in 34% (8) of cases and epistaxis and gum bleeding in 18% (4) of cases. Bleeding manifestations associated with thrombocytopenia were commonly seen among dengue cases during the phase of defervesence, with melena being the most common bleeding manifestation among these cases. Other conditions which presented with bleeding manifestations were septicaemia and all.

Although malaria is one of the common causes 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 22 cases and vomiting in 19 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 5 cases, GI bleeding and melena in 9 cases and epistaxis in 3 cases.

Anaemia was the commonest sign found in 70% (35) of the cases. Hepatomegaly was found in 41% (20) of cases, splenomegaly in 32% (16) of cases and hepatosplenomegaly in 55% (27) of cases. Lymphadenopathy was found in 5% (2) of cases.

Malaria cases were most commonly associated with hepatosplenomegaly or splenomegaly alone. Out of 18 cases of dengue, anaemia was seen in 62% (11) of cases and leukopenia was seen in 73% (13) of cases. Dengue fever was commonly associated with tender hepatomegaly (increase in liver size) during the phase of defervesence.

Platelets were transfused in 10 patients, which included patients with platelet count <10,000, patients with dengue shock syndrome and in patients with septicaemia. 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.

Outcome

Out of 50 patients, 48 of them had good recovery and 2 of them expired. In the 2 cases, 1 death (50%) was due to

septicaemia, 1 (50%) was due to complicated malaria.

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 50 cases with febrile thrombocytopenia, 26% were males and 24% were females. 41% of the patients were under the age of 10 years. According to Badvi A. J. *et al* [5], 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 [6, 7, 8].

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 [9].

In the present study, out of 18 cases of dengue, Dengue without warning signs (54%), dengue with warning signs (25%), sever dengue (21%). Ahmed S *et al* [10] studied 35 patients and found dengue haemorrhagic 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. Abdominal pain was seen in 22 cases, vomiting in 10 cases, petechiae and purpura in 5 cases, GI bleeding and melena in 9 cases and epistaxis in 3 cases. In Badvi A. J. *et al* study [5], 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, haematuria 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* [6].

In the present study, out of 18 cases of dengue, abdominal pain was the commonest associated symptom noted in 44% of cases followed by vomiting in 20% 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 18% of cases, petechiae and purpura in 10% cases and epistaxis in 6% of cases.

In Ahmed S *et al* study [10], frequently noted clinical features included fever (97%), malaria was the cause in 34% of cases. Finding of thrombocytopenia with anaemia is an important clue to the diagnosis of malaria in patients with acute febrile illness [11-13]. 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 pseudo thrombocytopenia due to clumping of platelets. Decreased thrombopoiesis has been ruled out, because platelet-forming megakaryocytes in the marrow are usually normal or increased [11, 14-16]. The association of thrombocytopenia with malaria was reported to be higher than the present study in certain other studies done by Ansari *et al* [7], Jamal A *et al* [17], Beale P *et al* [18] and Badvi A.J. *et al* [5] 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% in Jamal A *et al* [17] study. Sickle cell anaemia with septicaemia, enteric fever, and septicaemia constituted about 7%, 5% and 5% respectively. In Badvi A. J. *et al* study [5], 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 [5], 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 [19], 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 [21], Plasmodium vivax found in 66%, Plasmodium falciparum in 16% and mixed in 18% of cases. Ansari S *et al* [7] 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 al* [17] reported 72% thrombocytopenia in cases of Plasmodium vivax and 11% with Plasmodium falciparum species. Another study conducted by

Patel U *et al* [21] reported Plasmodium falciparum in 47.5% and Plasmodium vivax in 52.5% 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, [5] severe thrombocytopenia was seen in 60%, moderate thrombocytopenia in 20% and mild thrombocytopenia in 20% of cases.

In the present study, out of 17 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 al* [19] reported 38.71% cases with mild, 20.4% cases with moderate and 40.8% cases with severe thrombocytopenia among malaria cases. Guruprasada Shetty *et al* [20] 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 18 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 [10]. 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, dengue fever is the most common cause of febrile thrombocytopenia closely followed by malaria. 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 thrombocytopeniawere 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 warningsymptoms noted in this series. A rapid decline in platelet count with rising haematocrit heralds the onset of capillary leak.Platelet transfusions were carried out as per WHO guidelines. In most severe dengue 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 severe dengue 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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