STUDY OF CLINICAL PROFILE OF FEVER WITH THROMBOCYTOPENIA IN TERTIARY CARE HOSPITAL IN JHALAWAR DISTRICT OF SOUTH-EASTERN RAJASTHAN

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ABSTRACT

BACKGROUND

Fever is a common manifestation of an illness. Thrombocytopenia is the most frequent finding in febrile illness. Thrombocytopenia with fever narrows the differential diagnosis of clinical entity and help in reaching the diagnosis of febrile illness. The present study is carried out to find the cause of thrombocytopenia with fever and to assess the clinical complication associated with severity of thrombocytopenia and fever.

MATERIALS AND METHODS

This study was carried out in Department of General Medicine of Jhalawar Medical College, Jhalawar, Rajasthan during period of July 2016 to September 2017. Total 100 patients were enrolled in this study. Informed written consent was taken from patients. This is a hospital-based observational study.

RESULTS

Dengue was the most common cause of febrile thrombocytopenia (50%) followed by malaria (23%). The other causes were viral fever (19%), scrub typhus (4%), mixed dengue and scrub typhus (2%), and septicaemia (2%). The patients were in the age group 16 - 80 years with 60 male and 40 female. Maximum patients (76%) were found to have thrombocytopenia in range of 50,000 - 1,50,000/cumm, 16 cases had thrombocytopenia in the range of 20,000 - 50,000/cumm, while 8 cases had thrombocytopenia in the range of < 20,000 cumm. Bleeding manifestations were very rarely seen as present in 3 cases (3%) with petechiae as the commonest bleeding manifestation (2%). Severe thrombocytopenia was seen in dengue fever and falciparum malaria. Mortality was observed in 2 cases (2%) and multiorgan dysfunction was present in all those 2 cases.

CONCLUSION

Dengue is the commonest cause of febrile thrombocytopenia and severity of thrombocytopenia was not associated with increased mortality, but mortality was due to multiorgan dysfunction.

KEYWORDS

Dengue Fever, Malaria, Scrub Typhus, Septicaemia, Thrombocytopenia.

BACKGROUND

Fever is the most ancient health mark of disease, which is defined as the elevation in the body temperature above the normal circadian range as a result of change in thermoregulatory centre located in anterior hypothalamus. Morning temperature of > 37.2 degrees (98.9 F) or evening temperature > 37.7 degrees (99.9 F) would define fever.[1] Thrombocytopenia is defined as subnormal level of platelets in circulatory blood, e.g. counts below 1.5 lac/cumm.[2] A normal platelet count ranges from 1,50,000- 4,50,000/cumm. Often the patients of thrombocytopenia are asymptomatic, and thrombocytopenia becomes revealed on routine complete blood counts. Thrombocytopenia results in various processes such as accelerated platelets destruction, deficient

platelets production, abnormal distribution or pooling of platelets within the body and artifactual thrombocytopenia.[3] Thrombocytopenia due to decreased platelet production occurs in vitamin B12 and folate deficiency, leukaemia and sepsis as a result of bacterial and viral infection and hereditary disease. Thrombocytopenia due to increased destruction occurs in idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, disseminated intravascular coagulation, paroxysmal nocturnal haemoglobinuria, systemic lupus erythematosus, antiphospholipid syndrome, post-transfusion purpura and hypersplenism. Drugs causing thrombocytopenia are quinine, heparin, interferon, valproic acid, isotretinoin and chemotherapy. Occasionally, there may be bruising, purpura, petechiae, gum bleeding, epistaxis, menorrhagia and rarely platelets count below 5,000/cumm predisposing the life-threatening bleeding in the central nervous system from gastrointestinal and genitourinary tracts.[4] Infection is the commonest cause of thrombocytopenia and febrile thrombocytopenia is the thrombocytopenia associated with fever. Fever is the common manifestation of the infection in most of the cases with few exceptions like chronic kidney disease, alcoholic, immune compromise host. Infectious disease which

commonly present with fever and thrombocytopenia are malaria, enteric fever, septicaemia, leptospira, rickettsial infections like scrub typhus, dengue and other viral infections including human immunodeficiency virus.[5] Thrombocytopenia has relation with mortality and morbidity in various febrile illnesses such as dengue and thus serial monitoring of platelets count has prognostic significance. Hence, a well-organised systemic approach is carried out with awareness of cause of fever that will shorten the number of investigations and bring out the diagnosis. Therefore, the present study was carried out to know the underlying aetiology of febrile thrombocytopenia, the clinical profile of febrile thrombocytopenia and to assess the severity of thrombocytopenia in the various aetiology of fever with thrombocytopenia and relationship between platelet count and severity of disease and prognosis.

Aim and Objectives
To evaluate clinical profile of fever with thrombocytopenia and to identify the underlying aetiology of febrile thrombocytopenia, to assess severity of thrombocytopenia in the various aetiology of febrile thrombocytopenia and relationship between platelets count and severity of disease and prognosis.

MATERIALS AND METHODS
This is a hospital-based observational study and the present study was conducted on 100 patients admitted in Department of General Medicine of Jhalawar Medical College, Jhalawar, Rajasthan during July 2016 to September 2017. The patients were selected as per protocol based on inclusion and exclusion criteria. Informed written consent was taken from the patients and ethical committee approval was obtained.

Inclusion Criteria
All new patients of both sexes with age > 16 years admitted with fever (temperature > 99.9 F) and found to have thrombocytopenia (i.e. counts < 150.000/cumm).

Exclusion Criteria
1. Patients with thrombocytopenia diagnosed as haematological disorder or malignancy on treatment with chemotherapy and other immunosuppressive drugs.
2. Patients on treatment with anti-platelets and other drugs causing thrombocytopenia.
3. Patients with known case of immune thrombocytopenic purpura on treatment.
4. Patients with cirrhosis of liver, chronic kidney disease, connective tissue disorder like SLE.

Methodology
All the cases during the study period were included. Once the patients were admitted with fever and found to have thrombocytopenia, careful history was recorded, general physical and systemic examination was done, routine investigation including complete blood counts, peripheral smear examination, kidney function test, liver function test, electrocardiography and ultrasonography was done. The specific and special investigations were done as and when indicated. Temperature was measured orally by clinical thermometer after keeping the thermometer for 1 minute,

while asking the patient to take breath from nose. Complete blood counts were done, Agappe analyser, both thick and thin blood smear examined for malarial parasites as well as for total leukocyte counts, platelets count and any abnormal cells. Special investigations like NS1 antigen for dengue, IgM Elisa for dengue, IgM Elisa for scrub typhus, Widal test, blood culture and sensitivity, body fluid analysis and bone marrow analysis were done as and when needed. In whom final definitive diagnosis was reached were treated for the disease and platelet count was repeated in severe thrombocytopenia, bleeding manifestations and at the time of discharge.

RESULTS
Total 100 patients were admitted in our hospital over a period of July 2016 - September 2017 were studied. The study subjects were in the age group of 16 - 80 years with 60 males and 40 females (Figure 1). Febrile thrombocytopenia was common in young and middle age group, i.e. < 40 years (45%) with maximum number of patients in age group of 16 - 30 years. 30 patients were in the age group of 41 - 65 years and 25 patients were in the age group of 66 years (Figure 3). Febrile thrombocytopenia was more commonly seen in season of July to September affecting 62 patients. 19 patients were affected in October to December and 13 patients were affected in January to March and 6 patients were affected in April to June (Figure 4).

The commonest cause of febrile thrombocytopenia was dengue fever (50%) followed by malaria (23%). The other causes were in our study like viral fever (19%), scrub typhus (4%), mixed dengue and scrub typhus (2%), septicaemia (2%) (Table 1). Viral fever was labelled in the patients whose definitive diagnosis was not made after investigations. The least common cause of febrile thrombocytopenia was septicaemia (2%). In our study out of 23 cases of malaria, P.vivax with 12 (12%) cases was the most common type followed by P. falciparum with 7 (7%) cases and least common type was mixed P. vivax and P. falciparum with 4(4%) cases. Apart from fever, which was present in all cases. The commonest clinical manifestation was myalgia (85%) followed by chills and rigor (78%). The least common clinical feature was rash (3%). Bleeding manifestation was present in 3 (3%) cases and petechiae were the most common bleeding manifestation seen in 2 (2%) cases followed by subconjunctival haemorrhage seen in 1 (1%) case.

In our study, 8 patients had platelet count < 20,000/cumm, 16 patients in range of 20,000 - 50,000/cumm and 76 patients had platelet counts > 50,000/cumm.

Severe thrombocytopenia was seen in most cases of dengue fever and viral fever followed by P. falciparum. Moderate thrombocytopenia was seen more commonly in P.vivax and mixed malaria. Mild thrombocytopenia was seen in all cases of scrub typhus and septicaemia also had mild thrombocytopenia in our study (Table 2). Maximum bleeding manifestations were seen with platelet count < 20,000/cumm. No bleeding manifestation was observed with platelet count > 100,000/cumm (Figure 5). In our study, lowest platelet counts were 3,000/cumm. Platelet counts were repeated in patients with severe thrombocytopenia and bleeding manifestations. Definitive increase in platelet count was noted after the underlying cause was treated. Out of 100 patients, 98 patients had good recovery. 2 patients had expired (Figure 6). Mortality was seen in 2 cases, which was

due to multiorgan dysfunction caused by septicaemia and complicated malaria which was present in all those cases.
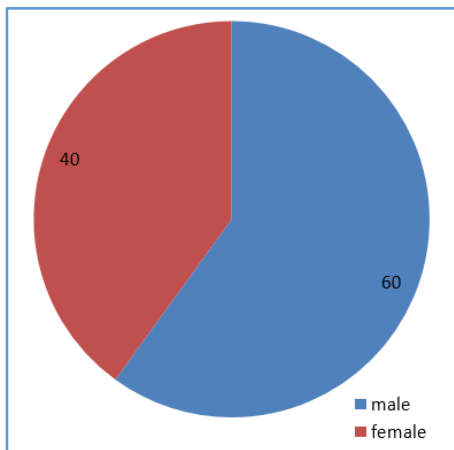

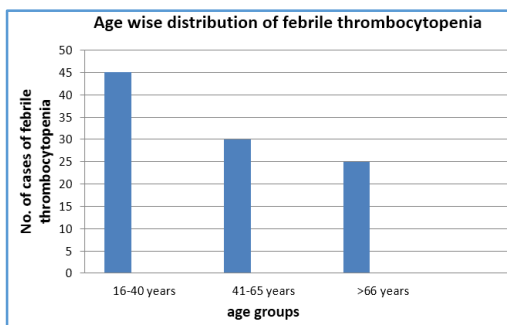*Figure 1. Sex Wise distribution of Febrile Thrombocytopenia*

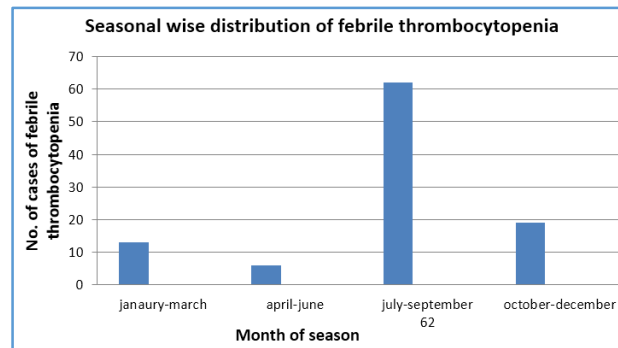*Figure 2. Age Wise distribution of Febrile Thrombocytopenia*

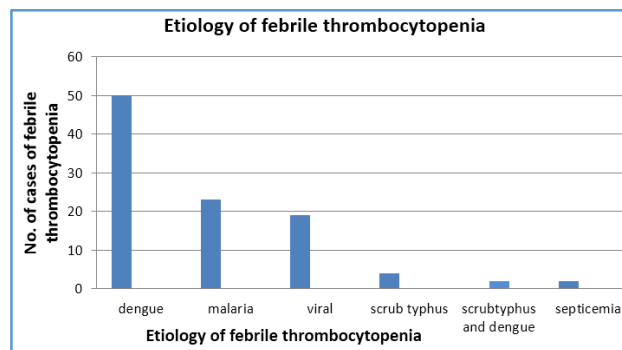*Figure 3. Seasonal Wise distribution of Febrile Thrombocytopenia*

*Figure 4. Aetiology of Febrile Thrombocytopenia*

Clinical Symptoms/ Signs	Number of Cases
Fever	100
Chills and Rigor	78
Headache	69
Body Ache	65
Myalgia	85
Joint Pain	35
Vomiting	51
Abdomen Pain	32
Loose Motion	23
Cough and Dyspnoea	12
Rash and Bleeding	3
Hypotension	15
Tachycardia	15
Pallor	14
Jaundice	2
Abnormal Renal Function Test	2
Abnormal Liver Function Test	2
Table 1. Clinical Manifestations of Febrile Thrombocytopenia	

Platelet Count	Dengue (n=50)	P.F (n=7)	P.V (n=12)	P.V + P.F (n=4)	Viral (n=19)	Scrub Typhus (n=4)	Septicaemia (n=2)	Scrub Typhus + Dengue (n=2)	Total (n=100)
<20,000/cumm	3	1	1	0	3	0	0	0	8
20,000-50,000/cumm	1	2	5	2	6	0	0	0	16
50,000-100,000/cumm	20	3	6	2	8	3	0	0	42
100,000-150,000/cumm	26	1	0	0	2	1	2	2	34
Table 2. Platelet Count distribution according to different Aetiology									
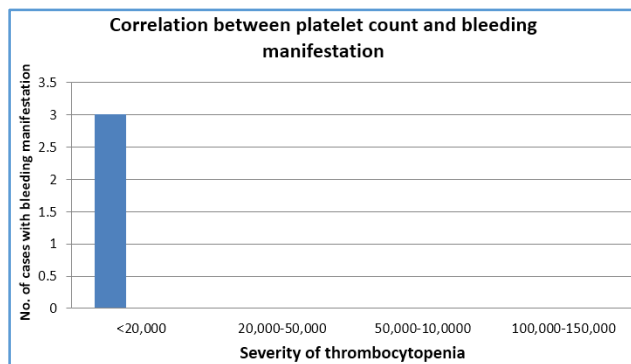
*Figure 5. Correlation between Platelet
Count and Bleeding Manifestation*

Figure 5 showing new information in relation between bleeding manifestation and severity of thrombocytopenia.
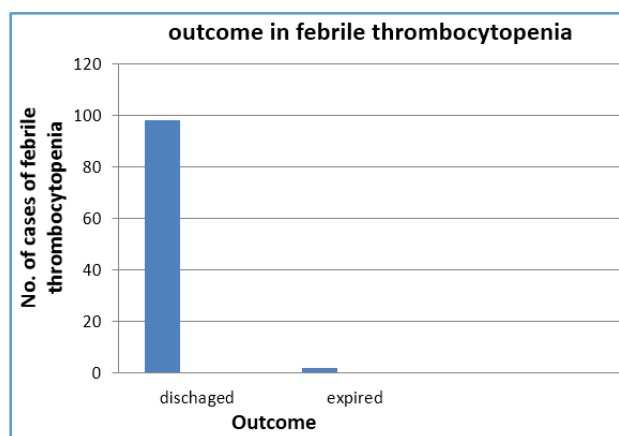
Figure 6. Outcome in Febrile Thrombocytopenia

DISCUSSION

Febrile thrombocytopenia is a common clinical condition and is caused by infectious and non-infectious disease. Total of 100 cases of febrile thrombocytopenia admitted over a period of one year in our hospital were studied. The affected populations were in the age group of 16 - 80 years with 60 male and 40 female with maximum number affected in age group of 16 - 30 years. Similar results were seen in study by Kumar P et al.[4] Febrile thrombocytopenia was more prevalent in the month of July to September in our study. This was because of high incidence of dengue and malaria in this region during that period. In our study, the commonest aetiology of febrile thrombocytopenia was dengue fever accounting for 50 (50%) case followed by malaria (23%), viral fever (19%), scrub typhus (4%), scrub typhus + dengue (2%) and septicaemia (2%). In previous study by Gandhi AA et al,[6] found malaria as the commonest cause for febrile thrombocytopenia. This difference might be due to seasonal and regional variation of the febrile illness. Malaria and dengue fever are predominantly present in rainy season, because there can be clustering of these cases in this season. In our study, myalgia was the most common clinical feature apart from fever and myalgia was predominantly present in dengue fever, viral fever, scrub typhus and leptospira. Similar results were observed in study by Tong Seng Fah et al,[7] i.e. myalgia being the commonest clinical feature. In the present study, bleeding manifestation were very rarely seen as present in only 3 (3%) cases with petechiae as common manifestation followed by subconjunctival bleed. In a study by Nair PS et al,[8] bleeding manifestation observed in 41.3% cases with petechiae and gastrointestinal bleed as most common bleeding manifestation. In our study, no patient was found to have gastrointestinal bleed which were present in the above described study. In our study, mild thrombocytopenia was most commonly seen in 76 (76%) cases. In study by Nair PS et al,[8] it was 56.8%. Platelet counts in the range of 20,000 - 50,000/cumm was seen in 16 (16%) cases. Severe thrombocytopenia, i.e. count < 20,000/cumm was observed in 8 (8%) cases. It was 25.7% in study by Nair PS et al[8] present study as compared to 13.39% cases in study by Gandhi AA et al.[6] Distribution of platelet counts correlates with the above-mentioned study. In our study, severe thrombocytopenia was present in dengue fever followed by falciparum malaria, while moderate thrombocytopenia was common in viral fever, vivax and mixed malaria. Scrub typhus and septicaemia had mild thrombocytopenia. In study by Gandhi AA et al[6] severe thrombocytopenia was seen in falciparum malaria, while moderate thrombocytopenia was common in vivax malaria. Thus, from these studies it is evident that moderate thrombocytopenia is a feature of vivax malaria and severe thrombocytopenia is commonly seen in falciparum malaria. Thrombocytopenia in malaria is probably due to increased splenic sequestration, immune-mediated destruction and shortened platelet survival and consumption by disseminated intravascular coagulation.[9] Along with quantitative defects, qualitative defects have also been documented which are platelet hyperactivity due to aggravating agents like immune complexes and damage of endothelial cells followed by platelet hypoactivity which returns to normal in 1 - 2 weeks. Thrombocytopenia along with acute febrile syndrome is having 100% sensitivity, 70% specificity, 100% negative predictive value and 86% positive predictive value in malarial diagnosis.[10] Another study had reported 60% sensitivity and 88% specificity of thrombocytopenia for malaria diagnosis in acute febrile patients.[11] So we observed in our study, thrombocytopenia is commonly mild in febrile thrombocytopenia. In our study severe thrombocytopenia was seen in 8 (8%) cases, while moderate thrombocytopenia was seen in 16 (16%) cases. Our results are similar with Gandhi AA et al.[6] Dengue is the most common arbovirus disease worldwide and occurs in tropical countries. Thrombocytopenia is an important finding and has got predictive and recovery parameter of dengue fever. The two mechanisms of thrombocytopenia in dengue fever are impaired thrombocytosis as a result of invasion of megakaryocytic by virus and peripheral platelet destruction.[12,13] In our study, we found 4 cases of scrub typhus with mild thrombocytopenia. In a study by Venkategowda PM et al.[14] In India, scrub typhus was found in the Sub-Himalayan region and Southern India like Tamilnadu and Kerala. High degree of clinical suspicion is necessary as the classical eschar is found in only few cases of scrub typhus and the disease remains undiagnosed due to non-specific clinical presentation and limited diagnostic resources. Recently, there are reported cases of scrub typhus in other part of the country. Also, early clinical suspicion and

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prompt institution of treatment reduce the development of the life-threatening complication in scrub typhus. In our study, we also found 2 cases of mixed infection with scrub typhus and dengue and 2 cases of septicaemia.

There is no previous study, in which scrub typhus with dengue was found. The aetiology of thrombocytopenia in sepsis is multifactorial. It is commonly associated with disseminated intravascular coagulation and caused by spleen destruction of immune coated platelet, platelet adherence to damage vascular surface and direct platelet toxicity caused by microorganism.[5] In our study, we did not find any cases of enteric fever as the possible cause of febrile thrombocytopenia. In previous studies, leptospira also is the important cause of thrombocytopenia. But in our study, we are unable to include leptospira as cause of thrombocytopenia, because of lack of diagnostic facility for leptospira in our institute. In our study mortality was seen in only 2 cases, but mortality was not related to the severity of thrombocytopenia. In our study, multiorgan dysfunction due to septicaemia and complicated malaria was seen in all those 2 cases. The similar results were observed in study by Lohitashwa et al.[15]

CONCLUSION

Febrile thrombocytopenia is an important clinical condition commonly caused by infection. In our study, the commonest aetiology of febrile thrombocytopenia was dengue fever. Thrombocytopenia due to infectious disease shows seasonal variation, most commonly seen during rainy and winter season mostly in the month of July to September. Mortality in febrile thrombocytopenia is not directly associated with degree of thrombocytopenia, but it is due to multiorgan dysfunction caused by septicaemia and complicated malaria and thrombocytopenia is usually mild in febrile thrombocytopenia and majority case of febrile thrombocytopenia were asymptomatic but rarely there were evidence of life-threatening bleeding in central nervous system, gastrointestinal and genitourinary system and even death. Hence, serial monitoring of platelet count is required and has predictive and recovery parameter in dengue fever. Chance of bleeding manifestation increase with platelet count below 20,000/cumm. So, platelet count should be asked in all cases with fever. Treatment of underlying condition will lead to rapid improvement in platelet count with complete clinical recovery. This study helps in correlating the clinical features, laboratory values to determine possible cause of thrombocytopenia plus helping in the diagnosis and management of these patients. Also, similar studies will help in finding changing trends of locally prevalent infectious disease and finding some new emerging disease not prevalent in the particular region.

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