

Study of febrile thrombocytopenia in adults

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Abstract

Introduction: Fever is a common manifestation of an illness. Thrombocytopenia is a frequent finding in febrile illness. Thrombocytopenia with fever narrows the differential diagnosis of clinical entity and helps in reaching the diagnosis of febrile illness. Hence this study is undertaken to identify the causes of febrile thrombocytopenia and to assess the severity of thrombocytopenia in various etiologies of febrile thrombocytopenia. **Material and Methods:** The study was done in Department of Medicine in Indira Gandhi Government Medical College, Nagpur during January 2011 to October 2012. The study is a hospital based observational study. Total 122 cases were enrolled for the study. **Results:** Malaria was the leading cause of febrile thrombocytopenia (44.26%) followed closely by viral fever (22.13%). The other causes were dengue fever (18.85%), septicemia (9.83%), leptospirosis (3.27%) and scrub typhus (1.63%). The patients were in the age group 13-58 years with 70 males and 52 females. Maximum patients (61.46%) were found to have thrombocytopenia in the range of 50,000-1, 50,000/cumm. 13 cases (10.65%) had thrombocytopenia in the range <20,000/cumm while 34 cases had thrombocytopenia in the range 20,000-50,000/cumm. Bleeding manifestations were present in 33 cases (27.06%) with petechiae as the commonest bleeding manifestation (13.93%). Severe thrombocytopenia was seen commonly in leptospirosis (50%), dengue fever (21.73%) and falcifarum malaria (10%) cases. Mortality was noted in 12 cases (9.83%) and multiorgan dysfunction was present in all those 12 cases. **Conclusions:** Malaria is the commonest cause of febrile thrombocytopenia. Asymptomatic thrombocytopenia was present in 89(72.94%) cases while symptomatic thrombocytopenia was present in 33(27.06%) cases. Petechiae was the commonest bleeding manifestation (13.93%) among symptomatic thrombocytopenia. Complicated malaria, septicemia, leptospirosis and dengue fever were the diagnosis of patients who died. Severity of thrombocytopenia was not associated with increased mortality. All 12 patients of febrile thrombocytopenia died due to multiorgan failure.

Keywords: Fever, Malaria, Thrombocytopenia.

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INTRODUCTION

Fever is the most ancient hallmark of disease which is defined as the elevation in the body temperature above the normal circadian range as a result of change in the thermoregulatory centre located in the anterior hypothalamus. An AM temperature of >37.2°C (98.9°F) or PM temperature of >37.7°C (99.9°F) would define

fever¹. Thrombocytopenia is defined as subnormal level of platelets in circulatory blood, i.e. counts below the normal limits of 1.5 lacs/cumm². Often the patients of thrombocytopenia are asymptomatic and thrombocytopenia becomes revealed on routine complete blood counts. Thrombocytopenia results from various processes like accelerated platelets destruction, deficient platelets production, abnormal distribution or pooling of platelets within the body and artifactual thrombocytopenia³. Infection is the commonest cause of thrombocytopenia and fever is the manifestation of infection in most of the cases with few exceptions like immunocompromised host, chronic renal insufficiency, alcoholics. A battery of tests needs to be done in finding out the cause of fever. Thrombocytopenia with fever helps in formulating the differential diagnosis of the clinical entity. Thrombocytopenia has relation with mortality and morbidity in various febrile illnesses and thus serial monitoring of platelet count has prognostic

significance. Hence a well organized systematic approach is carried out with an awareness of causes of fever that will shorten the number of investigations and bring out the diagnosis. Therefore the present study was carried out to study the clinical profile of febrile thrombocytopenia and to assess the severity of thrombocytopenia in various etiologies of febrile thrombocytopenia.

MATERIALS AND METHODS

This hospital based observational study was conducted in the General Medicine wards and medical intensive care unit of Department of Medicine in Indira Gandhi Government Medical College, Nagpur, Maharashtra during period from January 2011 to October 2012. The inclusion criteria includes patients of both gender with age >12 years admitted with fever and found to have thrombocytopenia. Sampling was done with random method. The exclusion criteria were patients of thrombocytopenia without fever, diagnosed cases of thrombocytopenic purpura on treatment, patients with thrombocytopenia diagnosed as haematological disorder or malignancy on treatment with chemotherapy, patients on treatment with antiplatelet and other drugs causing thrombocytopenia, patients having other causes of thrombocytopenia like cardiac prosthetic valves, cirrhosis of liver, portal hypertension, connective tissue disorder like systemic lupus erythematosus. Once the case is admitted with febrile thrombocytopenia, a careful history was recorded, general physical examination was done and detailed examination of the various systems was done. Routine investigations including complete blood counts, peripheral smear examination, kidney function tests, liver function tests, electrocardiograph (ECG), ultrasonography were done. The specific and the special investigations were done as and when indicated. Temperature was measured orally by clinical thermometer after keeping the thermometer for 2 minutes while asking the patient to take breath from nose. Complete blood counts were done on Agappe analyser. Both thick and thin blood smears were examined for malarial parasites as well as for total leucocyte count, platelet count and for any abnormal cells. Special investigations like NS1 antigen for dengue, IgM Elisa for dengue, widal test, quantitative buffy coat for malarial parasite, Elisa for HIV, HbsAg, IgM Elisa for leptospira, IgM Elisa for scrub typhus, blood culture and sensitivity, body fluid analysis and bone marrow aspiration were done as and when needed.

OBSERVATIONS AND RESULTS

A total number of 122 cases admitted in the period January 2011 to October 2012 were studied in this hospital. The study subjects were in age group 13-58 years with 70 males and 52 females. Febrile

thrombocytopenia was common in young and middle age group i.e. <40 years (79.5%) with maximum number of patients (41.80%) in decade 20-29 years.

Table 1: Etiology of Febrile thrombocytopenia

Etiology	Number of cases	Percentage (%)
Malaria	54	44.26
Viral fever	27	22.13
Dengue fever	23	18.85
Septicemia	12	9.83
Leptospirosis	4	3.27
Scrub typhus	2	1.63

The commonest etiology was malaria (44.26%) followed by viral fever (22.13%). Viral fever was labelled in patients whose definitive diagnosis were not made after investigations. Out of 12 patients of septicemia, 7 were having pneumonia and 5 were having cellulitis. The least common cause of febrile thrombocytopenia was scrub typhus (1.63%). Out of 54 cases of malaria, P. falcifarum malaria with 30 (24.59%) cases was most common type followed by p.vivax malaria with 13(10.65%) cases and least common type was mixed malaria (P.falcifarum + P.vivax) with 11(9.01%) cases.

Table 2: Clinical presentation of cases of febrile thrombocytopenia

Clinical sign/symptoms	Number of cases (%)
Fever	122(100%)
Chills and rigors	71(58.19%)
Cough	34(27.86%)
Jaundice	34(27.86%)
Pallor	66(54.09%)
Headache	64(52.45%)
Vomiting	57(46.72%)
Myalgia	84(68.85%)
Braeathlessness	34(27.86%)
Rash	14(11.47%)
Bleeding	33(27.04%)
Altered sensorium	18(14.75%)

Apart from fever which was present in all cases, the commonest clinical feature was myalgia (68.85%), followed by chills and rigors (58.19%). The least common feature was rash (11.47%). Bleeding manifestation were seen in 33 (27.04%) cases. Petechiae was the most common bleeding manifestation seen in 17 (13.93%) cases followed by ecchymosis in 9 (7.73%) cases, subconjunctival bleed in 5 (4.09%) cases and bleeding gums in 2 (1.63%) cases. None of the patient had epistaxis, gastrointestinal bleed, hematuria or life threatening intracranial haemorrhage.

Table 2: Severity of thrombocytopenia and clinical manifestations⁴

Platelet count	Clinical Manifestations
>100000	Asymptomatic
50000-100000	Haemorrhage after injury
20000-50000	Skin purpura
<20000	Spontaneous bleed from mucus membrane

From above Table, it is evident that bleeding from skin occurs as platelet count falls below 50,000/cumm and spontaneous bleed like epistaxis, oral bleed, hematuria occurs with platelet count <20,000/cumm.

Table 3: Severity of thrombocytopenia in cases

Platelet count	Cases	Percentage (%)
<20,000/cumm	13	10.65
20,000-50,000/cumm	34	27.86
50,000-1,00,000/cumm	67	54.91
1,00,000-1,50,000/cumm	8	6.55

The majority of patients were found to have mild thrombocytopenia i.e. platelet count >50,000/cumm. Severe thrombocytopenia with platelet count <20,000/cumm was seen in 13(10.65%) cases and moderate thrombocytopenia with platelet count 20,000-50,000/cumm was seen in 34 (27.86%) cases.

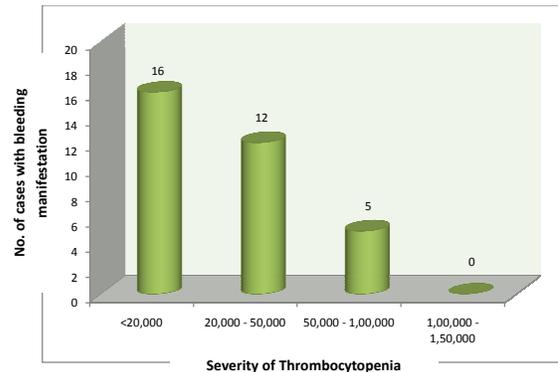


Fig. 1

Figure 1: Co-relation between platelet count and bleeding manifestation

From fig.1, it is evident that more the severity of thrombocytopenia, more chances of bleeding manifestation. Maximum bleeding manifestation were seen with platelet count <20,000/cumm. No bleeding manifestation was observed with platelet count >1 lacs/cumm.

Table 4: Platelet count distribution according to different etiology

Platelet count	P. Falcifarum (n=30)	P.Vivax (n=13)	Mixed malaria (n=11)	Viral fever (n=27)	Dengue (n=23)	Leptospirosis (n=4)	Septicemia (n=12)	Scrub typhus (n=2)	Total (n= 122)
<20,000/cumm	3	0	0	2	5	2	1	0	13
20,000-50000/cumm	7	0	6	4	10	2	5	0	34
50,000-1,00,000/cumm	18	11	5	17	8	0	6	2	67
1,00,000-1,50,000/cumm	2	2	0	4	0	0	0	0	8

Among different malarial species, only plasmodium falcifarum cases (10%) had severe thrombocytopenia i.e. platelet count <20,000/cumm. All patients of vivax malaria had mild thrombocytopenia i.e. platelet count >50,000/cumm. Moderate thrombocytopenia was more common (54.54%) in mixed malaria. Severe thrombocytopenia was also seen in dengue fever (21.73%), leptospirosis (50%) septicemia (8.33%) and viral fever (7.40%). Mild thrombocytopenia was also seen in both cases of Scrub typhus. 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. The mortality was in 12(9.83%) cases which includes 4 cases of complicated malaria, 4 cases of septicemia, 2 cases

each of dengue fever and leptospirosis. Multiorgan dysfunction was present in all those cases.

DISCUSSION

A total of 122 cases of febrile thrombocytopenia were studied with 70 males and 52 females. Majority of cases were seen in the age group 20-29 years (41.80%) followed by 30-39 years age group(28.60%).The middle age group (<40 years)was dominant with 97 (79.50%)cases. Similar results were seen in study by Kumar P *et al* (2014) ⁵. The commonest etiology of febrile thrombocytopenia in this study was malaria (44.26%). The other etiology were viral fever (22.13%), dengue fever (18.85%), septicaemia (9.83%), leptospirsis (3.27%), scrub typhus (1.63%). Similar results were obtained in study by Kumar P *et al* (2014)⁵ i.e. malaria

being the commonest etiology. Out of 54 cases of malaria, falcifarum malaria predominates with 30(24.59%) cases, vivax malaria with 13(10.65%) and mixed malaria with 11(9.01%) cases. The study by Gandhi AA *et al*⁶ found malaria being the commonest etiology in febrile thrombocytopenia patients with P. falcifarum malaria (20.54%) as predominant type of malaria followed by P.vivax malaria(16.07%) and mixed malaria (4.46%). Thus present study findings correlates with the above mentioned study. The previous study by Nair PS *et al*(2003)⁷ found septicemia as the commonest cause for febrile thrombocytopenia. This difference might be due to seasonal and regional variation of the febrile illnesses. Malaria and dengue fever are predominantly present in rainy season and there can be clustering of these cases in this season. A study by Gandhi AA *et al* (2015)⁶ also found dengue and malaria as the common causes of febrile thrombocytopenia. In the present study population, myalgia (68.85%) was the most common clinical feature. Myalgia was predominantly present in dengue fever, viral fever other than dengue fever, all cases of leptospirosis and scrub typhus. Similar result were obtained in study by Tong Seng Fahet *et al* (2006)⁸ i.e. myalgia being the commonest clinical feature. In the present study, bleeding manifestation were present in 33 (27.04%) cases with petechiae. (13.39%) as the most common manifestation followed by ecchymosis (7.73%), subconjunctival. Bleed (4.09%) and bleeding gums (1.63%). In the study by Nair PS *et al*(2003)⁷, bleeding manifestation observed in 41.3% cases with petechiae/purpura (9.2%) and gastrointestinal bleed(9.2%) as the most common bleeding manifestation. In another study by Kumar P *et al*(2014)⁵ bleeding manifestation seen in 11.05% cases which consists of gastrointestinal bleed (5.26%), petechiae (3.67%) and hematuria (2.10%). No patient found to have GI bleed or hematuria in the present study which were present in the above described studies. In the present study most common platelet distribution 50,000-1,00,000/cumm was seen in 54.9% cases. Similar results(56.8%) were obtained in Nair PS *et al*⁷ study for this platelet distribution range. Platelet count in the range of 20,000-50,000/cumm was seen in 27.86% cases in the present study as compared to 25.7% in Nair PS *et al*⁷ study. Our distribution of platelet count correlates with the above mentioned study. Severe thrombocytopenia, i.e. count <20,000/cumm observed in 10.65 % cases in present study as compared to 17.4% cases in study by Nair PS *et al* and 13.39% cases in study by Gandhi AA *et al*(2015)⁶. In the present study, severe thrombocytopenia was present in falcifarum malaria only (10%) while moderate thrombocytopenia was common in mixed malaria (54.54%) and all patients of vivax malaria (100%) had mild thrombocytopenia. In study by Gandhi

AA *et al* (2015)⁶ severe thrombocytopenia was seen in 39% cases of falcifarum malaria and 60% cases of mixed malaria while mild thrombocytopenia was seen in 72% cases of vivax malaria. In another study by Bhalara SK *et al* (2015)⁹, moderate thrombocytopenia was common in all types of malaria whereas severe thrombocytopenia was more common in falcifarum malaria. Thus from these studies it is evident that mild thrombocytopenia is a feature of vivax malaria and severe thrombocytopenia is commonly seen in falcifarum malaria. Both immunological destruction and immune mechanism involving specific platelet associated IgG antibodies that bind directly to malarial antigen in the platelets have been reported to play a key role for lysis of platelets¹⁰. In our study out of 23 cases of dengue fever, severe thrombocytopenia was seen in 21.73% cases while moderate thrombocytopenia was seen in 43.47%. Our result are similar with Gandhi AA *et al*⁶ study where moderate thrombocytopenia was seen in 50 % cases while severe thrombocytopenia was seen in 13.33% cases of dengue fever. The two mechanism for thrombocytopenia in dengue are impaired thrombopoiesis as a result of invasion of megakaryocytes by the virus and peripheral platelet destruction.¹¹ We found 4 cases of leptospirosis with thrombocytopenia of which severe thrombocytopenia was seen in 2 (50%) cases and moderate thrombocytopenia was seen in another 2 (50%) cases. In leptospirosis, platelets becomes adherent to activated endothelial cells and reflects the platelet consumption in the activated endothelial surfaces. Presence of disseminated intravascular coagulation (DIC) further lowers the platelet count.¹² In our study we also found 2 cases of scrub typhus with mild thrombocytopenia. Thrombocytopenia was observed in scrub typhus patients in study by Venkategowda PM *et al*(2015)¹³. 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 under diagnosed due to non specific clinical presentation and limited diagnostic resources. Recently there are reported cases of scrub typhus in other parts of the country also. Early clinical suspicion and prompt institution of treatment reduces the development of life threatening complications in scrub typhus. We didn't found any cases of enteric fever as a possible cause of febrile thrombocytopenia. Mortality was in 12(9.83%) cases out of 122 cases of febrile thrombocytopenia. Mortality was not related with the severity of thrombocytopenia but because of multiorgan dysfunction due to underlying etiology in all those 12 cases.

CONCLUSIONS

This study shows malaria as the commonest etiology for febrile thrombocytopenia. Also dengue and other viral fevers account for significant proportion of febrile thrombocytopenia cases. In symptomatic thrombocytopenia, petechiae is the most common bleeding manifestation. Chances of bleeding manifestation increases with platelet count below 20,000/cumm. This study might help in correlating the clinical features and laboratory values to determine possible cause of febrile thrombocytopenia and thus helping in the diagnosis and management of these patients. Also similar studies will help in finding changing trends of locally prevalent infectious diseases and finding some new emerging diseases not prevalent in the particular region.

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