STUDY OF AETIOLOGY AND CLINICAL FEATURES OF FEBRILE THROMBOCYTOPENIA

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ABSTRACT**BACKGROUND**

Febrile thrombocytopenia is one of the most challenging problems in the field of medicine. Fever with thrombocytopenia is the common manifestation of infective diseases. It helps to narrow the differential diagnosis and management. Treatment of underlying condition will lead to rapid improvement in platelet count and minimise bleeding manifestations and other complications. Hence, there is a need for study to know the aetiology and clinical features of febrile thrombocytopenia.

The aim of this study is to study the aetiology and clinical features of febrile thrombocytopenia.

MATERIALS AND METHODS

50 patients who were admitted with febrile thrombocytopenia over 2 months of period from July 20th to 20th September 2017 in King George Hospital, AMC, Visakhapatnam, were studied retrospectively.

RESULTS

In this present study, the incidence of febrile thrombocytopenia was more common in male (66%) as compared to female (34%). The study reveals that age up to 50 years constituting 78% of the cases and above 50 years constituting 22% only. Apart from fever (100%) in male patients vomiting (28%) and cough (20%) were the most common clinical features, while in female patients, body pains (20%) and headache (18%). Bleeding manifestations were more common in males (18%) than in females (10%). Malaria in 22 cases (44%) constitutes the most common aetiology of febrile thrombocytopenia of which falciparum 10 (20%), vivax 8 (16%) and both 4 (8%) followed by viral infection including dengue in 17 cases (34%). The present study reveals that severe thrombocytopenia (platelets < 20000/mm³) is present in 18% of cases, moderate (20000 - 50000/mm³) in 34% and mild thrombocytopenia (> 50000/mm³) is present in 48% of cases. Melena was the most common presenting manifestation followed by petechiae and haematochezia.

CONCLUSION

Though there is no absolute relation between platelet count and severity of bleeding, the risk of bleeding increases as the platelet levels fall below 20,000/μL. In majority of the cases thrombocytopenia was asymptomatic, but in a significant number of cases bleeding manifestations are seen which require prompt management to prevent life-threatening complications.

KEYWORDS

Febrile Thrombocytopenia, Aetiology, Malaria, Bleeding Manifestations.

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BACKGROUND

Febrile thrombocytopenia is one of the most challenging problems in the field of medicine. Fever is defined as A.M. temperature more than 98.9° F and P.M. temperature more than 99.9° F. Thrombocytopenia is defined as platelet count less than 1,50,000/μL in blood.¹ The fall in the platelet count may be due to decreased production, increased splenic sequestration and accelerated destruction.

Thrombocytopenia is characterised by bleeding, most often from small vessels. This can manifest as petechiae over the skin, haemorrhages from mucosa of gastrointestinal and genitourinary tract. Intracranial haemorrhage is a dangerous

consequence in thrombocytopenic patients.² Although, there are many causes for thrombocytopenia, fever is the commonest cause.

Febrile thrombocytopenia is commonly due to malaria, enteric fever, sepsis, leptospirosis, miliary tuberculosis, rickettsial infections, arbovirus such as dengue or yellow fever and human immunodeficiency virus (HIV). Febrile thrombocytopenia helps to narrow the differential diagnosis and management. Finding out the cause of thrombocytopenia is critical to treating the condition.

Aim

To study aetiological and clinical features of febrile thrombocytopenia.

MATERIALS AND METHODS

Sample was collected retrospectively from cases admitted with febrile thrombocytopenia in King George Hospital, Visakhapatnam over a period of 2 months' time (20th July 2017 to 20th September 2017). Detailed history and clinical examination were noted. Cases were analysed for various parameters like platelet count, QBC, dengue serology, x-ray

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and other lab investigations. Age, sex, duration of stay, severity, complications and mortality were noted.

Inclusion Criteria

Both sexes aged more than 12 years who were admitted with febrile thrombocytopenia in medical wards during 20th July 2017 to 20th September 2017 were included.

Exclusion Criteria

- Pregnant patients.
- Patients with cirrhosis and chronic liver diseases.
 - Diagnosed cases of platelet disorders and dysfunction.
 - Patients on antiplatelet therapy.

RESULTS

Age (in Years)	Gender		Total n= 50
	Male	Female	
11 - 20	8 (16%)	4 (8%)	12 (24%)
21 - 30	8 (16%)	1 (2%)	9 (18%)
31 - 40	8 (16%)	4 (8%)	12 (24%)
41 - 50	3 (6%)	3 (6%)	6 (12%)
51 - 60	4 (8%)	3 (6%)	7 (14%)
61 - 70	-	2 (4%)	2 (4%)
71 - 80	2 (4%)	-	2 (4%)
Total	33 (66%)	17 (34%)	50 (100%)

Table 1. Distribution of Cases according to Age and Gender

Figure 1. Distribution of Cases according to Age and Gender

In this present study, the incidence of febrile thrombocytopenia was more common in males (66%) as compared to females (34%).

In this study, the highest incidence was found in the age groups of 11 - 20 years and 31 - 40 years (24%) followed by 21 - 30 years (18%), then followed by 51 - 60 years (14%).

The present study reveals that age up to 50 years constitutes 78% and above 50 years constitutes 22% (Table 1).

Clinical Features	Gender		Total (n= 50)
	Male (n= 33)	Female (n= 17)	
Fever	33 (66%)	17 (34%)	50 (100%)
Vomiting	14 (28%)	6 (12%)	20 (40%)
Headache	8 (16%)	9 (18%)	17 (34%)
Body Pains	7 (14%)	10 (20%)	17 (34%)
Bleeding	9 (18%)	5 (10%)	14 (28%)

Manifestations			
Cough	10 (20%)	1 (2%)	11 (22%)
SOB	7 (14%)	1 (2%)	8 (16%)
Pain Abdomen	5 (10%)	0	5 (10%)
Loose Motions	4 (8%)	0	4 (8%)
Jaundice	3 (6%)	0	3 (6%)
Hypotension	2 (4%)	1 (2%)	3 (6%)
Decreased Urine Output	1 (2%)	2 (4%)	3 (6%)
LOC with GTCS	1 (2%)	1 (2%)	2 (4%)

Table 2. Distribution of Clinical Features according to Gender

Table 2 shows that fever (100%) was the most common symptom followed by vomiting (40%), headache (34%) and body pains (34%). While in a prospective cross-sectional observational study conducted by Modi T et al³ at PDUMC and Civil Hospital, Rajkot, Gujarat, India from 1st November 2014 to 31st March 2016, whereas fever was the most common symptom followed by Headache (49.61%), Bodyache (36.38%) and Vomiting (25.69%).

Figure 2a. Distribution of Clinical Features according to Gender

Figure 2b. Distribution of Clinical Features according to Gender

The study shows that apart from fever (100%), in male patients vomiting (28%) and cough (20%) were the most common clinical features, while in females, body pains (20%) and headache (18%). Bleeding manifestations were more common in males (18%) than in females (10%). Respiratory symptoms like cough and dyspnoea were commonly seen in male patients.

In this study GIT symptoms like pain abdomen, loose motions and jaundice were present only in males. Nervous system symptoms like loss of consciousness and seizures were equally present in both sexes (2%).

Aetiology	Gender		Total (n= 50)
	Male (n= 33)	Female (n= 17)	
Falciparum Malaria	6 (12%)	4 (8%)	10 (20%)
Dengue Fever	5 (10%)	3 (6%)	8 (16%)
Vivax Malaria	6 (12%)	2 (4%)	8 (16%)
Mixed Malaria	2 (4%)	2 (4%)	4 (8%)
Atypical Pneumonia	3 (6%)	1 (2%)	4 (8%)
UTI	1 (2%)	1 (2%)	2 (4%)
DSS	0	1 (2%)	1 (2%)
Sepsis	2 (4%)	0	2 (4%)
Enteric Fever	1 (2%)	0	1 (2%)
LL Pneumonia	0	1 (2%)	1 (2%)
Other Viral Fevers	7 (14%)	2 (4%)	9 (18%)

Table 3. Aetiology according to Gender

Figure 3a. Aetiology according to Gender

Figure 3b. Types of Malaria Cases with Thrombocytopenia

Malaria in 22 cases (44%) constitutes the most common aetiology of febrile thrombocytopenia, of which falciparum 10 (20%), vivax 8 (16%) and both 4 (8%) Figure 3b.

Followed by viral infection in 17 cases (34%), of which 8 cases (16%) were of dengue fever and 9 were (18%) of viral infection other than dengue.

Other aetiologies are atypical pneumonia 4 (8%), sepsis 2 (4%) and UTI 2 (4%), while enteric fever, DSS, lobar pneumonia each constitutes 1 (2%) (Table 3).

Similar findings were observed in Gandhi et al study,⁴ had malaria as the major cause of febrile thrombocytopenia. In another study conducted by Lohitashwa et al on 100 patients from March 2004 to September 2005 had similar observations (i.e. malaria being the commonest cause).⁵ Another prospective study, which was conducted on 228 patients with fever and thrombocytopenia in medical unit of Hayatabad Medical Complex during 2008 - 2010 was showing malaria as the commonest cause (53%), in which 68% were having falciparum malaria.⁶

While Modi T et al study³ and Raikar et al study⁷ had viral aetiology as the major cause of febrile thrombocytopenia.

Aetiology	Platelet Count (/mm ³)			Total (n=50)
	< 20,000	20,000-50,000	>50,000	
Falciparum Malaria	3	1	6	10
Dengue Fever	2	3	3	8
Vivax Malaria	-	4	4	8
Mixed Malaria	-	1	3	4
Atypical Pneumonia	-	2	2	4
UTI	-	-	2	2
RT LL Pneumonia	-	1	-	1
DSS	-	1	-	1
Sepsis	-	-	2	2
Enteric Fever	-	-	1	1
Other Viral Fevers	4	4	1	9
Total	9	17	24	50

Table 4. Aetiology of Febrile Thrombocytopenia in different Platelet Count

Figure 4. Aetiology of Febrile Thrombocytopenia in different Platelet Count

Present study reveals that severe thrombocytopenia (Platelet < 20000/mm³) is present in 18% of cases, moderate thrombocytopenia (20000 - 50000/mm³) in 34% and mild thrombocytopenia (> 50000/mm³) is present in 48% of cases. In Praveen Kumar and Kalpana Chandra study,⁸ platelet count was commonly > 50,001/mm³ (50%) followed by 20,001/- 50,000/mm³ (39.47%) and < 20,000/mm³ in 10.52% cases. The findings observed in the present study correlate with the above-mentioned study.

Severe thrombocytopenia (18%) is seen in viral fever (8%), Falciparum malaria (6%) and Dengue fever (4%). Rt. LL pneumonia and DSS are presented with moderate thrombocytopenia only. Mild thrombocytopenia is present in UTI, sepsis and enteric fever (Table 4).

Bleeding Manifestations	Platelet Count (/mm ³)			Total (14)
	< 20,000 (n= 9)	20,000- 50,000 (n= 17)	> 50,000 (n= 24)	
Haematochezia	1	2	-	3
Melena	-	3	2	5
Petechiae	2	1	-	3
Haematemesis	-	1	-	1
Haematuria	-	1	-	1
Epistaxis	1	-	-	1
Total	4	8	2	14

Table 5. Distribution of Bleeding Manifestations in different Platelet Count

In this study, bleeding manifestations are present in 4 out of 9 (44.4%) cases of severe, 8 out of 17 (47%) cases of moderate and 2 out of 24 (8.3%) of mild thrombocytopenia cases. Melena was the most common presenting manifestation followed by petechiae and haematochezia. Further, it is observed that petechial rash is the most common presentation in severe thrombocytopenia. Gastrointestinal bleeding is more common in this study (9 cases) followed by Petechiae (3), Haematuria (1) and Epistaxis (1). Epistaxis is seen in severe thrombocytopenia. Even moderate thrombocytopenia resulted in haematuria, Table 5.

Figure 5a. Distribution of Bleeding Manifestations in Severity of Thrombocytopenia

Present study reveals that clinical manifestations of thrombocytopenia (bleeding manifestations) were noted in

28% patients (GI bleed- 18% patients, petechial rashes- 6%, haematuria- 2% and epistaxis- 2%).

The study conducted by Praveen Kumar and Kalpana Chandra⁸ reveals that the bleeding manifestations were noted in 11.05% patients and GI bleed was the commonest manifestation. But the study conducted by Lohitashwa et al observed bleeding manifestation in 49% cases and petechiae was the commonest bleeding manifestation.⁵

Figure 5b. Distribution of Bleeding Manifestations in different Aetiology

Out of the 8 cases of dengue, 4 (50%) had bleeding manifestations. Out of the 10 cases of PF malaria, 3 (30%) had bleeding manifestations. Out of the 8 cases of PV, malaria 2 (25%) had bleeding manifestations. Out of the 9 cases of viral fevers, 3 (33.3%) had bleeding manifestations. In both cases of DSS and pneumonia, 1 out of 1 (100%) had bleeding manifestations.

Recovery	No. of Patients	Percentage
Good Recovery	47	94%
Deaths	3	6%

Table 6. Outcome

Figure 6. Outcome

In this study 3 cases out of 50 had mortality due to sepsis, viral fever and vivax malaria. All the cases had mild thrombocytopenia only, Table 6.

DISCUSSION

Infections cause decrease in platelet count due to effects on both platelet production and platelet survival.⁹ Geographic, seasonal and endemicity of infectious disease has a major impact on aetiology of febrile thrombocytopenia.

In this study, more incidence is found in the age up to 50 yrs. (78%) than age above 50 yrs. (22%). The highest incidence was found in the age groups 11 - 20 yrs. and 31 - 40 yrs. (24%). Incidence of febrile thrombocytopenia was more common in male (66%) as compared to female (34%). The reason for this increased incidence in males may be due to the prolonged outdoor activities and thereby increased chance of exposure to mosquito bites. Bleeding manifestations were seen only in 28% cases, indicates in the majority of cases thrombocytopenia is asymptomatic.

Malaria is the most common (44%) aetiology of febrile thrombocytopenia, out of which falciparum 10 (20%), vivax 8 (16%) and both 4 (8%). Thrombocytopenia during malarial infection may appear even before fever, anaemia and splenomegaly become manifest. Immune-mediated lysis, sequestration in the spleen and a dyspoietic process in marrow with diminished platelet production have all been postulated. During early stages of malaria, platelet agglutination as a result of endothelial cell activation and release of activated von Willebrand factor occurs, which may cause thrombocytopenia.¹⁰

Viral infection 34% constitutes the second most common aetiology, of which 16% were of dengue fever and 18% were of viral infection other than dengue.

Viruses produce thrombocytopenia by various mechanisms like impaired platelet production as a result of direct viral invasion, toxic effect of viral proteins on thrombopoiesis, virus-induced hemophagocytosis and increased platelet destruction by binding of virus-induced autoantibodies or viral antigen-antibody complexes.¹¹ Thrombocytopenia in Dengue fever is caused by bone marrow suppression (i.e. decreased platelet synthesis and increased immune-mediated destruction of platelets).¹²

In this study bleeding manifestations are present in 44.4% cases of severe thrombocytopenia, 47% in moderate and 8.3% in mild thrombocytopenia cases. It reveals that there is no absolute relation between bleeding and platelet count. Gastrointestinal bleeding is the most common presentation in this study and petechial rash in severe thrombocytopenia; 50% of dengue cases, 30% of PF malaria cases, 25% of PV malaria cases and 33.3% of viral fevers had bleeding manifestations. DSS and pneumonia, they themselves were presented with bleeding manifestations.

Mortality was present in mild thrombocytopenia cases. Hence, thrombocytopenia has no correlation to mortality.

CONCLUSION

1. Febrile thrombocytopenia is more common in males.
2. 78% cases were seen in the age group below 50 years.

3. The most common aetiology is malaria followed by viral infection.
4. Though there is no absolute relation between platelet count and severity of bleeding, the risk of bleeding increases as the platelet levels fall below 20,000/ μ L.
5. In the majority of cases thrombocytopenia was asymptomatic, but in a significant number of cases bleeding manifestations are seen which require prompt management to prevent life-threatening complications.

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