

Clinical Study of Acute Febrile Illness with Thrombocytopenia in a Tertiary Care Centre

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ABSTRACT

BACKGROUND

In the recent period there is an upsurge in the incidence of fever with thrombocytopenia in the Mid Karnataka. This may be due to the several emerging and re-emerging infections which cause frequent epidemics in the region. Early diagnosis and meticulous management will prevent fatal outcome. Studies on fever with thrombocytopenia are very few in Karnataka.

METHODS

This was a descriptive study conducted at J.J.M. Medical College, Davangere, over a period of one year from December 2017 to November 2018. The study includes 251 cases attending outpatient- and inpatient-departments in the Department of Medicine. All patients with a platelet count of less than 150000 was included in this study and detailed clinical and laboratory evaluation was done and assessed for the aetiology and outcome.

RESULTS

Among the 251 cases, dengue fever accounted for 54.5% of cases and 26.2% were other viral fever cases where the exact causative organism was not identified. Leptospirosis, malaria were also important causes of fever with thrombocytopenia. Major incidence of haemorrhagic manifestation occurred in the age group of 20 to 30 years whose platelet count was in the range of 10000 to 40000/mm³.

CONCLUSIONS

In this study, more than 50% had dengue fever and in 26.2% cases the exact aetiology could not be determined. This finding highlights the fact that there may be many unidentified infections which cause fulminant thrombocytopenia and there is a need for wider screening of infection.

KEY WORDS

Bleeding Manifestation, Dengue Fever, Infection, Prognosis, Thrombocytopenia

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BACKGROUND

Fever has been recognized as a cardinal manifestation of disease since ancient times, as recorded by ancient scholars like Hippocrates.¹ Seen first as a disease but later recognized as an accompaniment to a variety of disease entities, fever is an easily noted and reliable marker of illness.² Fever is a pervasive and ubiquitous theme in human myth, art and science. Fever is such a common manifestation of illness that it is not surprising to find accurate descriptions of the febrile patients in early-recorded history.³ Most cases of prolonged fevers are instances of well-known diseases manifesting them atypically. The actual pattern of graphic recording of fever is variable that it is not helpful in pointing to specific diagnosis at all times an aggressive diagnostic effort is usually justified because curative or palliative measures can so often be brought into use once the diagnosis has been achieved. Fever is defined as an elevation of the body temperature above the normal circadian range as the result of a change in the thermoregulatory center located in the anterior hypothalamus. An AM temperature of $>37.2^{\circ}\text{C}$ (98.9°F) or a P. M. temperature of $>37.7^{\circ}\text{C}$ (99.9°F) would define fever.³

Thrombocytopenia may be defined as a subnormal number of platelets in the circulating blood. A normal human platelet count ranges from 1, 50, 000 to 4, 50, 000 platelets/ μL of blood. Often intravascular coagulation (DIC), paroxysmal nocturnal patients with thrombocytopenia are asymptomatic and are diagnosed by routine complete blood count. Occasionally, there may be bruising, purpura, petechiae, nose bleeding and gum bleeding. Rarely, platelet count may be as low as 5,000/ mm^3 predisposing the patients to life-threatening bleeding in the central nervous system (CNS) or from the gastrointestinal and genitourinary tracts. Thrombocytopenia occurs due to decreased platelet production, which occurs in conditions such as vitamin B12 and folate deficiency, leukemia, sepsis (bacterial or viral infection) and hereditary disease. Thrombocytopenia may also occur due to increased destruction such as idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome (HUS), disseminated haemoglobinuria (PNH), systemic lupus erythematosus (SLE), antiphospholipid syndrome, post-transfusion purpura and hypersplenism. Drugs, which can cause thrombocytopenia are quinine, valproic acid, methotrexate, carboplatin, interferon, isotretinoin and heparin.

Febrile thrombocytopenia is the thrombocytopenia associated with fever. 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. The study was intended to know the underlying aetiology of febrile thrombocytopenia in our community, the various presentations and relationship between platelet level and severity of disease and prognosis. In the recent period there is an upsurge in the number of patients with fever and thrombocytopenia.⁴ This may be due to several emerging and re-emerging infections in the recent period. Patient with severe thrombocytopenia and bleeding manifestations have high mortality and early detection of aetiological factor is

important in reducing the mortality. Platelets play a central role in normal haemostasis and also in thrombosis.⁴ Bleeding due to thrombocytopenia usually occurs in small vessels and this manifests as petechiae over the skin, haemorrhages from mucosa of gastrointestinal and genitourinary tract.^{5, 6} Intracranial haemorrhage is a critical event in thrombocytopenic patients.⁷ Several studies have shown that arboviral infections like dengue fever, chikungunya, Kyasanur forest diseases and scrub typhus and leptospirosis and malaria, military tuberculosis typhoid and Human immunodeficiency causes fever and thrombocytopenia.^{8, 9}

There is seasonal variation in the epidemic of fever. At times non-infective causes and drugs can also cause thrombocytopenia and fever. The mortality is very high when there is severe thrombocytopenia² and mortality increases due to haemorrhagic manifestations. So, it is imperative that there should be regional studies to assess the aetiology of fever with thrombocytopenia. Though there are frequent epidemics of several arboviral infections in our area, there are only few studies which focuses the thrombocytopenia in patients with fever. Therefore, a well-structured systematic approach that is conducted with an awareness of different causes of fever with thrombocytopenia streamlines the differential diagnosis and determines the aetiology. This study was conducted to full fill this objective.

METHODS

This was a descriptive study conducted at J.J.M. Medical College, Davangere which is a tertiary care centre situated in the mid part of Karnataka. All the patients admitted with fever and thrombocytopenia attending the outpatient department and medical wards were included for the study. The study was for a period of one year from December 2017 to November 2018. All the patients with a history of fever less than two weeks with a temperature more than 37.2°C ($>98.90^{\circ}\text{F}$) and those with a platelet count less than 150000 in the age group of more than 15 years to years 85 were included. All patients with inherited thrombocytopenia, and on antiplatelets, autoimmune disorders, HIV, chronic liver diseases and hematological malignancy were excluded.

Once the patient is admitted with fever and for those who had thrombocytopenia, a careful history, general physical examination, detailed examination of various systems will be done. Routine investigations including the specific and special investigations will be done as and when indicated. In whom a final definite diagnosis is reached and treated for the disease full assessment will be repeated at the time of discharge. Details of history, general physical examination and laboratory and technical investigation reports will be noted down from time to time. The clinical profile will be assessed with procured data. Sampling method is universal sampling. Investigations such as Complete blood count, Urine routine, Chest X- ray, Renal function test, Liver Function Tests, Blood culture, Malarial parasite smear, Widal test, IgM dengue, IgM leptospira, USG abdomen, viral markers if required. Peripheral smear study, Bone marrow study if required.

Informed Consent was obtained. The diagnostic work-up of patients with fever and thrombocytopenia included battery

of investigations including biochemical tests; haemogram; peripheral blood smear etc. Once the patients are admitted with fever and those who have thrombocytopenia confirmed by peripheral smear, a careful history was recorded, general physical examination and detailed examination of various systems was done. Routine investigations and specific investigations were done as and when indicated.

Procedure

Details of history, general physical examination and laboratory and technical investigation reports were noted down from time to time. Once the specific diagnosis was reached, patients were treated for it specifically and symptomatically (mechanical ventilations, haemodialysis etc.). For bleeding complications platelet transfusions was done if platelet count was <20,000/ μ L.

Causes of Fever with Thrombocytopenia

1. Viral Causes: CMV; dengue; Parvo-B19; HSV, HIV, Hantana etc.
2. Bacterial Causes: Gram +ve and -ve Septicaemia, Miliary Tuberculosis, Leptospirosis, Typhoid etc.
3. Protozoal Causes: Malaria.
4. Others: Leukemia, lymphoma, etc.

Statistical Method

Descriptive statistical method like mean, standard deviation (SD), frequencies, proportions, was used. The data was entered and analyzed using appropriate software SPS 16.

RESULTS

The present study includes 251 patients, who were admitted for fever with thrombocytopenia in J.J.M. Medical College, Davangere. It was observed that those in the age group of 20 to 30 are affected age group people. Leptospirosis affected more among in the above 50 years. The duration of fever in the present study ranged from 1-14 days with mean duration of 4.98 \pm 2.35 (SD) days. 90% of the total cases had duration of < 10 days and majority recovered from fever with a period of 5 days. Considering the etiology, dengue fever was found to be the commonest and most important cause for fever with thrombocytopenia contributing for more than 50% of cases. The other causes for fever with thrombocytopenia are Non-specific viral fever (26.2%), Malaria (8%), Leptospirosis (5.6%) in decreasing order (Table 1).

Diagnosis	Cases	%
dengue fever	137	54.5
Viral fever	66	26.2
Malaria	20	8.0
Leptospirosis	14	5.6
Viral hepatitis	8	3.2
Lower respiratory tract infection	4	1.6
Pyelonephritis	2	0.8

Table 1. Distribution According to Aetiology

Headache (52%) contributed to most common symptom next to fever in the present study. Other prominent symptoms in the descending order include joint pain (42%), myalgia (35%), abdominal pain (22%) and vomiting (17%). Fever was present in 100% of cases. Jaundice contributed to

major sign in the present study (11%). Hepatosplenomegaly contributed to 8% followed in present study. In the present study platelet count varied from 10000-150000/ mm^3 with mean platelet count of 68868 \pm 32268/ mm^3 (SD). Thrombocytopenia was found in 35% of cases and 5% of patients had platelet count <20000/ mm^3 and they are at a high risk of bleeding complications. Majority of patients had platelet count >50000/ mm^3 (Table 2).

Platelet Count/ mm^3	No	%
10001-20000	12	5
20001-30000	24	10
30001-40000	20	8
40001-50000	28	11
50001-100000	134	53
100000-150000	33	13

Table 2. Distribution According to Platelet Count

Platelet Count	dengue	Viral Fever	Malaria	Leptospirosis
<50000	63(46)	7(10.6)	3(15)	8(57.1)
50000- 100000	65(47.4)	49(74.2)	13(65)	3(21.4)
>100000	9(6.6)	10(15.2)	4(20)	3(21.4)

Table 3. Thrombocytopenia in Different Infections

Total platelet count varied according to the aetiology. In dengue fever, 46% of cases had severe thrombocytopenia (count <50000/ mm^3). Of 56 cases of viral fever, 10% had counts <50000/ mm^3 , 90% had platelet count of >50000/ mm^3 . In leptospirosis, 57% of patients had Thrombocytopenia which is even higher than the dengue and 14% of patients had platelet count <20000/ mm^3 . In Malaria, 3 patients (15%) had a platelet count <50000/ mm^3 but none less than 40000/ mm^3 (Table 3).

Bleeding manifestation was found in 43 patients, 8 (out of 9) patients had platelet count 10000-19999/ mm^3 , 3 (out of 6) patients had platelet count between 20000-29999/ mm^3 . 21 (out of 33) had between 30000-39999/ mm^3 , 7 (out of 34) had platelet > 50000/ mm^3 and 4 (out of 134) had platelet count >50000/ mm^3 . This suggests that bleeding episodes were more common in patients with low platelet count. Bleeding manifestations in the form of petechiae is a common manifestation of thrombocytopenia. Petechiae with and without gum bleeding/epistaxis/conjunctival haemorrhage occurred in 12% of patients in the present study. There were 43 patients with bleeding manifestations out of which both mucosal and superficial bleeding was equally manifested in patients with platelet count between 10000-29999/ mm^3 and superficial bleeding was more seen in the category of patients with platelet count >30000/ mm^3 .

DISCUSSION

Febrile thrombocytopenia is a common clinical condition and is caused by infectious and non-infectious aetiology. This study was conducted in J.J.M. Medical College, Davangere which is a tertiary care centre in Karnataka over a period of one year from December 2017 to November 2018. We studied 251 patients of which 127 were males and 124 were females. Though male to female ratio was almost equal, it was observed that males were more affected in the second and third decades which might be due to their increased travel. The age of patients varied from 15 to 85 yrs. , which includes

all sections of the society. There was maximum incidence of fever among the age group of 21-30 years which constituted 22.3% of the study population. Only few cases were reported in the older age group.

In our study the most common presenting symptom was fever. In spite of being a major concern among general public and medical fraternity most of the cases of fever with thrombocytopenia recovered within 5 days of onset of fever. A study was conducted by Nair PS et al.¹⁰ (2003) at St. Stephen's Hospital, New Delhi, for period of one and half years. A total of 109 cases (76 male, 33 female patients) were studied with the same criteria as in our study. In present study 127 were males and 124 were female. In the present study the maximum prevalence of fever with thrombocytopenia was in the age group of 21-30 years of about 22.3%. In Nair study¹⁰ septicaemia with 29 cases was the leading cause of fever associated with thrombocytopenia. Second common cause was enteric fever 16 followed by dengue 15, Megaloblastic anaemia 13, malaria 10, Haematological malignancy with 4 cases respectively. In Srinivas study¹¹ malaria with 41 cases was the leading cause of fever associated with thrombocytopenia. Second common cause was enteric fever followed by septicaemia, dengue, leptospirosis with 24, 19, 2 cases respectively.

Disease Category	Nair et al ¹⁰		Srinivas Study ¹¹		Present Study	
	No. of Cases	%	No. of Cases	%	No. of Cases	%
dengue fever	15	13.8	14	14	137	54.5
Enteric fever	16	14.7	24	24	0	0
Viral fever	0	0	0	0	66	26.2
Malaria	10	9.2	41	41	20	8.0
Haematological conditions	17	15.6	0	0	0	0
Septicaemia	29	26.6	19	19	0	0
HIV	0	0	0	0	0	0
Hep. B (Viral hepatitis)	0	0	0	0	8	3.2
Leptospira	0	0	2	2	14	5.6
Unknown	20	18.3	0	0	6	2.4

Table 4. Comparison with Other Studies

In the present study dengue with 137 cases was leading cause of fever associated with thrombocytopenia. Second common cause was viral fever 66 followed by Malaria 20, viral hepatitis 8, and leptospira 14 cases. This might be due to seasonal, regional variations and other multi-factorial aetiologies. Headache was the second most common symptom which was reported in 52% of patients. Other common symptoms were joint pain (42%), myalgia (35%), abdominal pain (22%) and vomiting (17%). If a patient present with these symptoms, we should actively search for diseases like dengue fever, Leptospirosis, Malaria etc. Most common clinical sign in the present study was jaundice and it was observed in 11% of the patients. The other common clinical findings were hepatomegaly (8%), splenomegaly (8%) followed by pallor and conjunctival haemorrhage. There were rash and petechial spots in many of our patients with dengue fever. Jaundice was found to be frequently associated with Leptospirosis and Viral hepatitis due to hepatic involvement. Splenomegaly and Hepatomegaly was more seen in Malaria patients.

This study has shown that commonest cause of fever with thrombocytopenia was dengue (54.5%). This may be due to the fact that most of the patients admitted during the period have dengue and frequent epidemics were reported from the area. During this study detailed evaluation and diagnostic work-up was done in all cases but interestingly in

26.2% a definite aetiology or infectious agent was not detected. As shown in studies from several part of world different arboviral infection can cause thrombocytopenia. But these non-specific causes most of them have symptomatology of viral fever like headache myalgia, fever.

Malaria is the third most common cause of fever with thrombocytopenia which constitutes around 8% of the patients and still continues to be a major health problem in the society. It was more commonly seen in the immigrant population. Early identification and prompt treatment should be administered before complications occur, especially in Leptospirosis and Malaria where specific drugs are available.¹²

In a similar study conducted by Nair et al, Septicaemia was the leading cause of fever with thrombocytopenia (26.61%) followed by Typhoid fever (14.68%), dengue (13.8%), Megaloblastic anaemia (11.9%), Malaria (9.2%), Haematological malignancies (3.7%). This might be due to the seasonal and regional variability where the study was conducted. In our study more than 54.6% cases had dengue but in the study by Nair et al¹³ showed only 13.8% had dengue fever. This may be due to the regional variation in the epidemics or due to seasonal variations. Similarly, 15.6% cases were non-infective causes in study by Nair et al whereas non-specific causes constitute 26.2% cases in our study.

Study conducted by Gandhi et al leading cause of fever with thrombocytopenia was Malaria (42%) followed by dengue (26%), and other viral fever (17%), septicaemia (4.5%), enteric fever (4.45%).¹³ Whereas in our study dengue fever is the common cause followed by other viral fever causes 26.2% which is higher in our study. In Raikar et al study dengue (52%), malaria (42%), enteric fever (3%), non-specific viral fever (4.5%) in our study both dengue and non-specific viral fever was high.¹⁴

A detailed study of distribution of thrombocytopenia was done in our study and it was found that the distribution of platelet varied from 10000 to 150000 in our cases. Interestingly 35% of cases in this study had thrombocytopenia <50000 whereas platelet count less than 20000 occurred in 4.7%. Whereas Nair et al¹³ 25.7% of patients had platelet count in the range of 20000-50000/mm³. In patients with leptospirosis out of 14 cases 14% had platelet count <20000/mm³. This clearly shows that severe thrombocytopenia also occurred in Leptospirosis and is an important differential diagnosis of fever with thrombocytopenia. This finding shows that either dengue or leptospirosis should be considered early if severe thrombocytopenia noticed in febrile patients.

In patients with thrombocytopenia, Bleeding manifestations like petechiae, conjunctival haemorrhage, gum bleeding and melaena were seen in 17% of patients. Petechia was the commonest bleeding manifestation observed in 31 patients, followed by spontaneous mucosal bleeding like gum bleeding, haematuria and melaena. In Nair et al study spontaneous mucosal bleeding was the commonest bleeding manifestation followed by petechiae/purpura.¹³ Malaria was the commonest cause accounting 32.63%, which was followed by septicaemia (31.57%), dengue (15.78%), acute leukemia (8.42%), viral infection (6.31%), enteric fever (3.6%), pulmonary tuberculosis (1.055%) and Kala-azar (0.52%). In a study by

Lohitashwa et al on 100 patients from March 2004 to September had similar observation (i. e. , malaria being the commonest cause).¹⁵ Another prospective study, which was conducted on 228 patients with fever and thrombocytopenia in medical unit of Hayat Abad Medical Complex during 2008-2010 was showing malaria as a commonest cause (53%) out of which 68% were having falciparum malaria.¹⁶

Malaria is commonly accompanied by mild-to- moderate thrombocytopenia in 40.53-85% (78.4% by Jadhav et al, 80.6% by Medical Unit 3, JPMC, Karachi, 85.5% by Shaikh et al).^{17, 18, 19} In an observational study conducted by Malik et al at Karachi on endemicity of malaria and haematological finding in Gadap region on 392 patients observed malarial prevalence in 11.72%, out of which thrombocytopenia was observed in 70% cases.²⁰ Thrombocytopenia in malaria is probably due to increased splenic sequestration, immune-mediated destruction, and a shortened platelet survival and consumption by DIC. Along with quantitative defects, qualitative defects have also been documented, which are platelet hyperactivity, due to aggregating agent 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. Another study had reported 60% sensitivity and 88% specificity of thrombocytopenia for malaria diagnosis in acute febrile patients.²¹

Thrombocytopenia is the very common finding in septicaemia and is an independent prognostic marker. In a study conducted by Lee et al on 53 patients with septicaemia thrombocytopenia was observed in 57% patients and DIC in 35% patients.²² The aetiology of thrombocytopenia in sepsis is multifactorial. It is commonly associated with DIC and is caused by splenic destruction of immune complex coated platelets, platelet adherence to damaged vascular surfaces and by direct platelet toxicity caused by microorganisms.

It is also probably related to impaired production of platelets from within the bone marrow, active phagocytosis of megakaryocytes and other hematopoietic cells by monocytes and macrophages hypothetically due to stimulation with high levels of macrophage colony-stimulating factor (M-CSF) in sepsis and platelet consumption due to ongoing generation of thrombin. Dengue is the most common arbovirus disease worldwide and occurs in tropical countries. Thrombocytopenia is an important finding and has got predictive as well recovery parameter of dengue fever/dengue haemorrhagic fever/dengue shock syndrome (DF/DHF/DSS). Thrombocytopenia in DF is caused by bone marrow suppression (i.e. , decreased platelet synthesis and increased immune-mediated destruction of platelets).²³

Commonest symptom after fever was vomiting in 18.94%, abdominal pain in 16.31%, loose motion in 4.73% cases, GI bleed in 5.26% cases and respiratory symptom like cough and dyspnoea in 7.89%. Abnormal renal function was detected in 32.63% and abnormal liver function test in 24.73%. So, GI symptoms were the most common symptoms associated with febrile thrombocytopenia.

CONCLUSIONS

Fever with thrombocytopenia is a common condition which requires inpatient care in most of the patients. Dengue fever was the most common cause of fever with thrombocytopenia in this region which affected more than half of the study population. In 26% of cases with fever and thrombocytopenia, we could not find a definite cause. It may be due to the limited screening facility available for other infections which lead to thrombocytopenia. Severe thrombocytopenia was noticed in 32% of patients and 3.5% had platelet count less than 20000/mm³ and the majority of severe thrombocytopenia was caused by dengue fever. In our study Headache was the second most common presenting symptom after fever, the other common symptoms being joint pain and myalgia. When a patient presents with these complaints possibility of fever with thrombocytopenia has to be considered. Bleeding manifestations were commonly associated with severe thrombocytopenia, especially when platelet count is less than 20000/mm³. This study showed that in the recent periods, dengue fever was the most common cause of thrombocytopenia in fever patients, and interestingly in more than 26.2% cases a definite cause of thrombocytopenia could not be ascertained. This shows that more commonly diagnosed conditions are dengue, leptospirosis, malaria, typhoid or scrub; still, there are several infectious agents which cause fever and thrombocytopenia which cannot be easily diagnosed with routine laboratory tests. So, it is imperative that there should be more screening, and diagnostic techniques for detecting other viral infections especially in cases with severe thrombocytopenia with haemorrhagic manifestations should be made available in all major hospitals.

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