Clinical profile of Thrombocytopenia in Acute Febrile Illnesses; a hospital-based study

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ABSTRACT

Background

Thrombocytopenia is a common haematological abnormality noted in clinical practice, however, it can be missed in cases where specific investigations are not asked for. Acute Febrile Illness with thrombocytopenia is a diagnostic and therapeutic challenge, as thrombocytopenia has an inverse relation to mortality and morbidity in various febrile illnesses. Vector-borne and zoonotic diseases (like malaria, dengue, scrub typhus, and leptospirosis), infections and sepsis are some of the common causes of fever with thrombocytopenia.

Objective

To identify the causes of fever with thrombocytopenia, assess the clinical complications associated with febrile thrombocytopenia, and overall study the clinical profile of thrombocytopenia in a tertiary care hospital

Method

Medical records of all adult patients, admitted to a tertiary level hospital, with fever and thrombocytopenia (platelet count < 1,00,000 /mm^3) were assessed (from October 2009 to March 2011). Detailed case history, general physical examination findings, routine and specific examinations were recorded according to a pre-decided format. Data were analysed using SPSS 16.0

Result

Acute febrile illness with thrombocytopenia was most commonly seen in Dengue patients. Headache and arthralgia were more commonly encountered in scrub typhus. Platelet transfusions were necessitated in a large number of patients, especially in scrub typhus. Malaria patients had the highest mortality rate.

Conclusion

Acute Febrile Illnesses (AFI) are of varied origins, and proper diagnosis is imperative. The degree of thrombocytopenia in infections has a prognostic value. It can also help in differential diagnosis and clear identification of aetiology of acute febrile illnesses. Timely identification and management of thrombocytopenia in acute febrile illness can positively impact the overall patient outcome.

KEY WORDS

Acute febrile illness, Bleeding tendencies, Fever, Thrombocytopenia, Vector-borne diseases

INTRODUCTION

Acute febrile illness (AFI) is characterised by a rapid onset fever, with associated symptoms such as a headache, chills, myalgia, and/or arthralgia.[1] In South-East Asia, diseases which are majorly responsible for AFI include malaria, dengue, typhoid/paratyphoid, chikungunya, leptospirosis and scrub typhus.[2-4] Differential diagnosis of the aetiologies of AFI can be difficult as clinical signs and symptoms of most of these infections are almost identical.[1,2] Additionally, pathogen-specific diagnostic tests may or may not be available in all clinical settings, thereby further delaying timely treatment.

Thrombocytopenia can be defined as a condition where the platelet count is low and can arise due to multiple causes (such as splenomegaly, infections, drugs, liver disease, bone marrow failures, tumours, haematological disorders, etc.).[7] These can be mainly attributed to: reduced platelet production, increased platelet consumption/ destruction, abnormal platelet distribution, and dilutional loss.[8] Thrombocytopenia with fever often signifies serious underlying aetiologies, which require specific management. Mild thrombocytopenia is reversible and easily managed, however moderate to severe conditions require timely diagnosis and prompt management. In the last decade, parts of Asia have been witnessing an epidemic of severe fever with thrombocytopenia, and it has a high case-fatality rate.[9]

It has been established that anaemia, leucocytosis, and/ or thrombocytopenia in AFI, in tropical and sub-tropical countries, may be associated with malaria.[6] Scrub typhus and leptospirosis remain largely under-diagnosed, particularly in developing countries.[10,11] We, thus, chose to investigate cases of thrombocytopenia in AFI, and focus on its clinical profile in four diseases (Dengue, Malaria, Scrub Typhus, and Leptospirosis).

METHODS

This was a cross-sectional, observational study, which was carried out in a tertiary level hospital, attached to a medical college in Karnataka, India. The time duration for data collection was 18 months (October 2009 to March 2011), and consecutive sampling was done to include all adult patients meeting the inclusion criteria. Any patient, over 18 years of age, who was admitted to the hospital with fever and a platelet count < 1,00,000/mm^3 was included in the study. Patients treated for fever in the out-patient department were excluded. The sample size is 471.

Once admitted, a detailed case history was recorded of the patient, followed by detailed physical and biochemical examination. General physical findings and vital parameters, laboratory investigations, routine and specific examinations were carried out periodically, as indicated, and the findings were duly noted. The test for leptospirosis and dengue and was done using ELISA, Rapid diagnostic test (RDT) was done for malaria, and scrub typhus was diagnosed based on the results of either Weil Felix test or an immunofluorescence assay. Method of data collection was secondary in nature (from case files and medical records), of patients admitted at the time of data collection.

Data were analysed using SPSS 16.0 statistical software, for reporting of descriptive statistics and Chi-Square test for comparisons. Using appropriate statistical tests, the p-value was computed, and $p < 0.05$ was considered to be statistically significant.

This study was the thesis project for MD (Internal Medicine) degree in 2012, at Kathmandu University. Approval of the thesis protocol was taken from faculty at Kathmandu University (Nepal) and Manipal University (India) before the commencement of the study. Data has been anonymised to protect the identities and integrity of patients.

RESULTS

The total sample for this was 471. Of these, 68% (count 320) were males. Almost half the cases were diagnosed in patients in the age group of 18 to 30 years, while the age of patients was above 60 years in only 11% of the cases.

The study found that 31% of the cases were those of unspecified fever with thrombocytopenia (including enteric fever, leukaemia and other haematological malignancy and all serology negative cases). One-fourth of the cases were caused due to dengue, while malaria caused thrombocytopenia with fever in 22% of the cases. Other causes of thrombocytopenia with acute febrile illness were Scrub Typhus and Leptospirosis. There were no cases of co-infection present.

Table 1. Chief complaints of patients

Diagnosis	Frequency (N=471)	Complaints			
		Count	Headache	Arthral-gia	Bleeding Tenden-cies
Unspecified fever with thrombocy-topenia	146(31)	n= 146	51(34.9)	22(15)	8(5.4)
Dengue	118(25.05)	n= 118	34(28.8)	27(23)	21(18)
Malaria	104(22.08)	n= 104	37(35.5)	5(5)	14(10)
Scrub Typhus	60(12.74)	n= 60	28(46.6)	13(22)	13(22)
Leptospi-rosis	43(9.13)	n= 43	13(30.2)	6(14)	11(16)
Total	471(100)	N= 471	163(34.6)	78(16.6)	67(14.2)

All the patients presented with fever and thrombocytopenia. Other chief complaints are elucidated in Table 1. Only 15% of the patients complained of bleeding tendencies, out of which 35% manifested as Petechiae. Other

manifestations of bleeding tendencies were Bleeding gums (27%), Haematuria (19.4%), Epistaxis (6%), Malena (3%), Menorrhagia (3%), and the combination of two or more of the aforementioned manifestations was found in about one-third of the patients.

Table 2. Severity of thrombocytopenia

Diagnosis	Frequency	Grade of thrombocytopenia: Platelet Count		
		Mild: 1,00,000 to 50,000/mm^3	Moderate: 50,000 to 20,000/mm^3	Severe: <20,000/mm^3
Un-specified fever with thrombo-cytopenia	n=146	70(49)	45(10)	31(21)
Dengue	n=118	57(48)	28(24)	33(28)
Malaria	n=104	75(72)	17(16)	12(12)
Scrub Typhus	n=60	49(82)	6(10)	5(8)
Leptospi-rosis	n=43	22(52)	11(25)	10(23)
Total	N= 471	278	115	78

Majority of the patients (60%) had platelet counts in the range of 50,000 to 1,00,000/mm^3. (Table 2). Patients who presented with epistaxis or bleeding gums had initial platelet counts between 20,000/mm^3 and 50,000/mm^3. All other bleeding manifestations were reported in patients with platelet counts below 20,000/mm^3. Correlation between initial platelet count and bleeding manifestations showed that genitourinary bleeding occurred at very low platelet counts (< 10,000/mm^3).

Table 3. Signs and Symptoms diagnosed after general physical examination

Diagnosis	Frequency	Signs and Symptoms			
		Pallor	Icterus	Lymph-adenop-athy	Organo-megaly
Un-specified fever with thrombo-cytopenia	n=146	15(10)	27(19)	8(5)	43(29.5)
Dengue	n=118	11(10)	26(22)	1(0.8)	49(41.5)
Malaria	n=104	15(15)	25(24)	0(0)	61(58.6)
Scrub Typhus	n=60	7(12)	21(35)	19(32)	28(46.6)
Leptospi-rosis	n=43	11(25)	27(63)	1(2)	29(67.4)
Total	N=471	59(12.5)	126(26.7)	29(6)	210(44.6)

The findings of general physical examination are elaborated upon in table 3. Either one of Hepatomegaly, Splenomegaly, or Hepatosplenomegaly was found in 210 patients; isolated splenomegaly was more common in malaria (found in 25% cases, as against 5% in other aetiologies). Ultrasound revealed organomegaly in 235 patients (50%).

Specific system examinations revealed an abnormal respiratory system in 15% of the patients, of which the abnormalities were significantly higher in cases of malaria (22%) and leptospirosis (21%), (p=0.01 in both instances). Anaemia was found in 37% cases of Leptospirosis, which was significantly higher than the findings of anaemia (13%) in patients with other aetiologies. Leucocytosis was found in approximately one-fourth of all patients.

Liver function tests (LFT) were deranged in over 70% cases of leptospirosis, dengue, and scrub typhus. In malaria cases and cases of unspecified fever, however, the presence of abnormal LFTs was significantly lower (40%, $p < 0.05$). Close to two-thirds of the patients of leptospirosis and scrub typhus presented with abnormal renal function (RFT); when compared to the abnormal RFT in 30% cases of malaria and dengue, the difference was statistically significant ($p < 0.001$).

Platelet transfusions were done when the platelet count was below 10,000. Platelet transfusions were done in 60% of the patients. The proportion of leptospirosis and dengue patients (70%, each) receiving blood transfusion was significantly higher ($p < 0.005$) than those of malaria, scrub typhus, and unspecified fever (55%, each). The number of platelet transfusions done in the patients is described in Table 4.

Table 4. Number of platelet transfusions done in the patients

Diagnosis	Number of patients who received platelet transfusion	Number of platelet transfusions		
		< 5	5 to 10	> 10
Unspecified fever with thrombocy-topenia	81	38(47)	25(30)	18(23)
Dengue	82	26(31)	30(38)	26(31)
Malaria	55	31(56)	19(34)	5(10)
Scrub Typhus	32	8(25)	16(50)	8(25)
Leptospirosis	30	8(27)	16 (53)	6(20)

Apart from the prescribed medication for each of their conditions, 95% patients were prescribed antibiotics. All cases of malaria, leptospirosis, and scrub typhus were started on antibiotic coverage. Only 8% dengue patients, and 8% patients with unspecified fever were not prescribed antibiotics.

The majority (83.8%) of the patients showed an improvement within one week of hospitalisation and treatment, and their platelet counts were normalised. Some of the patients developed serious complications such as ARDS, multiorgan dysfunction syndrome and haemorrhagic manifestations.

The mortality rate in this study was 14% (66 patients). The mortality was significantly higher in cases of malaria (24% of all patients passed away). Additionally, a significant

proportion of leptospirosis patients (21%) and scrub typhus (18%) did not survive their disease and treatment. In dengue, the mortality was 16%, and it was 1.5% in unspecified fever cases.

DISCUSSION

Acute febrile illness with thrombocytopenia was diagnosed in males and females with a ratio of 2.1:1. Most of the patients (44%) were in the age group of 18 to 30 years, and 28% were between 31 and 45 years old. In a study done in South India, the mean age of patients according to the diagnosis was scrub typhus-45.5 years, malaria-35.8 years, and dengue-28.6 years.[4]

In a study done in Thailand on acute febrile illnesses, the aetiologies remained unknown in majority (61.3%) cases, as opposed to 31% cases of unspecified fever found in our study.[12] The same study diagnosed dengue in 5.7% cases, scrub typhus in 7.5% cases, and leptospirosis in 1.1% cases (which were found to be 25.05%, 12.74%, and 9.13%, respectively, in our study).[12] Chrispal et al. conducted a similar study in South India, and were unable to elucidate a clear diagnosis in 8% cases and had an alternate diagnosis (unspecified fever) in 7.3% cases.[4] Patients with AFI were diagnosed with scrub typhus (47.5%), malaria (17.1%), enteric fever (8%), leptospirosis (3%), rickettsiosis (1.8%) and Hantavirus (0.3%).

Similar studies done in Pacific regions yielded slightly different results. For example, in Papua New Guinea, a study of AFI reported dengue in 14.9%, malaria in 1.5% cases, and chikungunya in 2.1% cases.[13] On the other hand, a study in Indonesia, found the aetiologies of AFI to be typhoid (18%), pneumonia (13%), leptospirosis (12%), urinary tract infections (9%), rickettsioses (8.4%), dengue (7.5%), and meningitis/encephalitis (6.6%).[14]

The occurrence of a headache in Scrub Typhus was statistically higher (p=0.028) when compared to other causes. Nearly one-fourth of the patients of dengue and scrub typhus reported with joint pain, and this was significantly higher (p=0.03) when compared with other aetiological factors.

Literature suggests that most patients are asymptomatic and thrombocytopenia is incidentally diagnosed, and only a small proportion present with bleeding tendencies and our study also found a similar result.[8] Approximately 20% cases of dengue, and scrub typhus presented with bleeding manifestations, however, this finding wasn't statistically significant. Bleeding tendencies were even lower in the other diagnoses.

Leucocytosis was found in 35% of the cases of Leptospirosis, and this was significantly higher than the other groups (30% in scrub typhus, 22% in malaria, and 17% in dengue). Chrispal et al. had similar findings, wherein leucocytosis was an invariable feature of leptospirosis and frequently reported in scrub typhus.[4] A study conducted in Central India found that leucocytosis was common in malaria, however, there was no clear association reported.[6]

Table 5. Clinical profile of acute febrile illness and thrombocytopenia in vector-borne and zoonotic diseases

Parameter	Dengue (%)	Malaria (%)	Scrub Typhus (%)	Lepto-spiro-sis (%)
Frequency as aetiological factor for acute febrile illness and thrombocytopenia	25	22	13	9
Chief complaints Headache Arthralgia	 28.8 23	 35.5 5	 46.6 22	 30.2 14
Proportion of patients with bleeding tendencies	18	10	22	11
Proportion of patients with lymphadenopathy	0.8	0	32	2
Most common organomegaly	Hepato-megaly (27 cases)	Spleno-megaly (26 cases)	Hepato-spleno-megaly (26 cases)	Hepa-tomeg-aly (51 cases)
Deranged LFT/ Hepato-biliary systemic involvement	In 69 cases	In 40 cases	In 68 cases	In 79 cases
Most common systemic involvement	Renal	Renal and respiratory	Renal and hematopoietic	Renal
Grade of Thrombocytopenia frequently encountered	Mild	Mild	Mild	Mild
Average number of blood transfusions needed for treatment	5 to 10	< 5	5 to 10	5 to 10
Mortality Rate	16	24	18	21

The presence of pallor in patients of Leptospirosis was significantly higher (p=0.015) than the other groups. When compared with other aetiological factors, Icterus was significantly more common in Leptospirosis (p=0.005) and Scrub Typhus (p=0.05). Cervical lymphadenopathy was found in one-third of the Scrub Typhus cases but was uncommon in others.

A similar study conducted in 2010, reported that renal failure was seen most commonly in malaria (38.2%) followed by scrub typhus (19.6%), dengue (17.9%) and leptospirosis (16.7%).[4] Our study did not measure overt renal failure, however, abnormal renal function tests were recorded most commonly in scrub typhus (68%), followed by leptospirosis (60%), malaria (36%) and dengue (32%).

Rash and overt bleeding manifestations, normal to low leukocyte counts, moderate to severe thrombocytopenia are associated with dengue.[4] Our findings corroborate with the same, with close to 30% dengue patients presenting with severe thrombocytopenia.

It is an established fact that moderate to severe thrombocytopenia, renal failure, splenomegaly and hyperbilirubinaemia with mildly elevated serum transaminases are associated with malaria.[4] Isolated splenomegaly was found in one-fourth of all malaria cases in our study, 40% had deranged liver function tests, and 36% cases had abnormal renal function tests; however, malaria cases in our study were more commonly associated with mild thrombocytopenia (72%).

All patients were treated with antibiotics, and in retrospect, this may have been unnecessary. A study was done by Lathia et al. in 2004, it recommended that thrombocytopenia in AFI could prompt clinicians to suspect malaria in patients.[6] It is essential to screen all cases of acute febrile illness with thrombocytopenia for vector-borne and zoonotic diseases, identify the exact aetiology and initiate appropriate treatment at the earliest.

The mortality was 1.1% in the study conducted by Leelarasamee et al. and the deaths were caused mainly in the cases of fever of unidentified origin, due to nosocomial infections, respiratory collapse, sepsis and septicaemia.[12] In our study, malaria and associated complications were the leading causes of death.

This study encountered low platelet counts in vector-borne and zoonotic diseases, and the clinical profiles of these diseases are summarised in Table 5.

One of the major limitations of the study was that complete enumeration was not possible, since it was a time bound study carried out in a tertiary care hospital. Additionally, by excluding patients treated in the outpatient department and emergency triage, many cases of acute febrile illness with thrombocytopenia may have been missed.

CONCLUSION

Recording of a detailed history, and investigating platelet counts at the time of admission is, thus, very essential; these factors are known to have some correlation with severity of disease.[8] Delayed or incorrect diagnosis of AFI leads to many patients being injudiciously treated with antibiotics, and also many preventable deaths.[1] We conclude that presence of thrombocytopenia can be used as a prognostic indicator, and should promote an active search for vector-borne and zoonotic diseases, particularly dengue, malaria, scrub typhus, and leptospirosis.

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