Journal Of Medical Science And Clinical Research

IGM Publication   An Official Publication Of IGM Publication

Clinical Profile of Mortality due to fever with Thrombocytopenia during an Epidemic

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Abstract
Introduction: *Many of the acute infective diseases which present as febrile thrombocytopenia during an epidemic have overlapping clinical profile and many of them may not have a definite diagnosis even at the time of patients' mortality. However it is very important for the treating physician to have some clues from the patients' clinical details to help in initial management of each patient. This can be achieved only by studying the profile of patients who died in hospital due to an acute infective episode. Hence this study was carried out to demonstrate the clinical profile of such patients and to correlate with their final diagnosis.*
Objective: *To study the clinical profile of patients who presented with febrile thrombocytopenia and had a fatal end during hospital stay.*
Materials and Methods: *All patients who presented with fever and thrombocytopenia and had mortality during hospital stay during the study period of five months starting with monsoon were selected for the study. Their clinical profile was analyzed and the results are presented as descriptive data.*
Results: *Among the 45 patients who were screened for the study, 26 were included and studied. Symptoms present in more than 50% of the patients were body pain, breathlessness and bleeding episodes. The only clinical sign found to be altered significantly in majority was tachypnea and abnormal investigations were altered liver and renal functions. About half of patients belonged to acute undifferentiated fever, 38% were dengue infection and 12% were leptospirosis.*
Conclusions: *Even during an epidemic, the causes of febrile thrombocytopenia are varied and each patient requires individualized treatment plan. There is a need to formulate mortality indicators in patients with febrile thrombocytopenia.*
Keywords: *Febrile thrombocytopenia, mortality indicators, epidemic.*

Introduction

Fever and thrombocytopenia is a common presentation for many diseases prevalent in India. Common infective causes of febrile thrombocytopenia that present as epidemic are malaria, leptospirosis, rickettsial infections and dengue fever in southern states of India. Other conditions include primary hematological

disorders, infections like HIV, visceral leishmaniasis and systemic diseases like TTP, HUS and DIC. Infections like Dengue fever, Leptospirosis and certain other viral fevers have seasonal increase in incidence during monsoon.

The clinical symptoms and signs of many of these infections overlap to a great extent.

Dengue infection is diagnosed based on Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever issued by World Health Organization [1].The common symptoms described include fever, body pain, retro-orbital pain, rash, headache, bleeding episodes and abdominal pain.

Leptospiral infection also present with fever, myalgia, headache, bleeding manifestations and multi organ involvement including renal, pulmonary and hepatic dysfunction. Leptospirosis is diagnosed according to National Guidelines proposed by Program for Prevention and Control of Leptospirosis. [2]

Rickettsial infection is another disease that has clinical presentation very similar to Leptospiral infection and to a great extent, Dengue fever. Fever, myalgia, headache, nausea and respiratory involvement in the form of breathlessness and cough are the usual presenting features of Rickettsial diseases. The diagnosis is based on DHR-ICMR Guidelines for diagnosis and management of Rickettsial diseases in India. [3]

Other differential diagnosis like malaria has definite diagnostic techniques available, whereas certain diseases like acute undifferentiated viral illnesses may not have definitive diagnostic measures available to guide in initiation of treatment. However the clinical features of most of these diseases have great overlap as obvious from above mentioned diagnostic criteria.

A patient presenting with febrile thrombocytopenia and showing rapid clinical deterioration poses big challenge to treating physician regarding the mode of initiation of treatment as most of serological markers may not be available for decision making. In this study, patients who presented with febrile thrombocytopenia and had a fatal end during hospital stay were studied with specific emphasis on presenting symptoms, vital statistics and basic investigations that is freely available in a secondary and tertiary care center in Kerala. This would help the treating physician to have a syndromic approach to patients with febrile thrombocytopenia for initiating treatment till definitive diagnosis is made. This study also aimed to identify the prognostic markers for mortality in patients presenting with febrile thrombocytopenia during an epidemic.

Materials and Methods

All patients who presented with fever and thrombocytopenia and had mortality during hospital stay during the study period were selected for the study. Study period was five months starting with monsoon. Available investigations and clinical picture was correlated to the final diagnosis and cause of death documented in case records. After analyzing the final diagnosis, only patients with acute infective cause for death were enrolled in the study group. Among the patients in the study group, detailed history, physical examination details including vital statistics and basic investigations available in secondary and tertiary hospital in Kerala were recorded. All data were analyzed and presented as a descriptive data. Institutional ethical clearance was obtained at the beginning of the study.
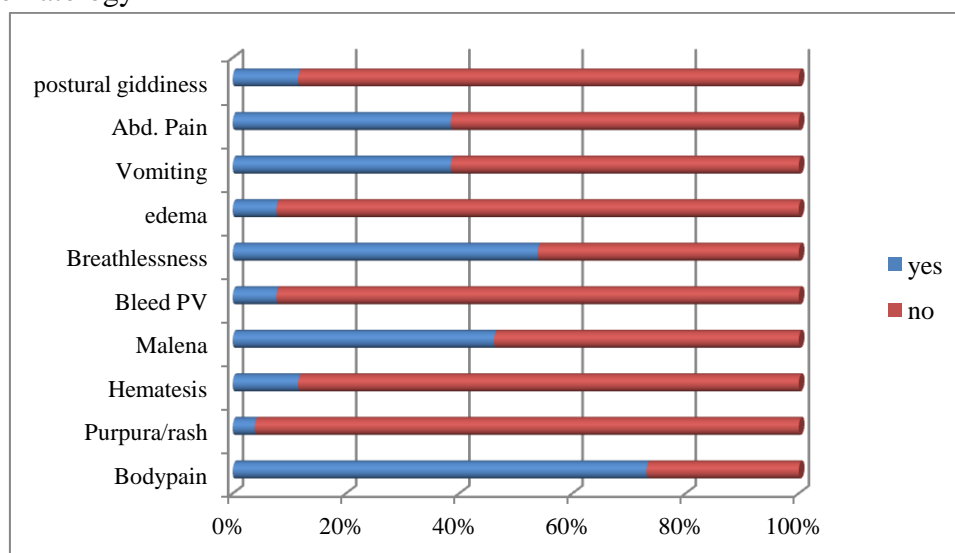
Results

There were 45 patients who presented to hospital during study period with fever and thrombocytopenia and died in the hospital. After analyzing the cause of death of each patient, 19 patients were excluded from the study because their cause of death was not due to an acute infective disease. Among the 26 patients included in the study, 10 patients had probable Dengue infection, 3 patients had probable Leptospirosis and 13 patients did not have positive result for any infections including Leptospirosis, Dengue, Rickettsial or Malarial infection.

The mean age of the study population was 46.08 years and ranged between 15 years and 75 years. There were 12 women and 14 men in the study group. The average duration of hospital stay was 3.72 days and ranged between 1 day and 19 days. Symptomatology of patients revealed that 73% of patients in the study group had body pain, 54% had breathlessness and nearly 50% of patients had any form of bleeding episode. All other symptoms like rash (04%), vomiting, abdominal pain (38% each), edema (08%) and postural giddiness (12%) were present in less than 50% of patients in the study group.

Table1. Symptomatology

Symptoms	Yes	No	Proportion of Yes in %
Body pain	19	7	73
Purpura/rash	1	25	04
Hematemesis	3	23	12
Malena	12	14	46
Bleed PV	2	24	08
Breathlessness	14	12	54
Edema	2	24	08
Vomiting	10	16	38
AbdominalPain	10	16	38
postural giddiness	3	23	12

Figure1. Symptomatology

Clinical examination of patients showed an abnormal mean respiratory rate of 28 per minute. The mean value of other vital parameters including pulse (91.9 per minute), systolic blood pressure (108.8 mm of Hg), diastolic blood pressure (74.5 mm of Hg) and pulse pressure (35.83) were in the normal range. Only 3 patients among 26 in the study group (12%) had palpable hepatomegaly.

Table 2. Vital signs

Vitals	min	max	mean
Systolic BP	70	160	108.8
Diastolic BP	50	90	74.5
pulse pressure	20	70	35.83
Pulse	68	140	91.9
respiratory rate	14	48	28

Routine blood investigations among the patients showed a mean platelet count of 35000 per mm^3,
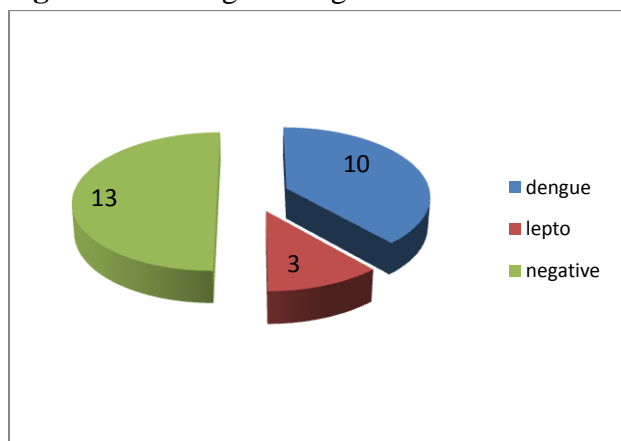
Bilirubin of 4.66 mg/dl, serum albumin of 3.14 mg/dl, SGOT of 474.8 U/L, SGPT of 284.7 U/L, blood urea of 68.08 mg/dl and serum creatinine of 1.76 mg/dl. However mean Hemoglobin, Leucocyte count and RBS were within normal limits.

Table 3 Investigations

Investigations	min	max	mean
Hb in g/dl	8	16	12.38
TC per mm^3	1400	26000	8687.5
PLCper mm^3	4000	109000	35000
SGOT in U/L	43	5460	474.8
SGPT in U/L	22	2920	284.7
TOT PROTEIN in g/dL	4.9	7.2	6.06
ALB in mg/dL	2.4	4.2	3.14
BILIRUBIN in mg/dL	0.4	18.2	4.66
UREA in mg/dL	10	210	68.08
CREAT in mg/dL	0.7	5.76	1.76
RBS in mg/dL	50	412	138.8

As mentioned in the brief description of the study population at the beginning of the results, serological studies showed positivity for dengue infection in 10 patients (38%) and leptospiral infection in 3 patients (12%). Remaining 13 patients (50%) did not have seropositivity towards any acute infections including dengue, leptospirosis, malaria or rickettsia.

Figure 2 . Etiological diagnosis

Discussion

Many of the acute infective diseases which present as febrile thrombocytopenia during an epidemic have overlapping clinical profile and many of them may not have a definite diagnosis even at the time of patients' mortality. However it is very important for the treating physician to have some clues from the patients' clinical details to help in initial management of each patient. This can be achieved only by studying the profile of patients who died in hospital due to an acute infective episode. Hence this study was carried out to demonstrate the clinical profile of such patients and to correlate with their final diagnosis.

The total number of death probably due to an acute infective episode who presented with febrile thrombocytopenia during study period of 5 months was 26 out of 45 patients. The remaining 19 patients were excluded from the study as their diagnosis was either primary hematological disease or a sub-acute to chronic condition which does not have an epidemic pattern of presentation. The mean age of the study population was 46.08 years and ranged between 15 years and 75 years.

There were 12 women and 14 men in the study group. These results were in consistency with the study conducted by Naveen Kulkarni et al[4] where the age group ranged between 13 and 79. Also the males were more affected with male to female ratio of 2.03:1. In a similar study conducted by Praveen Kumar et al[5] showed age distribution between 18 and 88 and male predominance in the ratio of 1.5:1. Another study done by M.P Gondhali et al[6] showed male to female ratio of 1.3:1. The average duration of hospital stay was 3.72 days and ranged between 1 day and 19 days. In Naveen Kulkarni's[4] study, the range of hospitalization was 3 to 21 days. The mean duration of hospital stay in study by Sing-Sin Sam et al[7] was 4.7 days.

Among the 26 study patients, the presenting symptoms in majority of patients were body pain (73%), breathlessness (54%) and nearly 50% of patients had bleeding episode in addition to fever and thrombocytopenia, which were in the inclusion criteria for selection into study. In study by Sing-Sin Sam et al[7], 89% of patients had body pain, 44% had breathlessness and 89% had bleeding episodes. Another study done by M.P Gondhali et al[6] demonstrated 92% patients had body pain. However in study conducted by Praveen Kumar et al[5], only 17% patients had respiratory symptoms and 6% had bleeding episodes. This contradiction may be explained by the fact that majority of patients in that study had septicemia and malaria as final diagnosis. The most notable factor is the absence of majority of symptoms included in diagnostic criteria for Dengue infection and Leptospirosis in this study population. This may indicate that though the known symptom complex may help in diagnosis, it may not predict mortality in this group and we need separate mortality indicators for triaging these patients and for early intensive interventions.

The mean value of pulse (91.9 per minute), systolic blood pressure (108.8 mm of Hg), diastolic blood pressure (74.5 mm of Hg) and pulse pressure (35.83) were in the normal range.

In study conducted by Praveen Kumar et al[5] showed presence of tachycardia and hypotension only in 44% and 38% of patients respectively and majority of patients had these parameters in normal range at admission. This again shows the progression of disease in hospital rather than presenting parameters are better predictors of mortality. The mean respiratory rate in this study group was 28 per minute. Many studies have not looked into this aspect and the respiratory rate at admission may be an important indicator for mortality even before significant tachycardia and hypotension has developed. Only 3 patients among 26 in the study group (12%) had palpable hepatomegaly. In study done by Sing-Sin Sam et al[7] showed hepatomegaly in 33% of patients.

The platelet count was 35000 per mm^3, Bilirubin of 4.66 mg/dl, serum albumin of 3.14 mg/dl, SGOT of 474.8 U/L and SGPT of 284.7 U/L. The presence of liver function abnormalities in different studies vary widely depending on the cause of death in each study. In study done by Naveen Kulkarni et al[4]where predominant infection was dengue, LFT abnormalities are as low as 6.5%. In study by Praveen Kumar et al[5]the higher proportion of LFT abnormality (39%) may be explained by Leptospirosis as one of the main cause of death. The mean blood urea was 68.08 mg/dl and serum creatinine was 1.76 mg/dl. The proportion of patients with abnormal renal function was 46%. In study conducted by Naveen Kulkarni et al[4] renal involvement was seen in only 3.5%, while study done by Praveen Kumar et al[5] showed renal involvement in 77.7% of study population. Renal involvement was again influenced by the final diagnosis of patients in each study population. Mean Hemoglobin, Leucocyte count and RBS were within normal limits. Study conducted by Praveen Kumar et al[5], which had predominantly patients with sepsis, had 94% of patients with leukocytosis while study done by M.P Gondhali et al[6], which had predominantly dengue infection as the infective cause, had 45% leukopenia.

Serological studies among patients in the study group showed serological positivity towards dengue infection in 10 patients (38%) and towards leptospiral infection in 3 patients (12%) and remaining 13 patients (50%) were sero-negative. Study conducted by Naveen Kulkarni et al[4] demonstrated 62.5% of patients to be in the undifferentiated category. Many other studies have included presumptive diagnosis rather than confirmatory diagnosis for statistical analysis.

Conclusion

1) Even during an epidemic, the causes of febrile thrombocytopenia are varied and each patient requires individualized treatment plan
2) Significant number of patients with febrile thrombocytopenia does not have confirmed serologically proven disease even at the time of mortality.About half of patients belonged to acute undifferentiated fever, 38% were dengue infection and 12% were leptospirosis.
3) Symptoms present in more than 50% of the patients were body pain, breathlessness and bleeding episodes. The only clinical sign found to be altered significantly in majority was tachypnea and abnormal investigations were altered liver and renal functions.
4) The diagnostic criteria for the diseases and its mortality indicators are not aligned to each other. Hence there is a need to formulate mortality indicators in order to help in triaging the patients for early intensive monitoring and interventions.
5) A syndromic approach to febrile thrombocytopenia may be more appropriate for initiating treatment during an epidemic.

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