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Etiological Factors Associated in Fever with Thrombocytopenia: A Clinical Study

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Abstract
Objective: *This study was conducted to investigate factors associated in fever with thrombocytopenia*
Patients and Methods: *The present observational study was done on 200 patients attending Medicine department, Medical College, Kozhikode for a period of one year. A proforma was set for the conduction of study with special emphasis on clinical history, physical findings, haemogram, biochemical estimation and serological test.*
Results: *Fever with thrombocytopenia was most common in patients between 40 and 60 years of age. Leptospirosis was the most common cause of fever with thrombocytopenia followed by viral fever (excluding Dengue and viral hepatitis), scrub typhus and vivax malaria in that order. Bleeding manifestations were commonly seen in leptospirosis and to a lesser extent in scrub typhus. There was a decline in platelet count which was proportinate to the rise in total and neutrophil count, ESR and serum creatinine. Further, in this study, thrombocytopenia also have co-assocition with hypoalbuminemia in producing the complications observed such as bleeding manifestations, carditis, pancreatitis and ARDS.*
Conclusion: *Leptospirosis is most commonest cause of fever associated with thrombocytopenia along with the bleeding with the bleeding disorder and other serious complaications.*
Keywords: *Fever, thrombocytopenia, leptospirosis, bleeding disorder, hypoalbumenia.*

Introduction

Fever is a clinical scenario in which there is elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in hypothalamic set point. An A.M. temperature of > 37.2 ℃ (>98.9°F) or a P.M. temperature of >37.7 ℃ (>99.9°F) would define fever.[1] Thrombocytopenia is defined as a reduction in the peripheral blood platelet count below the lower normal limit of 150000 /mm3.[2] Despite the number and diversity of disorders that may be associated etiologically, thrombocytopenia results from only four processes: Artifactual thrombocytopenia, deficient platelet production, accelerated platelet destruction and abnormal distribution or pooling of the platelets within the

body.[3] It is the most common cause of abnormal bleeding. Thrombocytopenia develops when there is profound disequilibrium in the balance between platelet production, distribution and destruction. More than one component may be affected in some disorder.[4] With normally functioning platelets, the following is expected, platelet count ≥100000 per microliter: patients have no abnormal bleeding even with major surgery. Platelet count between 50000 to 100000 per microliter: patients may bleed longer than normal with severe trauma. Platelet count of 20000 to 50000 per microliter: bleeding occurs with minor trauma, but spontaneous bleeding is unusual. Platelet count <20000 per microliter: patient may have spontaneous bleeding. Platelet count <10000 per microliter: patients are at high risk for severe bleeding.[5]

In this scenario, the present study aims to evaluate clinical and etiological profile of febrile thrombocytopenia and to determine the necessity of platelet transfusions for the management of thrombocytopenia

Patients and Methods
Study Design
The present observational study was done on 200 patients attending Medicine department, Medical College, Kozhikode for a period of one year.

Inclusion Criteria
Patient above the age of 13 admitted with fever and thrombocytopenia was included in the study. Fever was confirmed by thermometer measurement and thrombocytopenia by reliable laboratory investigation.

Exclusion Criteria
Patients presented with fever or thrombocytopenia alone was excluded from the study. Patients who were unwilling or non co-operative were excluded. Patients who could not be observed for the expected period of study or not having the relevant investigations done in time were excluded. Known cases of Malignancies, ITP, DIC etc.

A proforma was set for the conduction of study with special emphasis on clinical history, physical findings, haemogram, RFT, LFT, SE, Serum Amylase and Lipase, specific serological studies such as Widal test, Weil-Felix, IgM ELISA for Leptospira, IgM Chikungunya, IgM ELISA for dengue, HBsAg, Anti HAV, HIV 1&2, Anti HCV, Urine culture and sensitivity, Blood culture and sensitivity, Peripheral smear for malarial parasite, imaging studies, ECG and peripheral smear.

The cases were diagnosed by detailed history, clinical examinations and investigations. Given appropriate treatment. They were followed by monitoring the outcome with respect to morbidity and mortality and its relation to clinical and investigational datas.

The data were analyzed using SPSS computer package and the conclusions arrived. Statistical significance of different variables was calculated on the basis of relevant tests.

Results
The study encompasses 200 study subjects and high numbers of patients are in the age group of 50-59 years, followed by 30-39 years and minimum of group patients are in 70-79 years group.

The clinical features of the subjects enrolled in the study were as follows, the fever and headache were common in all the patients. Myalgia was present in 121 patients (60.5 %) and chills and rigor in 120 patients (60%). Jaundice was present in 68 patients (34 %) and the bleeding was visualized in 14 patients (7 %) respectively.

Based on the differential diagnosis the most common disease in our study group was Leptospirosis which affected 57 patients (28.5 %) followed by viral fever (excluding Dengue and viral hepatitis A which affects 52 patients (26%).

Regarding the age wise diagnosis, the most common age group affected with Leptospirosis was 40 years (30 patients) followed <20 years age group (14 patients). In the case of scrub typhus >60 age group was more affected.

Meanwhile in UTI and sepsis extremes of ages involved.

Compared to females males were more affected in leptospirosis, dengue, viral Hepatits A, plasmodium vivax malaria and enteric fever. Females dominantly affected in viral fever, scrub typhus and UTI sepsis. Males were found solely affected in falciparum malaria.

Examination of fever duration reveals that, Viral fever had lasted only for few days, whilst fever in the case of enteric disease, scrub typhus, leptospirosis and dengue have duration more than 7 days.

Regarding hospital stay duration, short period needed for treatment of dengue, viral fever, malaria, enteric fever and viral Hepatitis A. Meanwhile in the case of Leptospirosis and scrub typhus required relatively longer duration of hospital stay for the relief.

The anemic conditions were more prevalent in leptospirosis and *Malaria vivax* affected patients with the corresponding lower Hb values.

The urine protein concentration and creatinine level were predominantly elevated in leptospirosis and UTI sepsis respectively.

In the present study, the fever duration was more with Grade 2 and 4 platelet counts. When platelet count grade compared with hospital stay duration, it is found that as the platelet count gets decreased, hospital stay duration increased. Grade 4 counts were more in leptospirosis followed by viral fever, malaria vivax, scrub typhus, enteric fever, dengue in that order (Table 1).

Further, in our study by correlating the platelet with various biochemical parameters the following outcome was seen. ESR, TC, Neutrophil were increased with the lowering of platelet count.

The alkaline phosphatase (ALP) level was increased in viral hepatitis as that of the other conditions and the level of ALP was increased with the decreased platelet count level. The elevated level of SGOT and SGPT was observed in leptospirosis patient and there was no definite relations obtained when cross tabulated with the platelet count. Further, level of bilirubin and albumin was increased in leptospirosis conditions. Regarding complications, acute renal failure, Jaundice, ARDS, carditis, LRTI, Pancreatitis was more prevalent in leptospirosis cases.

Regarding transfusion, leptospirosis cases received more transfusions PRBC (7cases), heamodialysis (8cases) and the ICU admission was more in leptospirosis patients a total of 120 days in 19 cases.

Table 1: Hospital stay duration based on the platelet count in the study

Hospital Stay (in Days)	Grades of Platelet Count			
	1	2	3	4
1-3	8	21	5	13
4-6	16	22	32	29
>7	11	17	9	17

Discussion

The results of the study indicate that leptospirosis is more prevalent as that of the other conditions of fever with thrombocytopenia. Based on the above finding the following treatment approach is carried out, in leptospirosis, Inj. CP or Cap. doxycycline or combination of both used and is very effective.[6] Scrub typhus well responded to Cap. Doxycycline or Inj. CP and ciprofloxacin in combination.UTI with sepsis treated with ciprofloxacin or Inj. Amikacin or combination of both. Dengue fever was managed with Normal saline +symptomatic treatment. Viral hepatits A treated with IV fluids+ symptomatic. Viral fever treated symptomatically. Malaria treated with chloroquine, primaquine, and or doxycycline, and or artesunate.[7]

Out of 200 cases studied, 7 patients died. Leptospirosis is the main mortality producing disease found in our study. 5 patients died due to leptospirosis. 2 patients died due to UTI with sepsis. More incidence of leptospirosis are seen following monsoon season. Rain water contaminated with rat's urine in the fields act as the main source and manual labours are more prone to get the infection. Scrub typhus is tick born, and those who migrate to forest area or

exposed to bushy area are more affected. Complications produced by typhus cause morbidity and even mortality. Malaria are seen mostly in those people with a travel history to endemic area. So most are imported cases. Employees from other states are also admitted for the same. In few of those without a travel history (in our study 2 cases) a nearby imported source could be traced in the form of employees from other states of endemicity. Dengue in our area is not found in the severe form of DHF. [8,9]

Complications produced in this group of diseases are bleeding tendencies, Acute renel failure, jaundice, ARDS, carditis, LRTI and pancreatitis. Bleeding tendencies are generally anticipated when the platelet count is below 10,000. In this stud ,those with a count of 4000 had died due to complications and at the same time another one with the same count of 4000 had survived even without any trivial sequelae [10].

Bleeding manifestation also have occurred even at higher levels of platelet count -96000. A lower platelet count in leptospirosis is more threatening than that in a simple viral infection. Even within leptospirosis, not a threshold value of platelet count could be ascertained for the beginning of bleeding manifestations. So there should be some other factors also involving [11].

It is clearly noted that the hypoalbuminemia in association with thrombocytopenia can explain much more. When cut off value of albumin taken as 3.6 gm/dL, all the bleeding cases, including microscopic heamturia were occurred below this level (p value =.000). When cut off value of albumin fixed at 3.5 gm/dL, all bleeding manifestations excluding microscopic heamturia were occurred below this level. When cut off value of albumin taken as 3.6 gm/dL, all ARDS occurred below this level (p value =.007) and 16 out of 17 carditis occurred below this level (p value =.110) .When cut off value of albumin taken as 3.2 gm/ dL, all pancreatitis (10) occurred below this level (p value =.001).All these indicate the importance of hypoalbuminemia along with

thrombocytopenia in producing the complications in this category of diseases [12].

Conclusion

Leptospirosis was the most common cause of fever with thrombocytopenia followed by viral fever (excluding Dengue and viral hepatitis), scrub typhus and vivax malaria in that order. Thrombocytopenia also has co-association with hypoalbuminemia in producing the complications observed such as bleeding manifestations, carditis, pancreatitis and ARDS.

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