<u>Original research article</u>

Study of Thrombocytopenia in Patients with Acute Febrile Illnesses

Dr. Ashok Kumar[1], Dr. Rajiv Kumar[2]

[1] Associate Prof. Department of Medicine PMCH Patna

[2] Senior Resident, Department of Medicine PMCH Patna

Corresponding Author: Dr. Ashok Kumar

Abstract

Background: Thrombocytopenia is one of the most important haematological manifestation of many infections which may present as acute febrile illness. As per the WHO (World Health Organisation) case definition criteria, a case of acute febrile illness(AFI)[1] is defined as any individual with fever for at least 2days; or temperature on admission of 38.5C or greater; with no identified cause of fever, such as diarrhea or pneumonia; or suspected of having typhoid fever or brucellosis, as defined by WHO.

Methodology: This study is a prospective cohort study over a period of Two years. Department of General medicine, at Patna medical college and Hospital, Patna. 200 Patients admitted to the hospital with documented fever of >38.5C[5] and platelet count <1,50,000/µL were selected using purposive sampling techniques. They are followed from admission till recovery, discharge or death whichever is earlier.

Conclusion: Higher frequencies of mild to severe thrombocytopenia were observed in different etiologies in our study. Out of which malaria and dengue were the most common cause of thrombocytopenia among the acute febrile illness cases during presentation followed by other diseases. Hence the presence of thrombocytopenia in a febrile patient heightens the suspicion of these two diseases.

Keywords: Thrombocytopenia, Pneumonia, Typhoid fever, Platelet count.

Introduction

Thrombocytopenia is one of the most important haematological manifestation of many infections which may present as acute febrile illness. As per the WHO (World Health Organisation) case definition criteria, a case of acute febrile illness(AFI)[1] is defined as any individual with fever for atleast 2days; or temperature on admission of 38.5C or greater; with no identified cause of fever, such as diarrhea or pneumonia;or suspected of having typhoid fever or brucellosis, as defined by WHO. The normal range of platelet count is 1,50,000-4,00,000/µL. Thrombocytopenia is defined as a platelet count below the lower normal limit of <1,50,000/µL[2].This is due to decreased production, increased destruction (immunogenic and non-immunogenic causes),increased sequestration by thespleen. Infections of varying types (viral, parasitic, bacterial) like dengue, malaria, leptospirosis, typhoid, HIV, miliary tuberculosis and others have been associated with thrombocytopenia[3]. The risk of complications like bleeding is inversely proportional to the platelet counts. Identifying clinical features that differentiate any febrile illness with or without thrombocytopenia can help a

physician to decide whether to intervene with the case further. Severe thrombocytopenia can itself cause complications such as bleeding manifestations presenting as gastrointestinal or intracranial bleed[4] which if not properly intervened can cause death of the patients. This study was done to find out the causes for the thrombocytopenia on a background of acute febrile illnesses and to correlate the clinical features in them. Meanwhile, an effort is also made to find out the most common cause of thrombocytopenia among these patients.

Objectives
To find out the common cause of thrombocytopenia among patients with acutefebrile illnesses. To make an effort to correlate the clinical features of thrombocytopenia inthese patients.

Review of Literature
Sir William Osler stated 'humanity has three great enemies: fever, famine and war'. Of these by far the greatest, by far the most terrible is fever. Carl Reinhold august Wunderlich regarded as father of clinical thermometry described the normal diurnal variation of the body temperature and gave the first quantitative definition of fever. He also wrote that 'fever can give more certainly than anything else information as to the grade of the disease'. Because of his work, fever, which was previously been viewed as a disease, came to be recognized more appropriately as a clinical sign. The mercury thermometer had been perfected in Holland in the early 18 th century by Gabriel Daniel Fahrenheit. The work "thermometer" surfaced in the literature of Levrechons "Recreation mathematique" (1624) which mentioned the useof instrument "to test the intensity of fever". The concept of central set point temperature was introduced by Hammel HT who proposed an original neuronal model to explain regulation of set point temperature by preoptic nuclei. Heat production responses were shown to regulate near a Set-point of 37°C by the respective effector neurons. The term circadian was proposed by Franz Harberg in the late 1950's to denote daily cycles. In 1948, Kleitmann and Ramswaroop provided some of the first detailed information concerning endogenous and exogenous influences on the diurnal rhythm of core temperature. In most of their subjects there was a 12 hr difference between the maximum and minimum observed temperatures. The current concept of fever physiology is that, host cell derived molecules induce fever, which usually occurs in the context of an overall inflammatory response directed against pathogenic microbes. The host derived molecules responsible for fever used to be known as endogenous pyrogens as first demonstrated by Paul Beeson in 1948. He described temperature elevating effect of a substance obtained from single leucocytes. Kluger and co-workers provided proof that endotoxin induced fever is mediated by interleukin -1b with induction of IL-6, suggesting that IL-6 might be the final common pathway for such fever[8]. Milton and Wendlandt originally proposed that E-series prostaglandins (PGE) might mediate the febrile response to pyrogens. This consensus of opinion still favors the proposition that PGE2, the endogenous isoform of PGE plays an essential role in fever production. Rotondo et al. proposed that PGE2 involved in fever might be generated peripherally, transported to pre-optic/anterior hypothalamus (POAH) by the blood stream and then being lipophilic, either cross the Blood Brain Barrier (BBB) at this site or diffuse to POAH through the organum vasculosum laminae terminalis to cause the induction of fever. Since the time of Hippocrates, multiple cutaneous bleeding signs have been described as purpura. In Latin literature, the word purpura (from Greek porphyra) signifies the Precious purpledye, secreted by the purple snail, used as a status symbol during Antiquity in the middle Ages. Without knowledge of the different blood components and functions of course, no differentiation of bleeding signs was possible. Purpura was recognized as a manifestation of peltisutial fever 2000 years ago. Several factors are known to cause bleeding in association with infections of which thrombocytopenia is the common cause. Gram +ve and gram –ve septicemia, miliary tuberculosis, leptospirosis, typhoid, mycoplasma

pneumonia, etc. Septicemia resulting from both gram –ve and gram +ve is the commonest cause of thrombocytopenia. May be caused by disseminated intravascular coagulation (DIC) and the diagnosis of DIC may be apparent when coagulation studies are performed. About 46% of these patients have elevated platelet associated immunoglobulin G without evidence of DIC. Platelets adherence to damaged vascular surfaces also accounts for thrombocytopenia in certain bacterial infections, such as meningococcemia. In the study done by Gupta[16] et al,among a group of 230 patients,130 cases (56.51%) were positive for P.vivax, 90 cases (39.13%) were positive for P.falciparum and 10 cases (4.34%) had mixed infection. Mean hemoglobin value was 12.0 ± 2.1 gm% (ranging from 6.1 gm% to 15.2 gm%) and mean white blood cell count was 12,000 ± 1300/cumm (ranging from 2,800 to 19,400/cumm). Mean platelet count was 151,000 ± 50,000/cumm (ranging from 11,000 to 313,000/cumm). All the patients had fever (100%) at the time of presentation, followed by weakness (95%), nausea (90%), vomiting (86%), anorexia (80%) and diarrhea (5%). Most common sign was anemia (80%) followed by splenomegaly (20%), jaundice (10%), and hepatomegaly (2%). Malaria caused by P.vivax and P.falciparum is endemic in many parts of India. Malaria affects almost all blood components and is a true hematological disease. Thrombocytopenia and anemia are the most frequently malaria associated hematological complications. In endemic areas malaria has been reported as the major cause of low platelet counts. As per the study done by Tong Seng Fah[14] et al in Malaysia,a clinic-based cross-sectional study from May to November 2003,consecutive patients presenting with undifferentiated fever of less than 2 weeks were selected from the Primary Care Centre of Hospital Universiti Kebangsaan Malaysia.73 patients participated in this study. Among them, 45.2% had thrombocytopaenia.Myalgia and headache were common among all patients.However,nausea and vomiting occurred significantly more often among patients with thrombocytopenia than in patients with normal platelet count.Common symptoms reported among patients with thrombocytopenia were myalgia (69.7%), headache (66.7%), nausea/vomiting (69.7%) and arthralgia (39.4%).So they concluded any acute non-specific febrile patients presenting with symptoms of nausea and vomiting may have higher risk of thrombocytopenia and should be seriously considered for other investigations including a complete blood count. In the study done by Nair P S[15],thrombocytopenia was present with a platelet count of >81000/cumm and <1,50000/cumm in 229 patients (69.8%). Platelet count was >61000/cumm and <80000/cumm in 13.1% of patients, >41000/cumm and <60000/cumm in 8.2% of patients, >21000/cumm and <40000/cumm in 7%and <20000/cumm in 1.8%.Clinically bleeding manifestations was seen in 4 patients and concluded that viral fever was the commonest cause for thrombocytopenia with bleeding manifestations seen when thrombocytopenia was <20000/cumm.

Material and methods
This study is a prospective cohort study over a period of one anda half years.200 Patients admitted to the hospital with documented fever of >38.5C[5] and platelet count <1,50,000/µL were selected using purposive sampling techniques. They are followed from admission till recovery, discharge or death whichever is earlier. The data was collected from patients admitted to Patna medical college and Hospital Patna, Bihar. Study duration of two years. with documented fever of >38.5C and platelet count <1,50,000/µL.

The following investigations were done in all patients with acute fever. Heamoglobin, total count, differential count, erythrocyte sedimentation rate, platelet count, peripheral smear, Malarial parasite fluorescent test, If platelet count is <1,50,000/µL & Malarial parasite fluorescent test[7] is negative, IgM Dengue , IgM Leptospirosis, Blood culture were done, Chest Xray, Human immunodeficiency virus, Monospot for Infectious mononucleosis,bone marrow study were done only if required, If diagnosed with a specific disease, subsequent

investigations were done. Platelet count[10] were repeated on every third consecutive day of the progression of the illness. Based on the outcome and complications, other tests were repeated.

Inclusion Criteria
Those admitted in Father Muller Medical College Hospital having fever for atleast 2days or temperature on admission >38.5C, Platelet count <1,50,000/µL. Age more than 15 years.

Exclusion Criteria
Platelet count >1,50,000/µL. Age less than 15 years, Pregnant women, On long term medications which causes thrombocytopenia[6]. (Heparin,rifampicin, carbamazepine etc.)

Results
A total of 200 patients admitted to Father Muller medical college hospital for evaluation of acute febrile illness having thrombocytopenia were included in the study.

Table 1: SEX DISTRIBUTION OF CASES

SEX	NUMBER	PERCENT
MALE	119	59.5%
FEMALE	81	40.5%

Among the 200 cases studied, 119 (59.5%) were males and 81 (40.5%) werefemales. Ratio of male to female is 1.46:1 Fever was the presenting complaint in all the patients (100%). Headache wasobserved in 165 (82.5%) cases and vomiting in 69 (34.5%) cases, nausea in 29 (14.5%) patients, pain abdomen in 8 (4%) patients, yellowish urine in 15 (7.5%) casesand body pain in 114 (57%) patients.

Table 2: Haemoglobin (in gram %)

Haemoglobin (in gram %)	No. of patients (%)
8-12	72 (36%)
>12	128 (64%)

In the table, 72 (36%) patients of the study population had haemoglobin less than 12 g/dl and 128 (64%) patients were having haemoglobin greater than 12 g/dl. The mean haemoglobin in the study population was 12.62 g/dl.

Table 3: Total count

Total Count	No. of patients (%)
<4000	57 (28.5%)
4000-11000	136 (68%)
>11000	7 (3.5%)

The above table shows that 57 (28.5%) patients of the study population had total count <4000/cumm[12]. Total count >11000/cumm was seen in 7 (3.5%) patients.The mean total count in the study population was 5918/cumm.

Grading of thrombocytopenia [13]

Table 4: Platelet Counts

Grade	Platelet count	Number	Percentage
1	75000-150000	115	57.5%
2	50000-75000	45	22.5%
3	25000-50000	15	7.5%
4	<25000	25	12.5%

The mean platelet count was 79835/cumm with a standard deviation of 37009.4(ranging from 6000-150000). 57.5% patients were found to have platelet counts within the range of 75000-150000/cumm.

Table 5: Grading of thrombocytopenia in viral fever

Grade	Platelet count	No. of patients	Percentage
1	75000-150000	18	9%
2	50000-75000	4	2%
3	25000-50000	0	0%
4	<25000	2	1%

Among the patients diagnosed to have viral fever, grade 1 severity of thrombocytopenia were observed in 9%, grade 2 in 2% and grade 3 in none of the cases and grade 4 in 1%.

Table 6: Grading of thrombocytopenia in malaria

Grade	Platelet count	No. of patients	Percentage
1	75000-150000	46	23%
2	50000-75000	28	14%
3	25000-50000	8	4%
4	<25000	6	3%

Among the patients diagnosed to have malaria, grade 1 severity ofthrombocytopenia were observed in 23%, grade 2 in 14%, grade 3 in 4% and grade 4
in 3%.

Table 7: Grading of thrombocytopenia in other diseases

Grade	Platelet count	No. of patients	Percentage
1	75000-150000	6	3%
2	50000-75000	0	0%
3	25000-50000	0	0%
4	<25000	0	0%

Among the patients diagnosed to have other diseases (UTI, varicella zoster, pneumonia, acute gastroenteritis and viral hepatitis), grade 1 severity of thrombocytopenia were observed in 3%.

Discussion

Patients with acute febrile illness in a tropical country like India usually have an infectious etiology and may have associated thrombocytopenia. The inclusion criteria of fever correlates with the studies conducted by Gupta[16] et al , shin[17] et al and tong seng fah et al. Headache was observed 82.5% in our study was the second commonest symptom. It was seen in 83.2% in the study done by Shin et al and 66.7% in the study done by Tong Seng Fah et al. Vomiting

and Nausea was seen in 49% in our study, where as 16.8% in Shin *et al* and 86% in Gupta *et al*. Body pain was observed in 57% of our study group which almost correlates with the study conducted by Tong Seng Fah *et al* which was 69.7%.

Table 8: Comparison of clinical signs

Sign	Gupta (%)	Shin (%)	Present study (%)
Pallor	80	51	19.5
Icterus	2	11	3
Splenomegaly	20	42	29.5
Hepatomegaly	2	15.8	14.5

Pallor was present in 19.5% in our study while it was seen 80% in the study done by Gupta *et al*. Icterus was noted in 3% patients in our study which correlates with the study done by Gupta *et al* which was 2%, where as in Shin *et al* it was 11%. Hepatomegaly was noticed in 14.5% individuals in our study which correlates with Shin *et al* which was 15.8%. Splenomegaly was observed to be 20% in Gupta *etal* and 29.5% in our study which shows a close correlation whereas study done by Shin *et al* showed 42%. Among the causes which we evaluated for thrombocytopenia in cases of acute febrile illnesses showed the correlation with each of the following study as described. Study done by Bajpai[18] *et al* among the acute febrile illness patients during monsoon season in a tertiary care hospital of Mumbai showed Grade 1 thrombocytopenia among 14.5% cases compared to our study which was 57.5% and in a study done by Nair P S *et al* did not have any cases with Grade 1 severity.Grade 2 thrombocytopenia were observed in 22.5% cases which closely correlates with the data obtained in the study conducted by Bajpai *et al* which was 21.2% whereas it was 56.9% by Nair P S *et al.*

Table 9: Comparison of leading causes.

Diagnosis	Chrispal (%)	Nair P S (%)	Present study (%)
Leptospirosis	3	-	8
Dengue Fever	7	13.8	30.5
Malaria	17.1	9.2	44.5
Enteric Fever	8	-	2
Others	64.9	77	17.5

In the statistical analysis to find out the leading cause of thrombocytopenia among the cases, our study showed higher incidences of malaria(44.5%) compared to other studies done earlier by Chrispal[19] *et al* and Nair P S *et al* which was 17.1% and 9.2% respectively. The second most common cause was found to be dengue fever(30.5%) which was higher compared to other studies with 7% and 13.8% respectively. Leptospirosis and Enteric fever were found to be the cause among 8% and 2% of all the cases as compared to the study conducted by Chrispal *et al* which showed 3% and 7% of the cases. In the study conducted by Chrispal *et al* and Nair P S *et al* showed higher incidence of diseases other than malaria, leptospirosis, dengue fever, enteric fever, as the leading cause for thrombocytopenia, whereas our study supports only 17.5% of this category among all the cases.

Conclusion

Local prevalences of individual diseases influence the prioritization of the differential diagnosis of a clinical syndrome of acute febrile illness(AFI).This study was conducted in order to find out the etiology of the cause of thrombocytopenia among the patients who presented with acute febrile illness to our hospital and to describe the disease specific clinical

profiles. Higher frequencies of mild to severe thrombocytopenia were observed in different etiologies in our study. Out of which malaria and dengue were the most common cause of thrombocytopenia among the acute febrile illness cases during presentation followed by other diseases. Hence the presence of thrombocytopenia in a febrile patient heightens the suspicion of these two diseases. In conclusion, the early diagnosis of the disease, correlating the clinical and haematological changes and early, effective treatment can limit mortality and prevent further complications.

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