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Clinical, Haematological and biochemical Profile in Acute Febrile Illnesses with Thrombocytopenia

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ABSTRACT: Thrombocytopenia in acute febrile illness is an alarming finding and most commonly seen in malaria and dengue patients. In the present study we evaluated and followed up 200 patient of acute febrile illness with thrombocytopenia for ten days, for changes in both clinical, biochemical and haematological parameters. Majority of cases in present study were of dengue(45%) followed by malaria (22%), septicaemia(15%) enteric fever(4%) etc.
The patients of dengue presented earlier (4.11± 1.42) around 4th day as compared to other groups. The skin rash, bleeding tendency, tourniquet test positivity and respiratory abnormalities were seen in dengue patients($p<0.05$), while abdominal pain, diarrhoea, anaemia, jaundice, hepatomegaly and splenomegaly were more frequent in malaria patients($p<0.05$).
In dengue patients decrease in WBC count was noticed around 6th day of fever which gradually recovered, while in malaria there was increase in WBC count around 2nd day of fever which gradually recovered by 10th day . Fall in haemoglobin was also noticed in malaria cases. There was continuous fall in platelet count till 6th day of illness in dengue patient while in malaria platelet fall was noticed early i.e. from 2nd day of fever which gradually recovered.
KFT was more commonly affected in dengue while LTF in malaria. The duration of stay in hospital was higher in malaria as compared to dengue. We suggest that our findings may be used in remote area where facilities for specific test may not be available or during epidemics.

Key Words: Acute febrile illness, Thrombocytopenia, Dengue, Malaria

INTRODUCTION:

Acute febrile illnesses that present with thrombocytopenia are common in individuals living in tropical areas of Asia[1]. Febrile thrombocytopenia is one of the recognized complication that may be missed if platelet count is not done routinely. Diseases which commonly present with acute febrile thrombocytopenia include dengue, malaria, septicemia, leptospirosis, rickettsial infections, typhoid, borreliosis, rodent-borne viruses such as Hanta and Lassa fever, human immunodeficiency virus (HIV), visceral leishmaniasis and TTP-HUS[2,3].

Most of the aforementioned diseases present with similar symptoms and are associated with complications which may be avoided by early diagnosis and treatment. During epidemics, it is a challenge for physicians to clinically differentiate conditions presenting with fever and thrombocytopenia. There are several clinical parameters which are used to narrow down and diagnose the spectrum of fever with thrombocytopenia.

Dengue and malaria, the two most common arthropod borne diseases, are major concerns in tropical settings responsible for febrile thrombocytopenia. Their early diagnosis and specific management is of utmost importance and may reduce morbidity and mortality. Confirmation of dengue and malaria requires technical expertise which at times may be unavailable. Differences in certain haematological parameters which include low platelet count, haemoglobin concentration and hematocrit have been reported to be associated with malaria and dengue[4,5].

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MATERIALS AND METHODS

This study was conducted in the Department of Medicine, Lady Hardinge Medical College and Associated Hospitals in New Delhi during the period of November 2013 to March 2015. It was a hospital based observational study. A total of 200 patients admitted for acute febrile thrombocytopenia presenting to the Department of Medicine of Lady Hardinge Medical College and Associated Hospitals were included after written informed consent and ethical clearance. Patients with age > 18 years and history of fever (ie. oral A.M. temperature of >37.2°C (>98.9°F) or a P.M. temperature >37.7°C (>99.9°F) for 2-7 days and having thrombocytopenia (ie. platelet count less than 1,50,000) were included in the study. Patients who were previously diagnosed cases of other co-morbid diseases causing thrombocytopenia like ITP, CLD, DIC etc. were excluded. A detailed history was taken with emphasis on duration of illness, pattern of fever, associated symptoms followed by a thorough clinical examination which included general physical examination, per abdomen examination and examination of all other systems. All patients were then subjected to a battery of laboratory investigations which included routine blood investigations(complete blood count, liver function tests, kidney function tests etc) and various specific diagnostic tests(NS-1,Dengue Serology, Malaria antigen, Peripheral smear, serum Widal etc) to reach a specific diagnosis. Patients were followed during their stay in the hospital until an outcome(recovery or discharge in health or expiry) or till ten days from beginning of illness (ie. Day 1 of fever) was reached. Sample statistics like mean, median and standard deviation were calculated for Quantitative data. Tests of significance Chi-square test and difference of proportion was applied for categorical data. Mean and standard deviation was compared by Student T test. Statistical significance was set up at $p \leq 0.05$

RESULTS

A definitive diagnosis was made in 184 cases. Among the diagnosed cases, Dengue formed the largest group with 45% while other cases diagnosed were Malaria (22%) , septicemia (15%), enteric fever (4%) and other rarer causes(6%). 8% of the total cases could not be diagnosed with the available investigations.

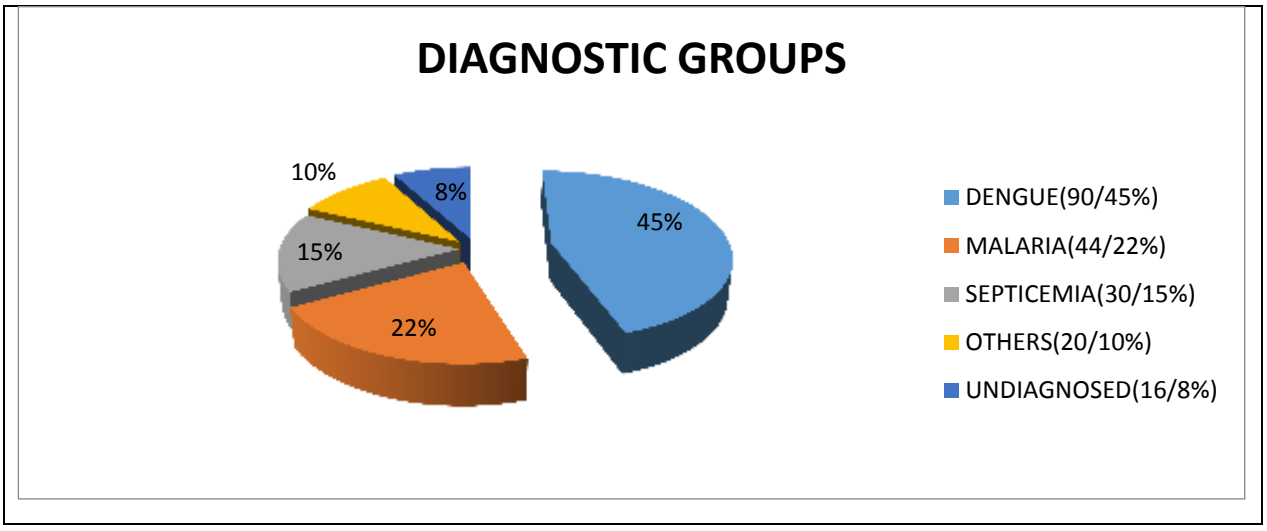

Figure 1

The age range of the patient was 18-85 years, with most (76%) of the patients being ≤ 40 years of age. Mean age of the sample population was 34.65±10.79 years and there was no significant difference between mean age of the patients in various diagnostic groups included in the study. There was a male preponderance noticed in our study population, with a male to female ratio of 67.5:32.5. The dengue patients presented early in the course of illness. The mean duration of illness at presentation was 4.11±1.42 days in dengue patients while it was 4.84±1.58 days in malaria and even higher in other diseases.

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TABLE 1-Age profile of patients included in the study

	Mean Age±SD (in Years)	Duration of fever at presentation±SD (in Days)
Dengue(n=90)	34.82±10.76	4.11±1.42
Malaria(n=44)	34.09±10.48	4.84±1.58
Septicemia(n=30)	34.7±12.52	5.2±1.56
Others(n=20)	34.55±9.61	6.0±1.25
Undiagnosed(n=16)	35.19±11.06	5.56±1.26
Total(n=200)	34.65±10.79	4.74±1.58

Clinical Features of various group are shown below in table 2 and table 3

TABLE 2

	Dengue	Malaria	Septicemia	Others	Undiagnosed	Total
Weakness	74.0%	81.8%	83.3%	80.0%	75.0%	78.0%
Nausea-Vomiting	66.7%	75.0%	40.0%	80.0%	37.5%	63.5%
Bodyache	42.20%	52.30%	43.30%	100.00%	56.30%	51.50%
Headache	53.3%	59.1%	30.0%	45.0%	37.5%	49.0%
Rash	51.1%	31.8%	30.0%	45.0%	37.5%	42.0%
Abdominal Pain	35.6%	61.4%	40.0%	40.0%	6.3%	40.0%
Cough	24.4%	36.4%	76.7%	20.0%	25.0%	34.5%
Dyspnea	21.1%	4.5%	46.7%	25.0%	18.8%	21.5%
Diarrhoea	8.9%	27.3%	10.0%	40.0%	31.3%	18.0%
Bleeding	16.7%	9.1%	16.7%	40.0%	25.0%	18.0%
Jaundice	6.7%	22.7%	6.7%	70.0%	6.3%	16.5%

TABLE 3

	Dengue	Malaria	Septicemia	Others	Undiagnosed	Total
Pallor	33.3%	47.0%	60.0%	50.0%	25.0%	41.5%
Torniquet Test	42.2%	27.3%	23.3%	50.0%	25.0%	35.5%
Petechie/Purpura	35.6%	22.7%	20.0%	25.0%	31.3%	29.0%
Splenomegaly	10.0%	47.7%	26.7%	60.0%	12.5%	26.0%
Icterus	11.1%	36.4%	3.3%	65.0%	6.3%	20.5%
Respiratory Abnormality	18.9%	2.3%	26.7%	5.0%	6.3%	14.0%
Hepatomegaly	4.4%	27.3%	13.3%	55.0%	18.8%	17.0%
Ascitis	20.0%	4.5%	6.7%	0.0%	15.0%	12.5%
Impaired Consciousness	8.9%	2.3%	3.3%	0.0%	0.0%	5.0%

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Haematological parameters during course of diseases of dengue is shown in table 4.

TABLE 4

DENGUE	DAY-2 (n=13)	DAY-4 (n=56)	DAY-6 (n=84)	DAY-8 (n=81)	DAY-10 (n=55)
MEAN WBC ±SD (/µL)	4369.2 ±1842.7	4201.8 ±2214.2	3871.4 ±1682.1	4835.3 ±1588.4	5720 ±1451.9
MEAN NEUTROPHILS ±SD (%)	66.4±9.2	58.5±12.7	47.3±10.9	53.8±15.7	54.9±14.9
MEAN LYMPHOCYTES ±SD (%)	24.6±9.2	29.6±9.9	40.0±9.4	33.7±12.7	31.3±10.7
MEAN HEMOGLOBIL ±SD (g/dl)	12.9±2.3	11.6±2.3	11.3±2.0	11.3±2.0	11.5±1.4
MEAN HEMATOCRIT ±SD (%)	39.8±6.2	35.6±7.4	35.3±7.1	34.2±6.6	35.2±5.4
MEAN PLATELET COUNT ±SD (X10 ^{3}/µL)	59.0±49.8	42.9±31.7	39.5±29.3	56.3±28.9	84.7±21.3

Haematological parameters of dengue showing falling trend till 6th day of illness.

Biochemical parameters during course of diseases of dengue is shown in table 5.

TABLE 5

DENGUE	DAY-2 (n=13)	DAY-4 (n=56)	DAY-6 (n=84)	DAY-8 (n=81)	DAY-10 (n=55)
MEAN BLOOD UREA ±SD (mg/dl)	52.0±14.5	42.2±22.3	36.4±19.6	34.3±15.9	30.9±14.6
MEAN SERUM CREATININE (mg/dl)	1.6±0.5	1.2±0.5	1.1±0.5	1.1±0.2	0.9±0.1
MEAN TOTAL SERUM BILIRUBIN ±SD (mg/dl)	1.5±0.8	1.7±1.2	1.6±1.5	1.6±1.9	1.1±0.3
MEAN SERUM ALANINE TRANSAMINASE ±SD (U/L)	168.0±165.5	106.1±125.0	86.9±124.3	70.4±66.2	64.8±35.3
MEAN SERUM ASPARTATE TRANSAMINASE ±SD (U/L)	187.6±196.5	86.8±99.2	68.3±81.6	64.5±80.9	45.8±23.5
MEAN SERUM ALKALINE PHOSPHATASE ±SD (U/L	246.4±147.5	133.0±84.8	137.3±86.4	145.6±102.5	163.2±118.6

KFT showed mild derangement on 2nd day which recovered to normal at 10th day .
Initial derangement of LFT recovered and returned to normal by 10th day.

Haematological parameters of malaria are shown in table 6.

TABLE 6

MALARIA	DAY-2 (n=3)	DAY-4 (n=24)	DAY-6 (n=33)	DAY-8 (n=44)	DAY-10 (n=36)
MEAN WBC ±SD (/µL)	9133.0 ±8544.7	5304.1 ±2835.7	3966.6 ±1824.7	5400.0 ±2971.5	5325.0 ±2211.3
MEAN NEUTROPHILS ±SD (%)	77.6±13.2	66.2±10.5	62.4±15.5	61.6±19.0	63.2±9.7
MEAN LYMPHOCYTES	18.3±11.5	25.8±8.4	28.1±12.4	26.8±15.7	24.5±9.4

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±SD (%)					
MEAN HEMOGLOBIL ±SD (g/dl)	9.4±1.0	9.5±1.6	10.3±2.4	9.7±1.8	9.5±1.5
MEAN HEMATOCRIT ±SD (%)	26.6±4.8	28.2±5.4	29.2±7.0	29.1±6.9	28.3±6.6
MEAN PLATELET COUNT ±SD (X10 ^{3}/μL)	21.3±8.0	59.6±40.0	43.1±28.3	56.8±37.3	72.6±35.0

Platellet count was least on 2nd day which gradually recovered.Initial polymorphonuclear leucocytosis returned to normal by 10th day.

Biochemical parameters of malaria are shown in table 7.

TABLE 7

MALARIA	DAY-2 (n=3)	DAY-4 (n=24)	DAY-6 (n=33)	DAY-8 (n=44)	DAY-10 (n=36)
MEAN BLOOD UREA ±SD (mg/dl)	74±1.7	34.3±12.6	32.1±8.1	40.8±23.1	39.7±21.2
MEAN SERUM CREATININE ±SD (mg/dl)	1.4±0.4	1.1±0.2	1.0±0.2	1.3±0.6	1.2±0.5
MEAN TOTAL SERUM BILIRUBIN ±SD (mg/dl)	10.4±1.0	2.9±1.7	2.9±2.2	2.0±2.0	1.7±1.5
MEAN SERUM ALANINE TRANSAMINASE ±SD (U/L)	500.6±725.1	114.4±163.1	99.3±93.9	135.9±120.8	135.3±125.2
MEAN SERUM ASPARTATE TRANSAMINASE ±SD (U/L)	349.0±476.3	88.5±126.5	83.5±53.0	102.3±91.0	108±82.3
MEAN SERUM ALKALINE PHOSPHATASE ±SD (U/L)	552.0±19.2	191.1±134.3	159.3±114.9	172.7±102.5	163.2±118.6

KFT recovered quickly on 2nd day .
LFT was deranged on 2nd day but rapidly improved on following days.

DISCUSSION:

Patients with acute febrile illnesses in a tropical country like India usually have infectious etiology and may have associated thrombocytopenia. Our study showed higher incidence of dengue 45% followed by malaria 22% ,septicaemia 15%,Others 10%(Enteric fever 4%,Alcoholic liver disease 2%,Viral hepatitis 1.5%,Megaloblastic anaemia 1%,Rickettsia 1%,leukaemia 0.5%),8% remain undiagnosed. This was different from other studies done earlier by Dash et al[6] and Kumar et al[7]. This difference from other studies might be explainable due to geographical and climatic differences among the regions where the studies were conducted.

The male predominance was noticed among all the groups but more significantly among malaria group which showed a male to female distribution of 77.4:22.6 which correlated with the study done by Epelboin et al[8], who also noticed this marked male predominance among malaria group ie. 77.9% as compared to 57.2% in dengue group. This is perhaps a reflection of the social demographics of our country whereby

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women being mostly housewives are less exposed to mosquito bites compared to men at workplace. The most affected age group was 18- 40 years of age which included 152(76%) out of the 200 patients. The factors responsible for the age pattern include outdoor work for young adult males and outdoor sleeping habits which thus are more prone to get mosquito bites.

Patients with dengue presented earlier as compared to any other group in our study ($p<0.05$) . The mean duration of presentation by dengue patients was 4.11±1.42 days while it was 4.84±1.58 day in malaria group and even more in other groups. This may be explained by early onset of severe constitutional symptoms in dengue patients.

Most common clinical symptom among the patients included in our study was generalized weakness(78%) followed by nausea-vomiting(63.5%), bodyache(51.5%), headache(49%), rash (42%)and abdominal pain(40%) apart from others. This finding correlated with the Malaysian study by Tong et al[10] while contradicts the Indian study by Kumar[4] and Chandra in UP.

The patients in dengue group more frequently($p<0.05$) had rash, dyspnoea, bleeding tendencies, tourniquet test positivity, ascitis and respiratory abnormalities while malaria patients ($p<0.05$)presented more frequently with abdominal pain, jaundice, diarrhoea, pallor, icterus, hepatomegaly and splenomegaly.

In dengue patients there was a gradual fall in the mean WBC count and platelet count till day 6 and started rising thereafter, while in malaria there was initial rise in WBC count on 2nd day which gradually settled to normal by 10th day. Malaria patients had significantly low haemoglobin and hematocrit values as compared to their dengue counterparts that can be explained by hemolysis in malaria.

Thrombocytopenia was the most marked finding in both dengue and malaria but there was a continuous fall in platelet count till day 6 in dengue patients and rise thereafter while in malaria platelet fall was noticed early on 2nd day of fever which gradually recovered

Kidney function tests were more commonly affected in dengue patients while liver function tests were more frequently and severely deranged in malaria patients, which gradually recovered but both had a tendency to normalize towards the end of the study with appropriate treatment.

Duration of illness and stay in hospital, both were higher among malaria group as compared to their dengue counterparts. Out of the 88 patients of dengue , 33 were discharged before 10th day of illness while rest of 55 were discharged on or after 10th day of illness. Patient with malaria had a late recovery with 36 out of 44 patients being discharged on or after day 10 of illness.

CONCLUSIONS AND RECOMMENDATIONS

Among the patients of acute febrile thrombocytopenia, most common cause is dengue followed by malaria, septicemia and enteric fever. Dengue patients presented earlier as compared to other groups. Generalized weakness is the most common clinical feature noticed in both dengue and malaria patients while other common features of these two groups were body ache, headache ,nausea and vomiting. The patients of dengue frequently had rash, dyspnea, bleeding tendencies, tourniquet test positivity, ascitis and respiratory abnormalities while malaria patients presented more frequently with abdominal pain, jaundice, diarrhoea, pallor, icterus, hepatomegaly and splenomegaly. Patients in malaria group had lower hemoglobin levels as compared to other groups. WBC and platelet count decrease till the day 6 of illness and rise later in dengue while in Malaria platelet fall was noticed early on 2nd day of fever which gradually recovered . Severity of thrombocytopenia is directly related to bleeding manifestations as most patients who had bleeding showed platelet count below 20,000/µL. Kidney function tests (blood urea and serum creatinine) are deranged in dengue group initially but normalize with appropriate treatment. Liver function tests are more severely deranged in malaria patients as compared to other groups. Patients in dengue recovered early as compared to malaria and other diseases causing acute febrile thrombocytopenia. We suggest that our findings may be used to differentiate between malaria and dengue in remote area where facilities for specific test may not be available or during epidemics. In other group of cases, no definite pattern was noticed this may be due to small number of cases.

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