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Early Recognition of Malaria or Dengue Complicated with Thrombocytopenia

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Authors' contributions

This work was carried out in collaboration between all authors including study design, literature research and final analysis of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aim of the Study: To observed changes in clinical, haematological and biochemical parameters of dengue and malaria over a period of ten days in patients who presents with low platelet count.
Place and Duration of Study: Lady Harding Medical College, New Delhi, India, November 2013-to March 2015.
Study Design: Prospective observational study.
Sample Size: Total 134 cases of thrombocytopenia with fever were included in the study of which 90 cases were of dengue and 44 were of malaria.
Methodology: Patients of acute fever who were diagnosed as malaria or dengue by peripheral smear, rapid antigen testing or serology were included. Complete blood count including platelet count; liver function test and renal function tests were done in all cases on day 2, 4, 6, 8 and day 10 to see progressive changes. Results were analysed subsequently.

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Results: The patients of dengue presented earlier (4.11 ± 1.42) around 4th day as compared to malaria. The skin rash, bleeding tendency, tourniquet test positivity and respiratory abnormalities were more frequent in dengue patients, while abdominal pain, diarrhoea, anaemia, jaundice, hepatomegaly and splenomegaly were more frequent in malaria patients.

White blood cells count showed initial rise in malaria and fall in dengue which gradually recovered by 10th day in both diseases. Fall in haemoglobin was seen only in malaria cases. There was continuous fall in platelet count till 6th day of illness in dengue patient while in malaria patient fall appeared early on 2nd day of fever but was inconsistent, which gradually recovered. Platelet fall was more severe in dengue as compared to malaria, so was bleeding tendencies. Bleeding tendencies were more frequent when the platelet count was below 20,000/µL.

Transaminase levels were more severely deranged and manifested early in malaria, while serum creatinine and blood urea were more deranged in dengue. Both these biochemical abnormalities return to normal by 10th day of illness.

Conclusion: There are certain differences between clinical, haematological and biochemical parameters in malaria and dengue for early diagnosis. We suggest that our observations can be used in remote areas where facilities for specific test are not available or limited by financial constrains or in epidemics.

Keywords: Thrombocytopenia; liver function tests; kidney function test; dengue; malaria; bleeding tendencies.

1. INTRODUCTION

Many diseases can present with fever and thrombocytopenia such as dengue, malaria, septicaemia, leptospirosis, enteric fever, human immunodeficiency virus (HIV), TTP-HUS, rickettsial infections, viral hepatitis, rodent born viruses such as Hanta and Lassa fever, leukaemia etc. [1-4] dengue and malaria are the two most common arthropod borne diseases in Northern India during rainy season and are responsible for large number of morbidity and mortality. Both can present with high grade fever with thrombocytopenia. Their early diagnosis and specific management is of utmost importance [5]. Confirmation of dengue and malaria requires technical expertise which at times may not be available. Differences in certain haematological parameters which include low platelet count, haemoglobin concentration and haematocrit have been reported to be associated with malaria and dengue [6,7]. In the present study we have compared the progressive alteration in clinical and routine laboratory parameters to differentiate between dengue and malaria.

2. METHODS AND STUDY DESIGN

All cases of acute fever with thrombocytopenia presenting in Lady Harding medical college, New Delhi, India, were included in this study.

2.1 Inclusion Criteria

Patients with (1) age > 18 years and (2) history of fever (i.e. oral A.M. temperature of >37.2℃ (>98.9℉) or a P.M. temperature >37.7℃ (>99.9℉) for 2-7 days and (3) thrombocytopenia (i.e. platelet count less than 150,000/µL) (4) Confirmation of Malaria was done by peripheral smear, malarial antigen testing, and of dengue by NS1 antigen, dengue serology.

2.2 Exclusion Criteria

All other causes of thrombocytopenia with fever. A detailed history and physical examination was done .All patients were subjected to a battery of laboratory investigations which included routine blood investigations like complete blood count, liver function tests, kidney function tests etc.

Patients were followed up with clinical features, haematological parameters and biochemical parameters on 2nd, 4th, 6th, 8th and 10th day of onset of fever, during their stay in the hospital until an outcome (recovery or discharge in health or expiry) or till ten days from beginning of illness (i.e. Day 1 of fever) was reached.

Results were statically analysed. Sample statistics like mean, median and standard deviation were calculated for Quantitative data. Tests of significance like Chi-square test and difference of proportion was applied for categorical data. Mean and standard deviation was compared by Student T test. Association between two continuous variables was assessed by correlation analysis and Spearman's correlation coefficient. Statistical significance was set up at $p \leq 0.05$.

3. RESULTS

A total number of 134 cases were included in the study of which, 67% were of Dengue and 33 % were of Malaria. High grade fever with chills and rigors was the main presenting feature and was present in 100% of patients.

The age range of the patient was 18-85 years. Mean age (Table 1) of the sample population was 34.65±10.79 years. The dengue patients presented early in the course of illness. The mean duration of illness (Table 1) at presentation was 4.11±1.42 days in dengue patients while it was 4.84±1.58 days in malaria. There was a male preponderance in our study population. Out of 90 patients of dengue 58(64.4%) were male and 32(35.6%) were females and out of 44 cases of malaria 34(77.3%) were male and 10(22.3%) were females.

3.1 Comparison of Clinical Symptoms and Signs in Dengue and Malaria

Generalized weakness, body ache, headache and nausea-vomiting were the common clinical features in both dengue and malaria groups. In dengue group rash, dyspnoea, bleeding tendencies, tourniquet test positivity, ascites and respiratory abnormalities were most frequent while in malaria patients abdominal pain, jaundice, diarrhoea, pallor, icterus, hepatomegaly and splenomegaly were more frequently as shown in Fig. 1 and Fig. 2.

Table 1. Age of patients and duration of fever in study population

Number	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

In dengue, mean total WBC count on day 2 was 4369.2/µL following which, there was a significant dip in mean total WBC count on Day 6 and then it significantly increased on Day 10 ($p<0.001$). The mean neutrophils percentage on day 2 was 66.4% that decreased till day 6 and then significantly increased till day 10 ($p<0.05$) opposite trend was noted in lymphocytes, which increased till day 6 and fell after day 10 ($p<0.05$).

The mean haematocrit and haemoglobin, both were within normal limits, but gradually decreased from day 2 to day 8 (<0.05). These stabilized thereafter on day 10. The mean platelet count on day 2 of the illness was 59.0 x 10^3/µL, and showed a decrease till day 6 and increased significantly thereafter ($p<0.01$). The lowest platelet counts were noticed on day 6.

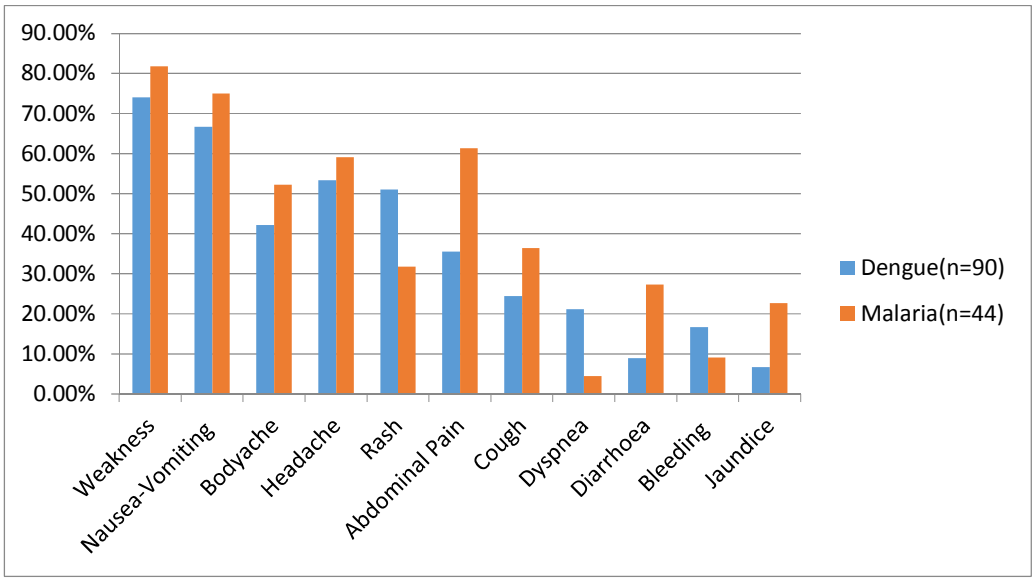

Fig. 1. Comparison of clinical symptoms in dengue and malaria

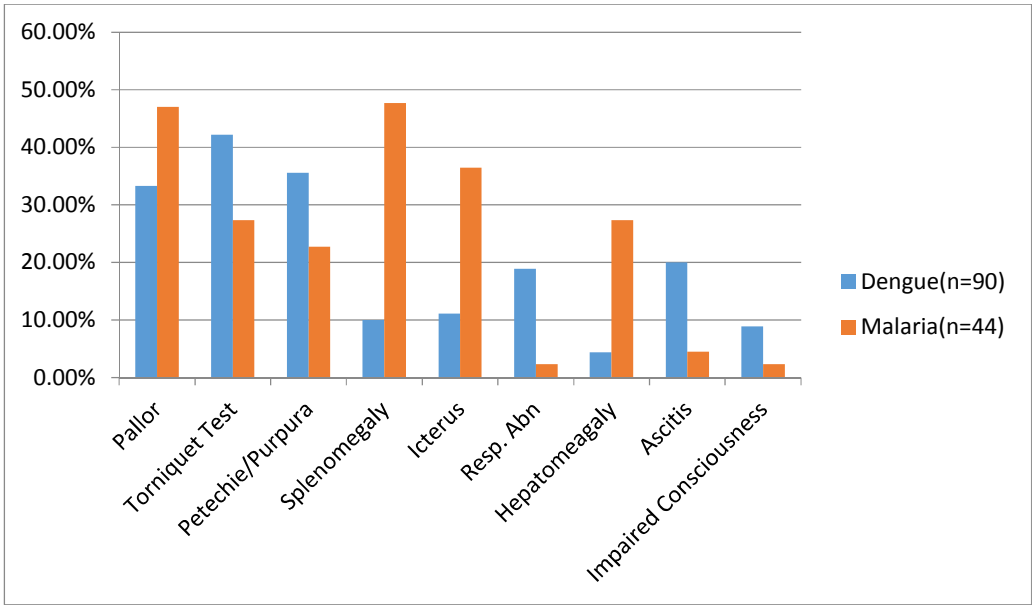

Fig. 2. Comparison of clinical signs of dengue and malaria

In malaria, the mean WBC count on day 2 was 9133/µL, that decreased till day 6 of fever and significantly increased thereafter till day 10 ($p<0.05$). The mean neutrophilic percentage followed a significantly decreasing trend from day 2 to day 8 i.e. from 77.6% to 61.6%. ($p<0.05$) Similarly lymphocytic percentage significantly increased in the same time period i.e. from 18.3% to 26.8% ($p<0.05$).

The mean haematocrit and haemoglobin, both were low at presentation on day 2 (9.4 g/dl and 26.6% respectively), and remained low throughout the study.

The platelet counts also showed a significant dip at day 6 and then increased gradually till day 10 ($p<0.05$).

3.2 Dengue versus Malaria- Haematological Profile

Patients presenting with dengue had slightly lower mean WBC as compared to malaria patients but this difference was not significant ($p>0.05$) except on day 2 when malaria patients had higher mean WBC values. Patients with malaria had a significantly higher percentage of neutrophils in blood as compared to their dengue counterparts ($p<0.05$) with a slightly decreasing trend in both groups. Patients in dengue group had a sharp dip on day 6 which was not seen in malaria patients.

Patients with malaria had lower haemoglobin level as compared to dengue patients ($p<0.01$). A similar trend was seen in haematocrit values too ($p<0.01$). Patients in dengue group had significant and consistent fall in the platelet count till day 6 with a rising trend thereafter as compared to patients of malaria who had a fluctuating trend till day 6 and significant rise on day 10 ($p<0.05$).

The finding of severe thrombocytopenia was more marked among the dengue patients ($p<0.05$) of which 81(i.e. 90%) out of 90, presented with a platelet count ≤50,000/µL as compared to only 33(i.e. 75%) patients out of 44 in malaria group.

None of the patient having platelet count above 50,000/µL developed any sign of bleeding (for e.g. petechie-purpura, melena, per-rectal bleed, gum bleed, menorrhagia, haematuria, epistaxis or sub-conjunctival haemorrhage), while 13.3% of the patients having platelet count between 50,000/µL to 20,000/µL developed bleeding tendencies and 37% of those having platelet count between 20,000/µL to 10,000/µL while 71.4% of those having platelet count below 10,000/µL developed one or more signs of bleeding.

Table 2. Haematological parameters during observation period in dengue

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 haemoglobin ±SD (g/dl)	12.9±2.3	11.6±2.3	11.3± 2.0	11.3±2.0	11.5±1.4
Mean haematocrit ±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±2 1.3

**WBC-White blood cell*

Table 3. Haematological parameters of malaria during observation period

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±1 5.5	61.6±19.0	63.2±9.7
Mean lymphocytes ±SD (%)	18.3±11.5	25.8±8.4	28.1±12 .4	26.8±15.7	24.5±9.4
Mean haemoglobin ±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

Table 4. Biochemical parameters during observation period in dengue

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 phosphatise ±SD (U/L	246.4±147.5	133.0±84.8	137.3±86.4	145.6±102.5	163.2±118.6

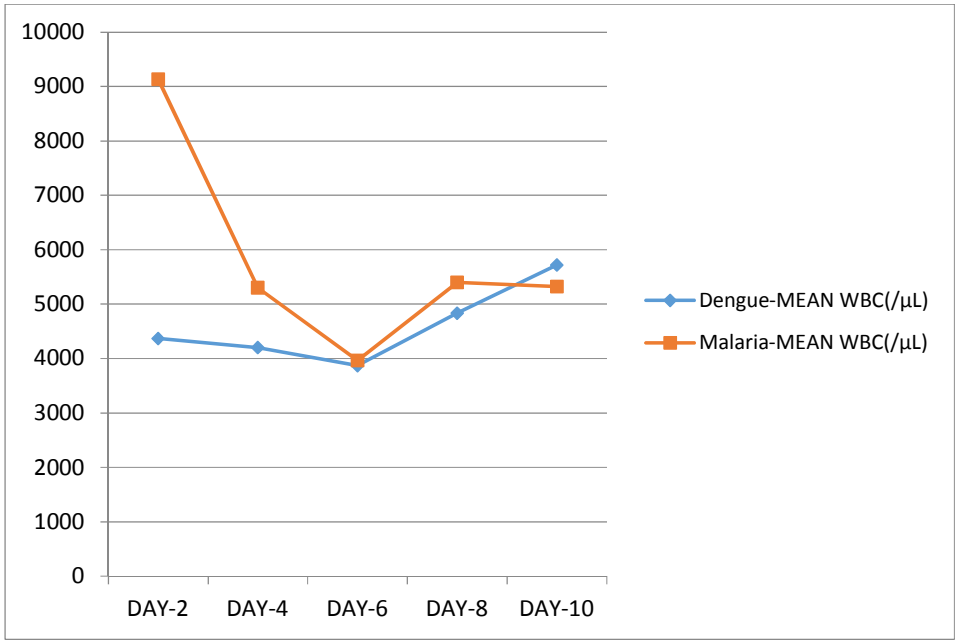

Fig. 3. Comparison of WBC in dengue and malaria

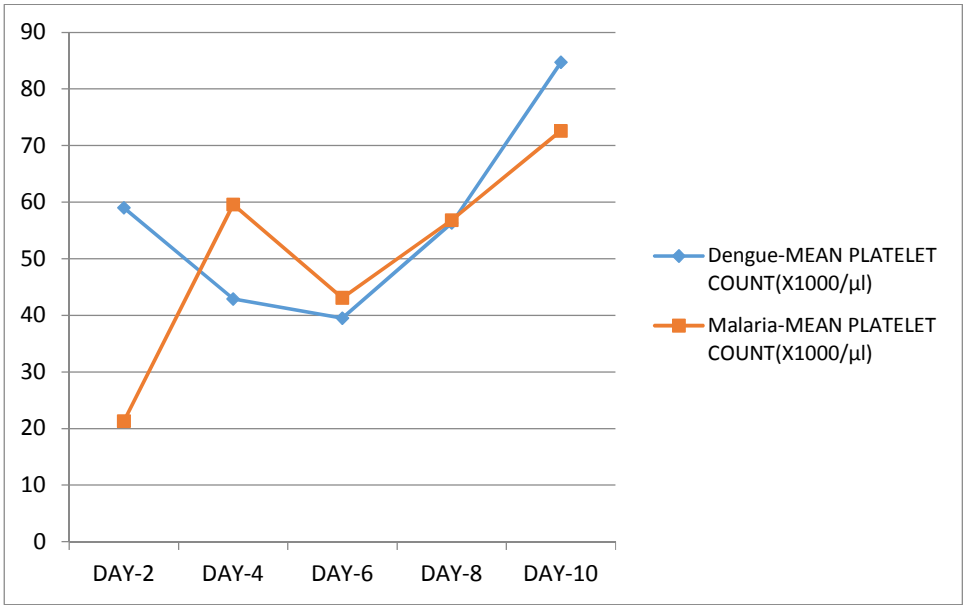

Fig. 4. Comparison of platelet in dengue and malaria

Dengue patients initially presented with relatively high mean blood urea and serum creatinine levels of illness but there was a significant improvement towards normal from day 4 onwards ($p<0.05$). The mean total serum bilirubin levels was initially deranged on day 2 (1.5 mg/dl) followed by normalization on day 10 ($p<0.05$). Liver enzymes also showed similar trend.

Mean blood urea and serum creatinine levels were significantly high on day 2 of the illness i.e. 74 mg/dl and 1.2 mg/dl but normalized later with appropriate treatment. Mean serum total bilirubin was significantly higher on initial days and decreased from day 4 onward in malaria patients ($p<0.05$). Liver enzymes were deranged on 2nd day but rapidly improved on following days.

3.3 Dengue versus Malaria- Biochemical Profile

Patients of dengue had a continuously decreasing trend in the mean blood urea and serum creatinine levels while malaria patients had a fluctuating course of the same with a significantly higher values on day 10 ($p<0.05$).

Patients with malaria had significantly higher values of mean serum total bilirubin and liver enzyme levels when compared to dengue from day 4 to 10 ($p<0.05$).

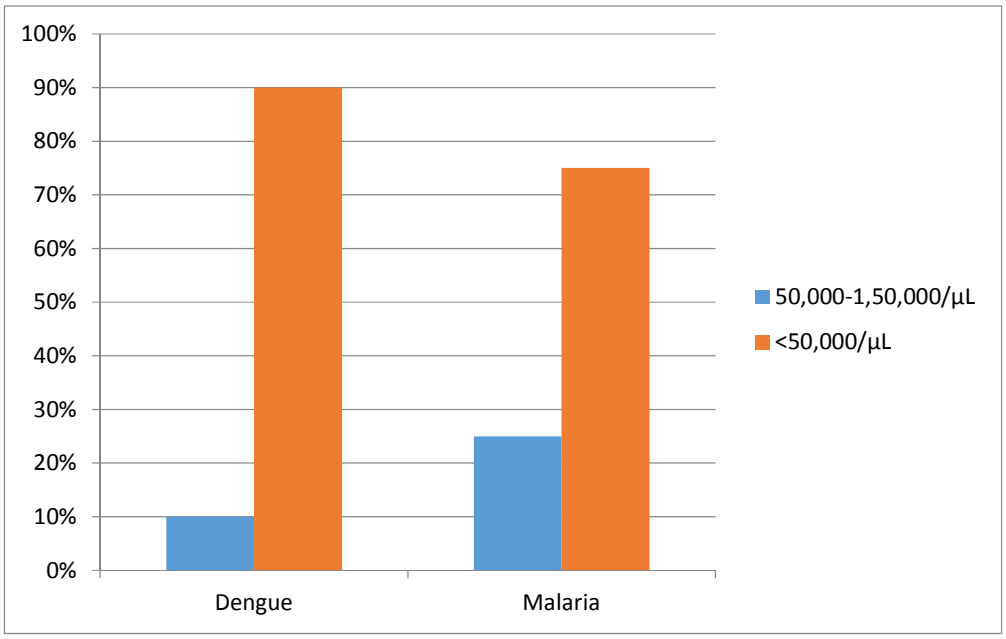

Fig. 5. Severity of thrombocytopenia in dengue and malaria

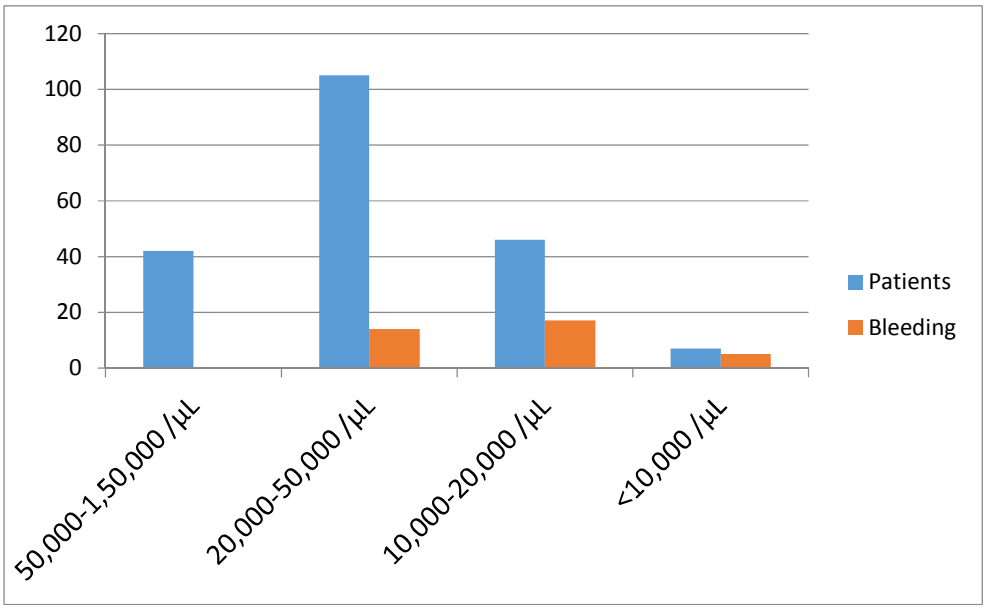

Fig. 6. Relationship between bleeding tendencies and platelet count

Table 5. Biochemical parameters of malaria during observation period

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 phosphatise ±SD (U/L)	552.0±19.2	191.1±134.3	159.3±114.9	172.7±102.5	163. 2±118.6

Of the 134 patients, 2 patients of dengue expired, one of whom was due to dengue shock syndrome and other was due to dengue haemorrhagic fever.

4. DISCUSSION

During rainy season dengue and malaria are the two most common mosquito born diseases in Northern India and frequently associated with thrombocytopenia and other complications. Our study showed a higher number of dengue patients (90) than malaria (44) with thrombocytopenia.

Table 6. Clinical outcome

Disease outcomes	Duration of illness (in days) of discharged patients				Expired
Days	4-5	6-7	8-9	≥10	
Dengue (n=90)	0	12	21	55	2
Malaria (n=44)	0	0	8	36	0

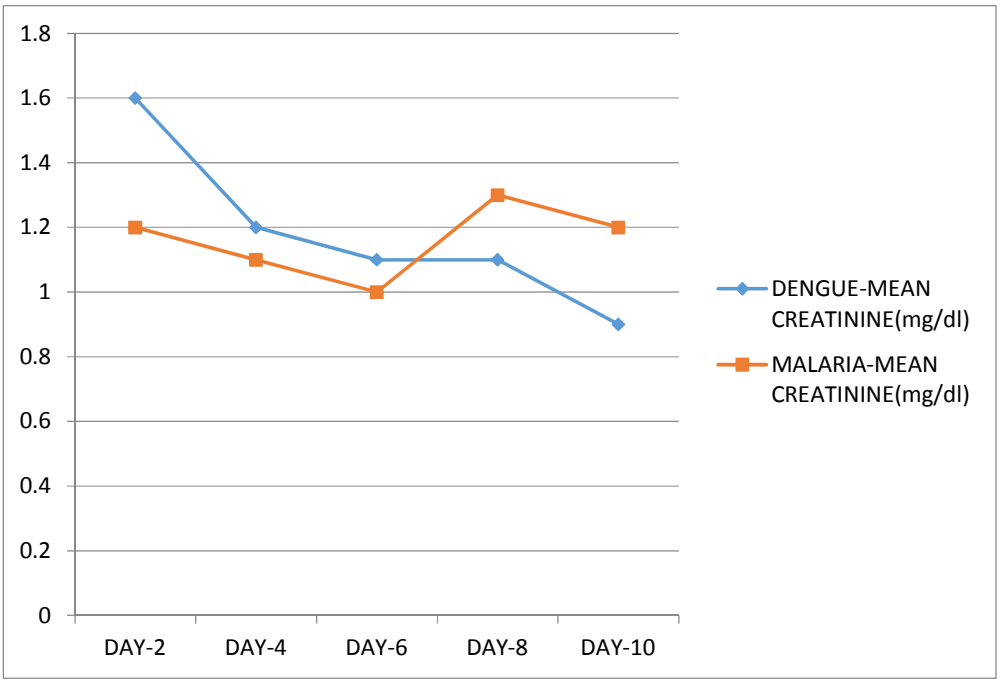

Fig. 7. Comparison of creatinine in dengue and malaria

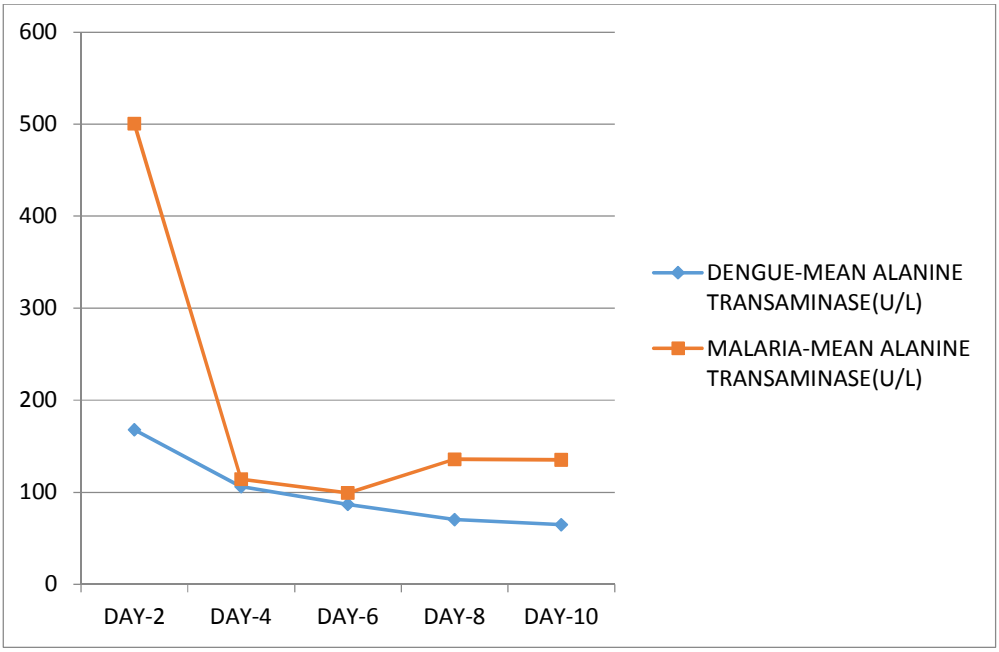

Fig. 8. Comparison of alanine transaminase in dengue and malaria

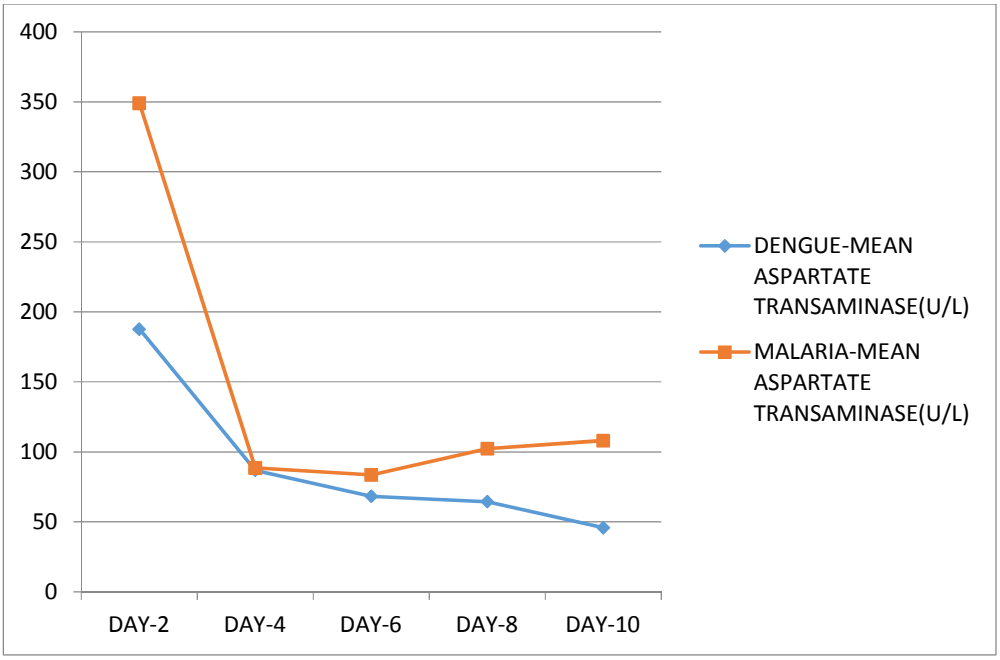

Fig. 9. Comparison of aspartate transaminase in dengue and malaria

Male predominance was noticed in both groups but more in malaria group which was similar to study done by Epelboin et al. [8], who also noticed a male predominance among malaria group i.e. 77.9% as compared to 57.2% in dengue group. This might be due to outdoor profession of males, and are exposed to more risks of mosquito bites and females are mostly housewives in our country.

Patients with dengue presented earlier as compared to malaria group. The mean duration

of presentation in dengue patients was 4.11±1.42 days while it was 4.84 ± 1.58 day in malaria group. This may be explained by early onset of severe constitutional symptoms in dengue patients.

Most common clinical symptom among the patients in our study was generalized weakness (78%) followed by nausea-vomiting (63.5%), myalgia (51.5%), headache (49%), rash (42%) and abdominal pain (40%). These finding correlated well with the Malaysian study by Tong et al. [9] while it contradicts the Indian study by Kumar and Chandra [10] in Uttar Pradesh, India.

The patients in dengue group frequently had rash, dyspnoea, bleeding tendencies, tourniquet test positivity, ascites and respiratory abnormalities while malaria patients presented frequently with abdominal pain, jaundice, diarrhoea, pallor. Icterus (20.5%), hepatomegaly (17%) and splenomegaly (26.5%).Our study contradicts the study done by Handargal et al. [11] in their malaria cases who noted icterus (2%), splenomegaly (6%) and hepatomegaly (3%) in their patients. Prevalence of petechie-purpura was noted in 29% of the patients in our study which correlates with the study by Dash et al. [12].

Tourniquet test positivity in dengue group was 42.2% in our study, which is similar to study by Mourao et al. [13] from Brazil, while Gomber et al. [14] from India found tourniquet test positivity in lesser number of patients. Tourniquet test was positive in 27.3% of the malaria patients also which suggests that tourniquet test is neither specific nor sensitive for diagnosis of the dengue.

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 initially WBC count was high on 2nd day which gradually settles to normal by 10th day. Malaria patients had significantly low haemoglobin and haematocrit values as compared to their dengue counterparts that can be explained by direct invasion of erythrocytes by plasmodium resulting in lysis of infected cells [15] and the RBC becomes more irregular in shape, more antigenic, and less deformable [16] and therefore become more prone to haemolysis.

Sever thrombocytopenia (platelet count ≤50,000/µL) was present in 90% of dengue patients while 75% of malaria patients. This was in consensus with the findings by Irfan Arshad et al. [17] from Pakistan and Palange et al. [18] from Maharashtra, India. 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. Both non-immunological destruction, splenic sequestration, shortened platelet survival and immune mechanism involving specific platelet-associated IgG antibodies that bind directly to malarial antigen in the platelets have been suggested to play a role in the lysis of platelets. [19-21] and by bone marrow suppression leading to decreased platelet synthesis [22]. Bleeding manifestations like Petechie-purpura, melena, bleeding per rectum, gum bleeding, haematuria, menorrhagia or epistaxis were more frequently seen among patients having platelet count ≤20,000/µL.

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, 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 dengue. Out of the 90 patients of dengue, 33 were discharged before 10th day of illness while rest of 55 were discharged on or after 10th day of illness, 2 patients succumbed to illness. Patient with malaria had a late recovery with 36 out of 44 patients being discharged on or after day 10 of illness.

5. CONCLUSIONS AND RECOMMENDA-TIONS

Dengue and malaria are the most common febrile illness in Northern India during rainy session (May to September).

Both can present with acute febrile illness with derangement of haematological, parameters, liver function tests and renal function tests.

Specific diagnosis may not be possible in all cases due to lack of expertise, laboratory and financial constrains.

The course of both diseases were observed for ten days in our study and found that dengue patients presented earlier due to sever

constructional symptoms than malaria. Generalized weakness, body ache, headache, nausea and vomiting were the common features in both diseases.

The patients of dengue frequently had rash, dyspnoea, bleeding tendencies, ascites and respiratory abnormalities while malaria patients presented more frequently with abdominal pain, jaundice, diarrhoea, pallor, icterus, hepatomegaly and splenomegaly.

White blood cells count showed initial rise in malaria and fall in dengue. Platelet fall was more sever in dengue as compared to malaria, so was bleeding tendencies. Bleeding tendencies were more frequent when the platelet count was below 20,000/µL.

Transaminase levels were more severely deranged and manifested early in malaria, while serum creatinine and blood urea were more deranged in dengue. Both these biochemical abnormalities return to normal by 10th day of illness.

We conclude that changes in these clinical, haematological and biochemical parameters can suggest some differentiation between malaria and dengue which may be very useful in remote areas or when facilities for specific diagnosis are limited or not available.

CONSENT

Consent of all patients taken prior to enrolment into the study.

ETHICAL APPROVAL

Ethical approval was taken from ethical committee of Lady Harding Medical College.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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