A study of the alteration in hematological parameters and liver function test with respect to the severity of dengue fever

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ABSTRACT

Background: Dengue is considered to be most common arboviral disease worldwide. Dengue is associated with major changes in haematological profile of patients. Even though liver is not the major target organ, findings such as hepatocellular necrosis and inflammatory cell infiltration have been identified in liver biopsy specimens of patients with Dengue and it is reflected by the derangement in liver enzymes. **Aims and Objective:** To study the alteration in hematological parameters and derangement of liver function test with respect to the severity of dengue fever. **Materials and Methods:** A prospective cohort study was conducted at tertiary health care centre Era's Lucknow Medical college and Hospital during the dengue outbreak occurring from 2017 to 2019. **Results:** Of the 324 patients; 228 patients were adjudged to be classical dengue fever whereas 87 belonged to dengue haemorrhagic fever. Mortality rate was 2.8% as all the 9 cases of DSS had fatalities due to multi-organ failure. Out of 321 cases having thrombocytopenia, 162 patients had mild, 108 patients had moderate and remaining 51 patients had severe thrombocytopenia. A statistically significant association was found between the age groups and severity of thrombocytopenia. Also, a significant correlation of degree of thrombocytopenia with the severity of the disease was observed. While performing liver function tests, we found an increase in ALT levels in 237 patients and raised AST in 231 patients. Elevation in both the transaminases showed strong, statistically significant correlation with the severity of liver disease and dengue. **Conclusion:** Thrombocytopenia and raised transaminases are good markers for the assessment of severity of dengue viral infection.

Key words: Dengue fever; thrombocytopenia; liver damage

INTRODUCTION

Dengue fever re-emerged in past 20 years with an expanded geographic distribution of the viruses and emergence of dengue hemorrhagic fever in new geographic regions.[1] In the past few decades, the total number of arboviral epidemics has significantly increased.[2] With increased epidemic transmission, hyper-endemicity developed in Southeast Asian cities and epidemic dengue hemorrhagic fever (DHF) emerged.[3-5] Characteristic findings in dengue fever are thrombocytopenia, leukopenia, and elevation of hematocrit values. However, in the last few years, atypical manifestations of dengue epidemic have been described, including involvement of the hepatic tissue with elevations in aminotransferase levels.[6]

This study was proposed to shine a light on newer manifestation for e.g. hepatic involvement by dengue viral infection.

The various objectives supposed to be achieved at the end of the study were to study the demographic picture of the viral disease at the tertiary health care center and the correlation of the severity of the parameters with respect to age, gender and severity of disease.

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MATERIALS AND METHODS

A prospective cohort study was conducted at tertiary health care centre Era's Lucknow Medical college & Hospital during the dengue outbreak occurring from September 2017 to July 2019. All patients with acute febrile illness, admitted with symptoms like headache, body ache, myalgia, arthralgia, retro orbital pain, abdominal pain, nausea and vomiting, bleeding from any site, hypotension or thrombocytopenia were tested for dengue.

The study enrolled 526 patients of suspected dengue of whom 324 were confirmed by serum NS1 antigen detection.

Proper history along with clinical examination (including the tourniquet test) were performed. Haematological and biochemical investigations were done at the time of admission and were followed on daily basis as and when required until discharge.

Chest radiograph, abdominal ultrasonography and change in haematocrit values were evaluated to assess the plasma leakage. Patients presented with sign of neurological manifestation, hepatic dysfunction, cardiac involvement, pancreatic or dermatologic features were worked up accordingly and classified as having dengue fever, dengue haemorrhagic fever or dengue shock syndrome in accordance with WHO guidelines.

Ethical committee clearance

The patients' anonymity was maintained as only the unique hospital identification number of the patient was recorded for the purpose of study along with age and sex. The data available of dengue patients was analysed. This study was approved by the Hospital Ethical Committee.

RESULTS

Out of 324 confirmed cases of dengue, 204 were males and 120 were females (Table 1).

82 patients were of less than 18 years i.e., in paediatric age group, 78 patients belonged to age group of 18-25 years, 96 to age group of 26-50 years and 68 were more than 50 years of age (Table 1).

Average duration of hospitalization was 6.25 days. 228 (70.4%) patients were adjudged to be classical dengue fever whereas 87 (26.8%) belonged to dengue haemorrhagic fever. Mortality rate in our study was 2.8% (9 cases) and all fatalities were due to multi-organ failure probably due to DSS (Chart 1).

Table 1: Age-wise & Gender-wise distribution of patients

Sr.No	Age group	Male	Female	No.of patients
1	<18 years	50	32	82
2	18-25 yrs	49	29	78
3	26-50 yrs	58	38	96
4	>50yrs	47	21	68
		204	120	324
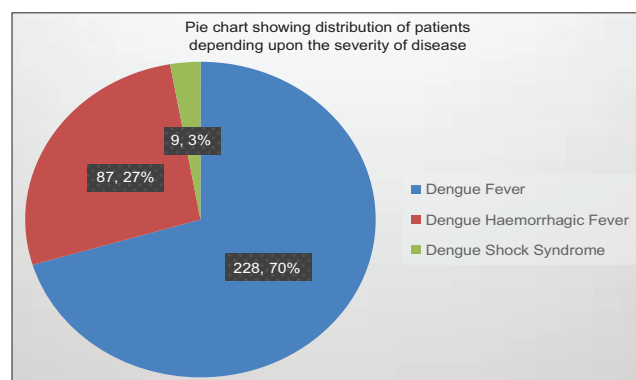
Chart 1: Pie chart showing distribution of patients depending upon the severity of disease

Among the common presenting symptoms, headache and fever was present in all patients, retro-orbital pain in 211 (65%) patients, nausea and vomiting in 185 (57%) patients and body ache, itching and rashes were recorded in 279 (86%),143 (44%) and 250 (77%) cases respectively. 169 (52%) patients presented as acute gastroenteritis and hepatomegaly was observed in 237 cases (73%). Third space fluid collections in the form of ascites were evident in 224 (69%) cases whereas pleural effusion was seen in 231 (71%).

In this study, we found patients suffering from thrombocytopenia (platelet count <1 lakh) in 321 (99.07 %) cases; only 3 cases out of 324 were found to have platelet counts towards the lower side of normal range (platelet counts between 1 to 1.5 lakhs) ; others all had mild to severe thrombocytopenia during the course of the disease. Further, depending upon the platelet counts, thrombocytopenia had categorised as mild (platelet counts between 51,000 and 1 lakh), moderate (platelet counts between 21,000 and 50,000) and severe (platelet counts <20,000). Out of 321 cases, 162 patients had mild thrombocytopenia (50.46%), 108 patients had moderate thrombocytopenia (33.64%) and remaining 51 patients had severe thrombocytopenia (15.88%). The severity of thrombocytopenia showed correlation with age of the patients. A statistically significant association was found between the age groups and severity of thrombocytopenia as p values come out to be <0.001 which is shown in Table 2.

We also found that there is a strong correlation of degree of thrombocytopenia with the severity of the disease as all patients suffering from DSS had severe degree of thrombocytopenia; similarly, more patients from DHF as compared to dengue fever have severe thrombocytopenia; which is statistically significant and shown in the Table 3.

In this study we found leukocytopenia in 256 cases approximating 79 % of the total patients, which shows that along with thrombocytopenia; leukocytopenia is also a marker of this viral infection and should be taken into account while discussing the differential diagnosis of the infection.

While performing liver function tests, we found an increase in ALT levels in 237 patients (73%) and raised AST in 231 patients (71 %). Both ALT and AST were raised in all the 9 cases (100%) of DSS; among which 3 cases (33%) had both enzymes raised to an extent that the values were >1000 IU/L whereas 6 cases (67%) had ALT values in the range of 500 IU/L – 1000 IU/L and AST values between 590 IU/L – 1000 IU/L. 83 cases (95%) out of total 87 DHF patients showed elevated ALT levels, in which 68 cases (82%) had ALT values in between 50 IU/L – 500 IU/L and rest 15 patients (28%) had values between 500 IU/L - 1000 IU/L. Similarly, 77 cases out of 87 patients were showing raised AST values, among whom 65 cases (78%) showed values between 59 IU/L – 590 IU/L, and remaining 12 cases (22%) had values 590 IU/L -1000 IU/L. 145 patients out of 228 Dengue fever cases had raised transaminase values accounting for 64% cases of DF but all showed values in the range of 50 IU/L – 500 IU/L for ALT and 59 IU/L - 590 IU/L for AST signifying lesser hepatic injury in cases of dengue fever as compared to DHF and DSS. Elevation in both the transaminases

showed strong, statistically significant correlation with the of severity of disease as shown in table and chart 2 and thus gave an important impression of involvement of hepatic tissues by the viral infection.

DISCUSSION

In our study among the typical manifestations, headache and fever was present in all 100% patients and retro-orbital pain in 65% patients. A Laul et al. in their study also found that 87% of patients had headache as chief complaint and 41% had typical retro-orbital pain.[7]

Abdominal symptoms are important in dengue fever. In present study, 52% patients presented as acute gastroenteritis and nausea and vomiting were documented in 59 %. The similar problems were seen in 70% of patients in study by Nimgadda et al.[8]

In our study thrombocytopenia is found in 99% cases, 50.46% patients had mild thrombocytopenia, 33.64% patients had moderate thrombocytopenia and remaining 15.88% patients had severe thrombocytopenia. A statistically significant association was found between the age groups and severity of thrombocytopenia in our study as it's more severe in paediatric age group (age less than 18 years).

Similar results are seen in previous studies. Study done by K. Jayashree et al showed that 70% cases had thrombocytopenia (<1L) while the remaining 30% had normal platelet counts .The distribution of cases having thrombocytopenia was, 36 patients had (48.64%) had mild thrombocytopenia (counts between 51,000 and 1 lakh)), 31 patients (41.89%) were suffering from moderate thrombocytopenia (counts between 21,000 and 50,000) while 7 patients (9.45%) had platelet counts <20,000 i.e. were suffering from severe thrombocytopenia. This study also put light upon age related severity of thrombocytopenia as severe thrombocytopenia was observed in age groups of <18 years than in the older age group and this difference was significant (*P* < 0.05).[9] Other studies also

Table 2: Correlation of age with severity of thrombocytopenia

Sr.No.	Age (Years)	Severity of thrombocytopenia		
		Mild	Moderate	Severe
1	<18	29	37	26
2	18-25	45	23	10
3	26-50	69	21	6
4	>50	30	27	9
Total		173	108	51

Table 3: Correlation of degree of thrombocytopenia with the severity of the disease

Sr.No.	Severity of Dengue	Thrombocytopenia		
		Mild	Moderate	Severe
1	Dengue Fever	162	60	3
2	Dengue Haemorrhagic Fever	0	48	39
3	Dengue Shock Syndrome	0	0	9
	Total	162	108	51
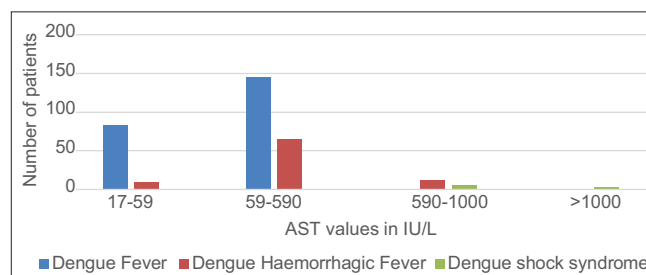
Chart 2: Correlation of raised Aspartate aminotransferase values with severity of disease

show similar results as an another study done by Khan et al, out of 76 patients with thrombocytopenia (platelet count <1 lakh), 38 (50.0%) had mild thrombocytopenia (platelet count 51,000 – 1 lakh), 28 (36.8%) had moderate thrombocytopenia (platelet count 20,000 – 50,000) and remaining 10 (13.2%) had severe thrombocytopenia (platelet count < 20,000). Thrombo-cytopenia was found to be more severe in age group <15 years, when compared to other age groups. A statistically significant association (p<0.05) was found between the age groups and severity of thrombocytopenia.[10] In another study, thrombocytopenia was found in 54% of the cases but age correlation was probably not studied.[11] Similarly, study done by Kishore, J et al revealed thrombocytopenia in 80% of cases.[12]

In a study correlating leukocyte count along with platelet count with course of disease shows that the lowest blood counts values throughout the course of illness were Hb: 13.2 +/- 1.9 gm/dl, WBC: (2.77 +/- 1.63) x 10^3/mm^3, Platelet: (8.7 +/- 5.5) x 10^4/mm^3. Leukopenia (WBC less than 4000/mm^3) was present in 38 (76%) of the cases,[11] which observation is quite similar to what we found in our study as 79 % of the cases showed Leukopenia.

In our study we found hepatomegaly in 73% patients with an increase in ALT levels in 67% and raised AST in 63%. All the 9 cases (100%) of dengue shock syndrome showed both elevated ALT and AST values; among which 3 cases (33%) had both enzymes raised to an extent that the values were >1000 IU/L. Remaining 6 cases accounting 67% of the all DSS had ALT values in the range of 500 IU/L – 1000 IU/L while in the same patients the AST values were between 590 IU/L – 1000 IU/L. Out of total 87 dengue haemorrhagic patients, 83 cases which accounts to 95% of the DHF cases showed elevated ALT levels; out of which 15 cases (28%) had ALT values in between 500 IU/L - 1000 IU/L while remaining 68 patients (82%) had values between 50 IU/L – 500 IU/L. Similarly, 77 cases out of 87 patients were showing raised AST values. Only 12 cases (22%) had values 590 IU/L -1000 IU/L whereas 65 cases (78%) showed values between 59 IU/L – 590 IU/L. Among 228 Dengue fever cases 145 patients had raised transaminase values accounting for 64% cases of DF but all showed lesser elevation in the values of transaminases ranging between 50 IU/L – 500 IU/L for ALT and 59 IU/L - 590 IU/L for AST signifying lesser hepatic injury in cases of dengue fever as compared to DHF and DSS. Elevation in both the transaminases showed strong and statistically significant correlation with the severity of disease; thus, gave an important impression of involvement of hepatic tissues by the viral infection.

Yet another study conducted by Kuo et al on liver enzymes of dengue patients also observed abnormal levels of AST and ALT in 93.3% and 82.2%, respectively in 270 seropositive cases in their study mild to moderate rise in transaminase levels was found in most of the cases, but AST levels reached 10 times above the normal upper limit in 11.1% and 7.4% of the patients showed similar rise of ALT levels. In their study it was observed that the rise in AST levels was usually greater than for ALT, which comes to normal values in three weeks' time. This observation could be due to myocyte damage during dengue infection which causes release of AST.[13] Similarly, one another study Souza LJ et al, showed liver damage was greater in patients with DHF; acute hepatitis (grade D) was diagnosed in 8.5% of these patients. Hemorrhagic form of the disease showed greater increase in mean values of AST and ALT.[14] In a study done by Wahid et al. for 50 serologically confirmed cases in which 25 cases were of classic dengue and 25 were of DHF, serum levels of AST and ALT were found significantly greater among patients with the hemorrhagic form of the disease.[15]

Linda k et al showed that 595 (86%) cases had AST above the upper normal limit whereas 316 (46%) cases had ALT above the upper normal limit. Seven patients (1.0%) were categorised having severe dengue according to WHO 2009 criteria concurrent with AST or ALT≥1000 U/L while three additional patients had severe dengue on the basis of elevated AST or ALT≥1000 U/L levels only.[16]

CONCLUSION

There are plenty of studies done on dengue patients relating hematological parameters and liver tissue involvement with severity of disease but any single parameter was not found to assess the severity of disease moreover the atypical manifestation has created another world of complexity to management and prognosis of the patients. In our study we tried to find the correlations between different parameters and severity and prognosis of disease.

One among the hematological parameters is platelet count which seems to have certain correlation with respect to the severity of disease and thus can be used in two ways; one as assessment of the severity of the disease depending upon which treatment can be modified and second for the overall prognosis as all the 3 fatal cases, we found in our scenario had also severe thrombocytopenia. Similarly, hepatic involvement which was assessed in our study by assessing the liver enzyme assays, showed that in severe cases the enzyme values were very high, so we can say that in severe form of the disease more intense involvement of the hepatic tissues can be seen.

Thus, in nutshell both thrombocytopenia and raised transaminases are good markers for the assessment of severity of dengue viral infection.

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Author's Contributions
KT - Concept and design of the study; prepared first draft of manuscript; **SA -** Statistically analysed and interpreted the result, reviewed the literature and manuscript preparation; **SI -** Concept, coordination, review of literature and manuscript preparation; **AS -** reviewed the literature and revision of the manuscript; **HP -** revision of the manuscript.

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