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Research Article

Clinical and laboratory profile of different dengue sub types in dengue virus infection

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ABSTRACT

Background: Dengue infection, an arthropod-borne viral hemorrhagic fever is caused by *Arbovirus* of *Flavivirus* genus and transmitted by *Aedes aegypti*, *Aedes albopictus.* Liver involvement in dengue fever is manifested by the elevation of transaminases representing reactive hepatitis, due to direct attack of virus itself or the use of hepatotoxic drugs. The objective of the study was to investigate clinical and laboratory profile of different dengue sub type's patients admitted for dengue fever.
Methods: All the adult patients with clinical features such as fever and later confirmed positive by dengue serology test admitted as inpatients were included in the study. Vitals parameters and systemic examination were performed. Investigation of dengue serotology, liver function test, routine investigations like hemoglobin percentage, total count, ESR, packed cell volume, platelet count, partial thromboplastin and activated partial thromboplastin time, blood urea, serum creatinine, and blood sugar estimation were done.
Results: On comparison of clinical signs in different dengue subgroups it was observed that the mean value of pulse, blood pressure and respiratory rate were significantly more deranged in the DSS group as compared to the DF group. Platelet count was significantly lower in all the sub groups whereas PT/aPTT was more dearranged in the DSS and DHF group as compared to the DF group. Comparison between the mean values of liver function test in different dengue sub groups had been shown, elevated transaminases, hypoproteinaemia and hypoalbuminaemia, in higher frequency in dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) as compared to classical dengue fever (DF) (P values significant). SGOT was significantly higher than the SGPT levels and SGOT was much more elevated in the DSS sub group compared to the DFS and DF group.
Conclusions: The liver enzymes serum aminotransferase levels were significantly raised in patients with dengue shock syndrome compared to other two groups. Serum aminotransferases directly correlate with severity of infection in all the sub groups. Patients with secondary dengue infection were more prone for developing bleeding manifestations and shock syndrome.

Keywords: DHF, DSS, DF

INTRODUCTION

Dengue infection, an arthropod-borne viral hemorrhagic fever, continues to be a major challenge to public health, especially in South-East Asia.[1] It is one of the world's most common viral hemorrhagic fever disease, most geographically widespread of the arthropod-borne virus illnesses. Throughout the tropics this infection has an annual incidence of 100 million cases of DF with another 2,50,000 cases of DHF and mortality rate of 24000-25000 per year.

Dengue is caused by *Arbovirus* of *Flavivirus* genus with 4 serotypes (DENV-1, DENV-2, DENV-3, DENV-4) of

the family Flaviviridae which are the most important arbovirus diseases in humans, in terms of geographical distribution, morbidity and mortality. It is transmitted by *Aedes aegypti, Aedes albopictus, Aedes polynesiensis* and several species of the *Aedes scutellaris* complex. Each of these species has its own particular geographical distribution and they are in general less efficient vectors than *Ae. aegypti*. Transovarian transmission of dengue viruses has been documented but its epidemiological importance has not been established.[2]

All four dengue serotypes are capable of causing dengue fever or DHF, depending on the immune status and probably age of the host, as DHF occurs almost exclusively in children under the age of 16 years and is associated with secondary dengue infection.

4 spectra of illness are seen; an asymptomatic phase, acute febrile illness, classic dengue fever (DF), dengue hemorrhagic fever (DHF) which includes dengue shock syndrome (DSS). Dengue is also categorizes in primary and secondary dengue infection in which a secondary infection of dengue carries a greater risk of dengue hemorrhagic fever and dengue hemorrhagic shock as compared to the primary infection of dengue as shown by few studies.[3,4]

Though dengue is subdivided into new WHO classification into 3 groups and with or without warning signs but the new classification lacks specificity so in our present study the old classification is taken into account.

The involvement of liver in dengue fever is not uncommon as reported in literature since 1970. In most cases, hepatic involvement prolongs the clinical course of this self-limiting viral infection, but it does not constitute a sign of worse prognosis.[2,5] Atypical manifestations include liver involvement with elevation of enzymes, central nervous involvement (encephalopathy) and cardiac alterations (myocarditis). Liver involvement in dengue fever is manifested by the elevation of transaminases representing reactive hepatitis, due to direct attack of virus itself or the use of hepatotoxic drugs.

The objective of the study was to investigate clinical and laboratory profile of different dengue sub type's patients admitted for dengue fever.

METHODS

The study was performed on patients admitted for dengue fever in Aarupadai Veedu Medical College, Puducherry, India from June 2013 to May 2014.

Inclusion criteria

All the adult patients with clinical features such as fever & later confirmed positive by dengue serology test admitted as inpatients will be included in the study.

Exclusion criteria

- Age >18 years.
- Chronic liver disease.
- Viral hepatitis (Hepatitis B, Hepatitis C).
- Malaria (MP, MF).
- Leptospirosis.
- History of Hepatotoxic drugs.
- History of alcohol abuse.

All patients were evaluated with detailed history including age, sex, presenting symptoms; history of co morbid illness; alcohol consumption and use of hepatotoxic drugs were noted. The World Health Organization (WHO) grading system was used to classify patient as having classic dengue fever (DF) and dengue hemorrhagic fever (DHF).[6] DHF was defined as fever with thrombocytopenia (platelet count less than 100,000/mm^3) and evidence of plasma leakage as manifested by either increase in hematocrit of ≥20% during the course of hospitalization or a rise in hematocrit to more than 20% of baseline (average normal no.)

Examination

Vitals parameters and systemic examination were done.

Investigations

The following investigations were done with special emphasis;

Dengue serology

Done by immunochromatographic method.

Liver function test

AST and ALT was estimated by IFCC (International Federation of Clinical Chemistry) without pyridoxal phosphate activation. Total bilirubin, total protein, albumin and ALP were estimated by colorimetric assay.

Routine investigations

Hemoglobin percentage, total count, ESR, packed cell volume (PCV), platelet count, PT and APTT, blood urea, serum creatinine, and blood sugar estimation was done.

RESULTS

The study was done in Aarupadai Veedu Medical College and Hospital. 60 Dengue IgM positive patients were included in the study after they had fulfilled the inclusion and exclusion criteria.

The study period was for 2 years. Of 60 patients reactive for dengue virus specific IgM antibody, dengue virus-specific IgG antibody was also positive in 20 (33.33%)

patients. As per WHO classification (1997), 45 (75%) patients were classified as dengue fever, 10 (16.66%) as dengue hemorrhagic fever, and 5 (7.1%) as dengue shock syndrome.

Mean age of dengue fever in patients was 34.63±13.28. Maximum numbers of patients were seen in the age group of 21 to 30 years i.e. 20 patients.

The study group included 32 females and 28 males, with female is to male ratio nearly equal. The sex distribution of patients with dengue infection is shown in Figure 1.

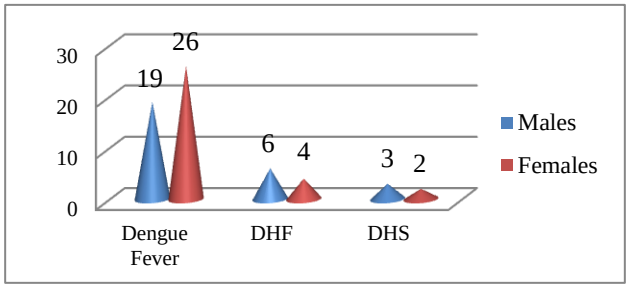

Figure 1: Sex distribution of dengue sub groups.

Statistically the difference of parameters between males and females was not significant.

The main symptoms were fever which was present in all the patients (100%), headache in 47 patients (78.33%), myalgia 33 patients (55%), arthralgia 32 (53.33%), hemorrhagic manifestations in 26 patients (43.33%), vomiting in 20 patients (33.33%), and abdominal patients 16 (26.66%).

Fever and headache was present in all the dengue subgroups. Occurrence of retro-orbital pain, arthralgia, myalgias, vomiting, pain abdomen and hemorrhagic manifestations were statistically significant in DHF and DSS Compared to classical dengue fever patient. Haemorrhagic manifestation was present in 43% of the patients and was absent in 57% of the total patients.

Bleeding manifestations were further subdivided into major and minor groups which are shown in Figure 2.

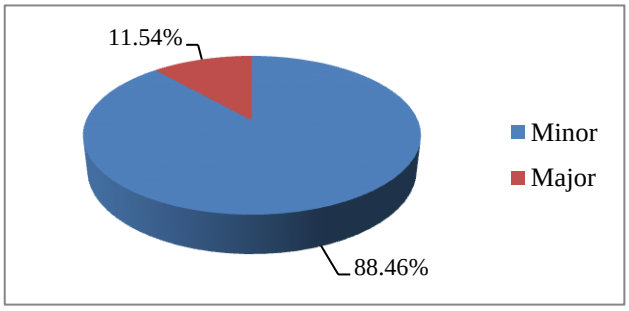

Figure 2: Major and minor hemorrhagic manifestation.

Various types of minor bleeding manifestations like, petechial rash, bleeding gums, epistaxis, erythymatous rash were observed in patients (Table 1). Petechial rash was the most common hemorrhagic manifestation 8 (30.76%) followed by bleeding gums 5 (19.23%) which was most common site of hemorrhage. Table 3 shows major and minor bleeding manifestation in different dengue sub groups.

Table 1: Bleeding manifestation in different dengue sub groups.

Bleeding manifestations	Minor(n=23)	Major (n=3)	P value
DF	13	0	0.0513
DHF	10	0	0.048
DSS	0	3	0.00024

It was observed that patients with dengue shock syndrome were in much higher risk for bleeding tendencies as compared to those in the other two groups. It was also observed that patients with secondary dengue infections had a much higher incidence of bleeding as compared to the primary dengue infection of dengue.

Table 2: Clinical signs in different dengue sub groups.

Variables	Temperature	Pulse rate	Respiratory rate	SBP	DBP	p value
DF	97.28±2.772	78.789±3.495	18.552±0.828	116.285±3.39	76.985±2.354	0.8431
DHF	98.49±2.71	87.032±4.212	18.822±0.514	118.984±4.899	77.36±3.384	0.065
DSS	98.754±0.102	102.65±0.324	19.546±0.097	106.75±1.687	75.249±3.257	0.0387

On comparison of clinical signs in different dengue subgroups i.e. DF and DHF, it was observed that the mean value of pulse was significantly different in the two groups. Pulse, blood pressure and respiratory rate were significantly more deranged in the DSS group as compared to the DF group. When compared to DF and DHF, DSS has the significant value (0.0387) than DF and DHF (Table 2).

After measuring blood pressure in the patients it was observed that the patient in the DSS group had lower systolic blood pressure and diastolic blood pressure than

those patients in the DHF and DF group. The patients who were both secondary infection, they had a higher frequency of hypotension as compared to other group which was only primary infection.

When of hematological parameters were compared between various dengue sub groups, it was noted that PCV was significantly increased in DHF and DSS group as compared to the DF group. Platelet count was significantly lower in all the sub groups whereas PT/aPTT was more dearranged in the DSS and DHF group as compared to the DF group (Table 3).

Table 3: Comparison of hematological parameters between different dengue sub groups.

	PCV Increased	Total platelet count decreased	PT/aPTT3 Increased	P value
DF (N=45)	6	40	3	0.054
DHF (N=10)	4	10	6	0.026
DSS (N=5)	4	5	3	<0.001

Comparison between the mean values of liver function test in different dengue sub groups had been shown elevated transaminases, hypoproteinaemia, and hypoalbuminaemia, were seen in higher frequency in DHF and DSS as compared to classical DF (P values significant). We can see that SGOT was significantly higher than the SGPT levels and SGOT was much more elevated in the DSS sub group compared to the DFS and DF group (Table 4).

Table 4: Comparison of liver function test in dengue sub groups.

Variables	DF	DHF	DSS	P value
Total bilirubin	0.342±0.1332	0.64±0.108	1.375±0.188	0.036
Direct bilirubin	0.176±0.086	0.342±0.104	1.029±0.086	0.00532
Total protein	2.473±0.187	1.875±0.046	1.86±0.043	<0.0001
Albumin	1.299±0.144	1.191±0.068	0.975±0.05	0.0312
AST	72.64±27.633	126.36±30.24	410.47±190.38	<0.004
ALT	44.424±17.87	66.96±15.714	287.67±14.216	<0.0001

Of the 60 patients reactive for dengue virus specific IgM antibody, dengue virus specific IgG antibody was also positive in 20 patients. As per WHO guidelines 1997, 45 patients were classified as dengue fever, 10 as dengue hemorrhagic fever, and 5 as dengue shock syndrome (Figure 3).[6]

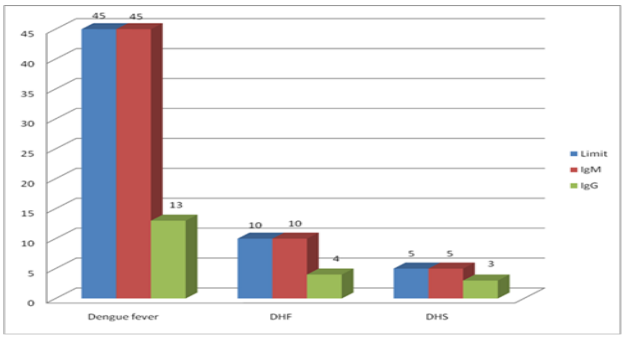

Figure 3: Comparison of primary and secondary infections in dengue.

The frequency of secondary infection is significantly higher in the DSS sub group as compared to the DHF and DF sub groups and it was statistically significant.

By comparing numbers of days of hospital stay in different dengue sub groups, it was noted that the number of days of hospital stay is significantly higher in the DSS group when compared to the DHF and DF group (Table 5).

Table 5: Number of days of hospital stay in different dengue sub groups.

Disease	Males (no. of days of hospital stay)	Females (no. of days of hospital stay)	P value
Dengue fever	03	04	0.046
DHF	04	06	0.0074
DSS	07	08	0.0032

DISCUSSION

The biochemical impact of dengue virus on liver function was studied in 60 serologically confirmed cases of dengue IgM infection. In this study, DHF and DSS were present in 16.66% (10) and 7.1% (5) patients respectively. This is as with the results of a recent study from Punjab done by Chhinaet al (DHF and DSS in 13.6% and 5.1% respectively) and from Delhi done by Makroo et al (DHF and DSS in 9.3% and 2.2% respectively).[7,8] However a few other studies had reported a higher percentage of DHF.[9,10]

The mean age of patients in our study was 34.63± 13.28 years, with male to female ratio being near equal. In a recent study done by Chhina et al mean age was 31.6 years with a range of 15 to 80 years, with predominant male patients (male : female ratio = 3.3:1).[7]

The commonest symptom in our patient was fever (100%), followed by headache (78.33%), myalgia (55%), arthralgia (53.33%), vomiting (33.33%), abdominal pain (26.66%) and hemorrhagic manifestations (43.33%). In a study done recently by Babaliche et al similar findings were present.[11] However in our study the symptomatology in the form of abdominal pain, vomiting, retro orbital pain and hemorrhagic manifestations were much higher in the DFS and DSS sub group compared to the DF group.

The dearrangement of clinical signs in the form of increased respiratory rate, increased pulse rate and decrease in the systolic and diastolic blood pressures were higher in the DSS sub group compared to the DF and DHF sub groups. It was also observed that the patient in DSS sub group had a longer hospital stay as compared to the DHF and DF sub group. It was also observed that those patients with both IgM and IgG positive antibody presented with hypotension and bleeding manifestation, subsequent shock than the patient who were only IgM positive. It was also observed that though platelet count was low in all the sub groups. PCV was significantly lower in the DSS sub group compared to the DFS and DF sub group.

Jaundice in dengue infection has been associated with fulminant liver failure and by itself is a poor prognostic factor.[12] In our study hyperbilirubinemia was significantly more common in patients with DSS and DHF when compared to DF patients with or without hemorrhage. Chhinaet al found Hyperbilirubinemia to be significantly more common in patients with DSS, DF patients with hemorrhage and innon-survivors.[7] Thus, observations support the fact that high bilirubin may act as a bad prognostic marker in patients with dengue infection.[7]

Biochemical liver dysfunction, in the form of increased transaminases, was found in most of the patients in our study 96.6% - 99.3%, similar to the results of Chhina et al (93.9%-97.7%) and other studies.[7,9,10,12]

The aspartate aminotransferase (AST) levels in dengue infection tend to be greater than alanine aminotransferase (ALT) levels.[14] Comparing the three subgroups of dengue infection (DF, DHF and DSS), it was observed that the frequency of liver dysfunction (raised AST, ALT and ALP) was equally common in all the groups. Similar results were noted in Ithaet al.[10] However, Wahid et al found liver dysfunction to be more common in DHF than in DF patients.[15] The severity of hepatic dysfunction in dengue infection has been associated with disease severity. In a study by Souza et al AST and ALT were deranged only in 63.4% and 45% patients respectively.[16] In our study, increased levels of ALP and serum bilirubin were noted in a smaller proportion of patients, as with the results of Chhinaet al and Itha et al.[7,10]

It was also observed that patients with 10 fold increases in SGOT and SGPT levels were more prone for dengue shock syndrome and bleeding manifestations.

In our study, the mean bilirubin, AST, ALT, total protein, albumin and coagulation profile values were significantly deranged in patients with hemorrhage as compared to those without. Chhina et al observed that the mean bilirubin, ALT and ALP values were significantly higher in patients with hemorrhage as compared to those without hemorrhage, and were even higher in those with GI hemorrhage.[7] Wahid et al also observed that the ALT and ALP levels were significantly higher in DHF patients with spontaneous bleeding than those without bleeding ($p < 0.05$).[15]

Patients with DHF and DSS had significantly raised PT and APTT values in our study. Chhina et al observed increased percentage of patients with deranged PT index significantly more in the DSS group as compared to the DF group.[7]

CONCLUSION

From the study we conclude that the liver enzymes serum aminotransferase levels were significantly raised in patients with dengue shock syndrome compared to other two groups. Serum aminotransferases directly correlate with severity of infection in all the sub groups. Patients with secondary dengue infection were more prone for developing bleeding manifestations and shock syndrome.

Though, platelet count was low in all the sub groups. PCV was significantly lower in the DSS sub group compared to the DFS and DF sub group.

Moreover, patients with secondary dengue infection were more prone for developing bleeding manifestations and shock syndrome. This emphasizes the importance of early identification and regular monitoring of such patients.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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