

Prediction of severity of dengue infection in children based on hepatic involvement

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Abstract: The aim of study is to know the severity of dengue illness in children based on range of hepatic involvement and to know relation between liver enzyme derangements and severity of dengue illness which can help in prognostication of the disease. This prospective observational study is conducted from January 2016 to December 2016. During the study period 100 cases of serologically diagnosed dengue fever cases were studied for liver involvement. Among these 100 cases 48 were classical dengue fever (DF) and 52 were severe dengue fever (SDF), 51% of the children were within 5-9 years of age. Deranged total bilirubin, serum albumin, AST, ALT and ALP were present in 23%, 79%, 87%, 73% and 80% of patients respectively. The mean total bilirubin and serum albumin levels were 1.48 mg/dl and 2.9 gm/dl respectively. The mean Aspartate Transaminase (AST), Alanine Transaminase (ALT) and Alkaline Phosphatase (ALP) values were 415.7 U/L, 253U/L and 243.8U/L respectively. AST levels were significantly elevated compared to ALT levels. The degree of liver function derangement is significantly high in SDF group as compared to DF group. Mortality is observed in 3(3%) cases. Elevated AST level can be used as a good positive predictive factor in the prognostication of Severe Dengue Fever.

Keywords: Dengue fever, severe dengue fever, hepatomegaly, AST, ALT and ALP.

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I. Introduction

Dengue is the most common mosquito borne, endemo-epidemic arboviral infection in many tropical and subtropical regions of the world. In the past 50yrs, the prevalence of dengue fever has increased 30 fold with increasing geographic expansion to new countries and from urban to rural settings. Up to mid 20th century it is considered as mild febrile illness, however the image of dengue underwent a drastic change in the mid 1950s. By 1975 it had become a leading cause of hospitalization and death among children in many countries^[1]. The recent epidemics in Srilanka and India were associated with multiple dengue virus serotypes, although DEN-3 is distinctly prominent. Dengue in its most severe form manifests clinically as dengue hemorrhagic fever (DHF) and dengue shock syndrome(DSS). Unusual clinical manifestations of dengue fever have become more common in the last few years. Although liver is not a major target organ, hepatic dysfunction is a well-recognized feature, often characterized by pain in the right hypochondrium, hepatomegaly, jaundice and raised aminotransferase levels. Case fatality rates vary from 1% to 5%, but can be <1% with early and appropriate treatment. It has many names like dandy fever, dengue, denge, dunga, break bone fever, bouguet, seven-day fever, chapenonad, tokkive-ana and coup-d-bare etc.,

II. Methodology

This study is a hospital based prospective observational study conducted from Jan 2016 to Dec 2016 at Dept. of Paediatrics, Government General Hospital, Siddhartha Medical College, Vijayawada, AP. There has been increasing incidence of dengue fever in recent years hence the following study is conducted in 100 patients of ages between 2months to 12years with dengue fever who were admitted and showed signs and symptoms of dengue fever and were also serologically dengue positive (NS1 & Dengue IgM positive) and there by detecting severity of dengue illness based on hepatic profile. Informed consent is taken from the parents. Inclusion criteria- all children between 2months to 12years who are NS1 & Dengue IgM positive are included in the study. Exclusion criteria - IgM negative dengue like illness, IgG positive for dengue, children with pre-existing liver diseases, children with concomitant infections affecting liver such as malaria, typhoid, hepatitis A and B, patients age <2 months and >12 years, parents who refused to give consent for the study. A detailed history and thorough clinical examination were performed in all cases. Data is collected in a predesigned, pretested proforma. The study population is subcategorized into dengue fever (DF) without and with warning signs as

Group 1 and severe dengue fever (SDF) such as dengue hemorrhagic fever and dengue shock syndrome as Group 2. All standard protocols for the diagnosis and treatment followed after admission^[2,3]. The association of hepatic involvement with severity of dengue illness is statistically analyzed with the help of Mann-Whitney U test with Z critical value of 1.645 at $\alpha=0.05$, Z score value more than Z critical value is taken as statistically significant. The incidence of clinical symptoms and signs of dengue illness are compared between DF and SDF groups with the help of Chi-square test of independence with p-value of <0.05 taken as statistically significant.

III. Observations and Results

Dengue fever is primarily a disease of infants and children. In the present study mean age of presentation of DF and SDF were 6.87 and 6.3 years respectively. Out of 100 cases of dengue fever studied, 52 children showed some evidence of severe plasma leakage leading to shock, hemorrhagic tendencies or severe organ involvement, so the incidence of SDF in this study is 52% and DF is 48%. Hepatomegaly is the most common sign seen in 95% of cases followed by petechiae, splenomegaly, edema which were seen in 61%, 46% and 34% of cases respectively.

Table 1. Age wise distribution of total cases of dengue fever

Age (years)	DF (n=48)	Severe DF (n=52)	%
1-4	13 (27.1%)	17 (32.7%)	30
5-9	26 (54.2%)	25 (48.1%)	51
10-12	9 (18.7%)	10 (19.2%)	19

Table 2. Compares the various signs in DF and SDF.

Signs	DF n=48(%)	SDF n=52(%)	P=
Edema	12(25%)	22(42.3%)	0.067(NS)
Petechiae	24(50%)	37(71.2%)	0.03(S)
Hepatomegaly	44(91.7%)	51(98.1%)	0.14(NS)
Splenomegaly	15(31.3%)	31(59.6%)	0.004(S)

Chi-square test is used to analyze data

Petechiae(71.2%), splenomegaly(59.6%) were more common in children with severe dengue fever compared to dengue fever with a significant p value (<0.05). Hepatomegaly is slightly more common in children with severe dengue fever (98.1%) as compared to DF (91.7%) but has no statistical significance. Edema is seen in both groups at presentation.

Table 3. Various laboratory parameters observed in the study

Measurement	Mean	SD	Range	
			Min	Max
Hemoglobin	9.74	1.98	3.3	13.9
Haematocrit	31.7	7.24	13	52
Platelet count	1.09	0.62	0.11	3
Total bilirubin	1.48	1.47	0.5	8
Sr. albumin	2.9	0.59	2	4
AST	415.7	984.4	16	6758
ALT	253	576.5	16	3479
ALP	243.8	155.9	19	770

The mean hemoglobin, haematocrit and platelet counts at presentation were 9.74 gm/dl, 31.7 and 1.09 lakhs/cu.mm respectively. The mean total bilirubin, serum albumin, AST, ALT, ALP levels were 1.48 mg/dl, 2.9 g/dl, 415.7 U/L, 253 U/L and 243.8 U/L respectively.

Table 4. Compares the various biochemical liver parameters between DF and SDF.

Measurement	DF		SDF		DF Vs SDF		
	Mean	SD	Mean	SD	ZScore	Z crit	significance
Total bilirubin	0.69	0.25	2.19	1.73	6.05	1.645	significant
Direct	0.19	0.20	1.29	1.38	5.53	1.645	significant
Indirect	0.50	0.12	0.88	0.46	5.66	1.645	significant
Serum albumin	3.12	0.60	2.70	0.51	4.18	1.645	significant
AST	91.3	81.75	715.1	1292.6	6.0	1.645	significant
ALT	66.2	45.89	425.4	758.48	4.8	1.645	significant
ALP	163.7	75.61	317.7	173.41	5.39	1.645	significant

Mann-Whitney U test is used to analyze data.

All the liver function tests (total bilirubin, direct and indirect bilirubin, sr. albumin, AST, ALT and ALP) are deranged in children with severe dengue fever (SDF) compared to dengue fever (DF). Total bilirubin, direct and indirect bilirubin, albumin, AST, ALT and ALP derangements are highly significant with Z score values greater than Z critical value.

The degree of AST levels elevation is evaluated and classified into four grades. Grade A patients with normal AST levels (i.e.<40U/L). Grade B in whom AST levels are increased but not more than 3 times the normal value. Grade C whom AST levels are between 3 and 10 times the normal. Grade D in whom AST levels are elevated >10 times the normal. Higher levels of AST derangements are seen in patients with SDF compared to DF which is statistically highly significant with Z score value (=6) more than Z critical value (=1.64).

Table 5. Shows grading and comparison of AST/SGOT between DF and SDF.

AST (U/L)	Grades	DF (%)	SDF (%)
<40 (n)	A	27.1	0
40-120 (1-3)n	B	45.8	23.1
121-400 (4-10)n	C	27.1	48.1
>400 (>10)n	D	0	28.8

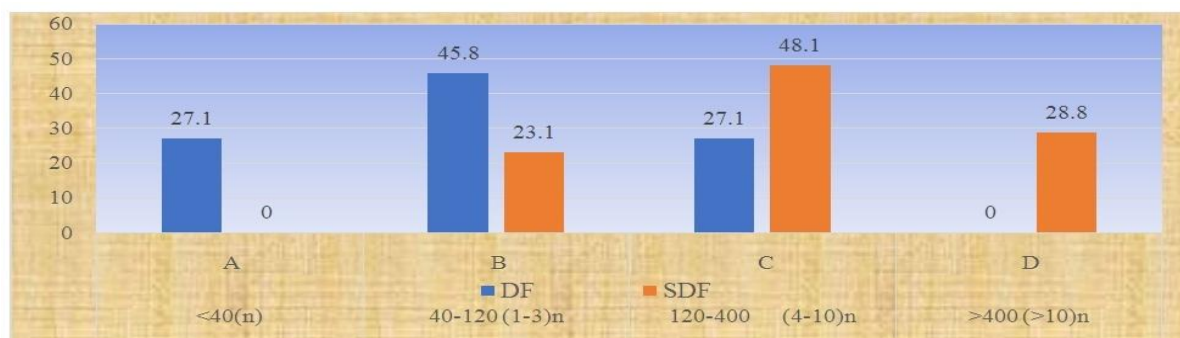


Fig 1. Shows AST levels in DF and SDF groups.

Table 6. Shows grading and comparison of ALT/SGPT between DF and SDF groups.

ALT (U/L)	Grades	DF (%)	SDF (%)
<40	A	37.5	17.3
40-120	B	45.8	25
120-400	C	16.7	40.4
>400	D	0	17.3

The degree of ALT levels elevation is evaluated and classified into four grades. Grade A with normal ALT levels (i.e.<40U/L). Grade B, ALT levels are increased but not more than 3 times the normal value. Grade C, levels are between 3 and 10 times the normal. Grade D, levels are elevated >10 times the normal. Higher levels of ALT derangements are seen in patients with SDF compared to DF which is statistically significant.

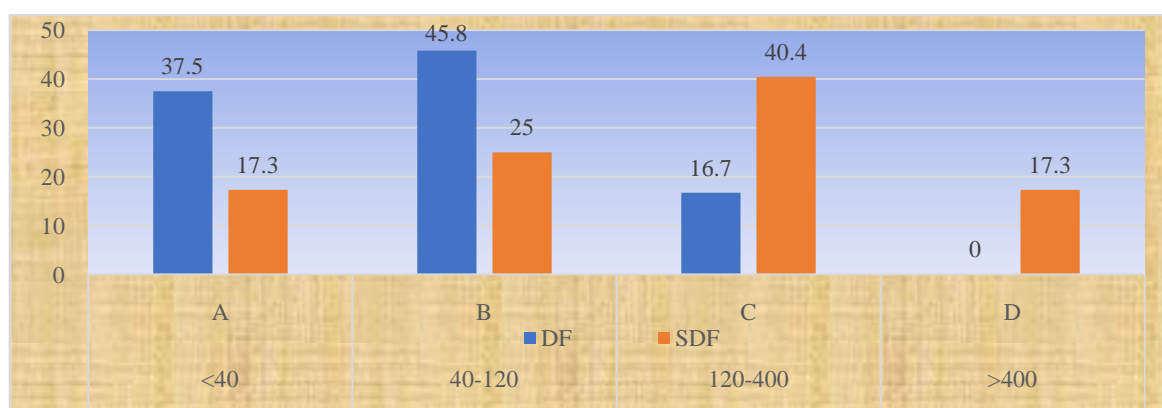


Fig 2. Shows ALT levels in DF and SDF groups.

Higher levels of alkaline phosphatase (ALP) are seen in patients with Severe dengue fever (SDF) compared to patients with dengue fever (DF) which is statistically significant (Z score > Z critical).

Table 7. Shows grading and comparison of ALP levels between DF and SDF groups.

ALP (U/L)	DF	SDF
<125	33.3%	7.7%
125-250	58.4%	28.8%
>250	8.3%	63.5%

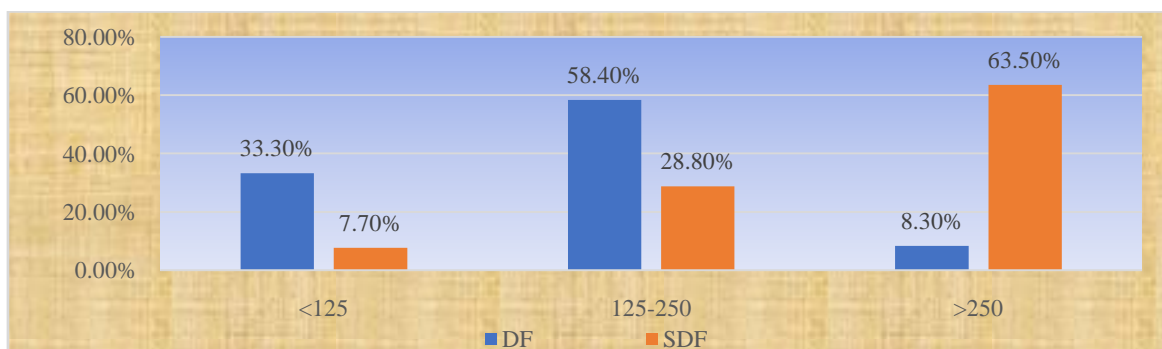


Fig 3. Shows ALP levels in DF and SDF groups.

Lower levels of serum albumin is seen in patients with severe dengue fever (SDF) compared to patients with dengue fever (DF) which is statistically significant (Z score > Z critical)

Table 8. Shows grading and comparison of serum albumin levels in DF and SDF.

Serum Albumin (g/dl)	DF	SDF
2.0-2.4	10.4%	36.5%
2.5-2.9	12.5%	30.8%
3.0-3.4	41.7%	26.9%
>3.5	35.7%	5.8%

Table 9. Correlation between Hepatomegaly and AST/SGOT levels:

Hepatomegaly	Normal AST	Abnormal AST	Row Totals
Present	10 (12.35) [0.45]	85 (82.65) [0.07]	95
Absent	3 (0.65) [8.5]	2 (4.35) [1.27]	5
Column Totals	13	87	100 (Grand Total)

Chi-square test is used to analyze data

The chi-square statistic is 10.27. The p-value is 0.0013, this result is significant with p-value <0.05. Hepatomegaly is significantly seen in patients with abnormal AST levels i.e., greater than 40U/L compared to patients with normal AST values(<40U/L), which is statistically significant with p-value <0.05.

Table 10. Correlation between Hepatomegaly and ALT/SGPT levels:

Hepatomegaly	Normal ALT	Abnormal ALT	Row Total
Present	24 (25.65) [0.11]	71 (69.35) [0.04]	95
Absent	3 (1.35) [2.02]	2 (3.65) [0.75]	5
Column Total	27	73	100 (Grand Total)

Chi-square test is used to analyze data

The chi-square statistic is 2.908. The p-value is 0.08, this result is not significant with p-value <0.05. Hepatomegaly is not significantly seen in patients with abnormal ALT levels i.e., greater than 40U/L compared to patients with normal ALT values <40U/L, which is statistically not significant with p-value <0.05.

IV. Discussion

Dengue is the most frequent arboviral infection with more than 100 million infections throughout the world annually including 250,000 -500,000 cases of severe dengue fever and 24,000 deaths. Hepatic involvement in dengue infections is usually mild and all stages of dengue can co-present with elevated transaminases. Significant elevations in transaminases can occur in severe dengue fever and fulminant hepatitis is occasional. In dengue infection levels of AST/SGOT are greater than ALT/SGPT levels, which is in contrast to normal finding in viral hepatitis and this may be due to excess release of AST from damaged monocytes also apart from liver during dengue infection. Although liver size does not correlate with disease severity or abnormal liver function tests, an enlarged liver is observed more frequently in SDF compared to DF group. Almost 87% have elevated AST level and 73% have elevated ALT level. The mean AST and ALT levels were 415.7 and 253 U/L respectively. The mean value of AST is significantly higher than the mean values of ALT which is comparable to study done by Chhina R S et al^[4] (mean AST, ALT levels were 353.7 and 218.6 U/L respectively). This abnormality may act as an early indicator of dengue infection. The mean total bilirubin level is 1.48mg/dl which is in accordance with study done by Wong M et al^[5] (1.68mg/dl) and Cam B V et al^[6] (1.22mg/dl). Other studies Chhina RS et al and Prakash O et al^[7] reported mean total bilirubin level of 0.8mg/dl to 0.93mg/dl. This may be due to the different age groups taken for study. The mean albumin level is 2.9 g/dl which is slightly low compared to the mean albumin level of 3.2g/dl reported by Chhina RS et al and 3.8 g/dl reported by Wong M et al. This difference can be explained on the basis that in the present study all patients are children while their study group included both children as well as adults.

Hepatomegaly is present in patients with abnormal AST levels compared to normal AST levels which is statistically significant with p-value <0.05 but no such relation is found between hepatomegaly and ALT levels. AST levels >3 times the normal value (grade C and D) is seen in patients with SDF compared to DF. AST and ALT levels are deranged in 87% and 73% of the patients respectively in the present study. A similar trend was observed in earlier studies done by Souza LJ et al^[8] and Souza LJ et al^[9]. Higher levels of alkaline phosphatase are seen in patients with SDF compared to patients with DF, which is of statistical significance. Jaundice and elevated alkaline phosphatase levels also reported in earlier studies^[8,9] which is in accordance with the present study.

The severity of hepatic dysfunction in dengue infection has been associated with disease severity. Indeed, liver injury has been proposed to be a good positive predictive factor for the development of SDF. The present study noted a greater degree of hepatic injury in the SDF group (significantly higher values of AST and ALP) as compared to the DF group, suggesting that the degree of liver injury may be related to the severity of dengue infection. Similar data have been suggested by and Souza et al^[9]. In the present study the mortality rate is 3% and all the patients have low platelet counts and deranged liver enzymes. All other patients with deranged liver function tests recovered with supportive treatment, which is comparable with earlier studies by Chhina RS et al (3.2%) and Prakash O et al (2.7%).

V. Conclusion

This prospective observational study is conducted from January 2016 to December 2016. During this study period 100 cases of serologically diagnosed dengue fever were studied for liver involvement. Among these 100 cases 48 were classical dengue fever and 52 were severe dengue fever, 51% of the children were within 5-9 years of age. The mean age is 6.87 years for DF and 6.3 years for SDF. Deranged total bilirubin, serum albumin, AST, ALT and ALP were present in 23%, 79%, 87%, 73% and 80% of patients respectively.

The mean total bilirubin and serum albumin levels are 1.48 mg/dl and 2.9 gm/dl respectively. The mean AST, ALT and ALP values are 415.7 U/L, 253U/L and 243.8U/L respectively. AST levels were significantly elevated compared to ALT. The degree of liver function derangement is significantly high in SDF group as compared to DF group. Mortality is observed in 3(3%) cases. According to the present study liver injury with elevation of liver enzymes especially elevated AST level can be used as a good positive predictive factor in the prognostication of Severe Dengue Fever.

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