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Original Research Article

Pattern of changes in hepatic aminotransferases level during dengue infection in children aged 1-12 years

Satyawathi Swamy*, Sadashiva B. Ukkali, Nagamani Kulkarni, Achyut N. Thobbi

Department of Pediatrics, Al-Ameen Medical College, Bijapur, Karnataka, India

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***Correspondence:**
Dr. Satyawathi Swamy,
E-mail: satyawathi3022@gmail.com

ABSTRACT

Background: Dengue fever is a pandemic viral disease carried by mosquito-borne flavivirus. Dengue infection is the most common arthropod infection in humans. The study is done with the aim to establish a relation between hepatic dysfunction and outcome in patients with dengue fever. It was found that hepatic transaminases were significantly deranged in dengue with warning signs indicating poor prognosis and need for early initiation of supportive treatment which can reduce mortality and morbidity in these children. Liver function tests can be of profound benefit in indicating the prognosis of children with dengue fever in resource-limited settings.
Methods: Cohort prospective observational study in Al-Ameen children hospital over 2 years. Patients aged 1-12 years fulfilling WHO case definition of fever and ≥2 of following: nausea/vomiting, rashes, aches and pains, tourniquet test positive, thrombocytopenia or any warning sign and serologically confirmed NS1Ag positive were studied. Once serologically positive, a blood sample was taken while establishing an intravenous line.
Results: Dengue with warning signs and dengue without warning signs were the classifications given to the patient. Both AST and ALT were found to be higher in groups having dengue with warning signs, with AST higher than ALT.
Conclusions: In dengue infection, hepatic dysfunction was common. Enzymes were significantly deranged in dengue with warning signs indicating prolonged illness and poor prognosis and need for early initiation of supportive treatment for better outcomes.

Keywords: Dengue fever, Aspartate transaminase, Alanine transaminase, Dengue with warning signs, Dengue without warning signs

INTRODUCTION

Dengue fever is a pandemic viral disease carried by mosquito-borne flavivirus. The WHO estimated that 50 million dengue infections occur annually. In the last 50 years, the incidence has increased 30-fold with geographical distribution to about 100 countries making it the most rapidly spreading arboviral infection.[1] Dengue infection is the most common arthropod borne viral infection in humans. Hepatic involvement may present as elevation of serum aminotransferases, fulminant hepatic failure, hepatic encephalopathy, severe coagulopathy.[2] The degree of liver dysfunction varies from mild injury with elevation of transaminases to severe injury with jaundice and liver cell failure.[3,4] The WHO 2009 guidelines defined AST, ALT more than 1000 units/liter as the criteria for severe dengue.[5] Dengue fever is considered to be the leading cause of morbidity and mortality in children less than 12 years. Through early detection and timely initiation of appropriate supportive treatment, this study can reduce morbidity and mortality. It aims to establish the relation between hepatic dysfunction and outcome in cases with dengue fever.

METHODS

This is the cohort observational study conducted from May 2022 to April 2024. Children aged 1-12 years who have tested serologically positive for NS1 antigen were included in the study. This study was conducted in the Al-Ameen women and children hospital of Bijapur, Karnataka.

Inclusion criteria

Patients aged 1-12 years, patients willing to give informed consent, WHO dengue case definition: Fever and ≥2 of the following: nausea/vomiting, rashes, aches and pains, tourniquet test positive, thrombocytopenia or any warning sign and patient who is serologically confirmed NS1 antigen positive were included

Exclusion criteria

Patient who did not give written informed consent for the study, patients tested positive for HbsAg, HAV, HBV or known cases of liver disease, the case of ITP/hematological malignancy, diagnosed with platelet disorder or on treatment with antiplatelet drugs were excluded.

Sample size

Sample size was determined by using formula:

$n=(z2p(1-p))/d^2$

Where,

Z=z statistics at 5% level of significance, d=the margin of error, p=the anticipated proportion of cases.

Dropout rate is negligible as IPD patients are evaluated for liver enzymes at a point of time.

Total sample size is 100.

After obtaining approval and clearance from the institutional ethics committee, the patients fulfilling the inclusion criteria were enrolled for the study after obtaining written informed consent. Patients were examined for vitals and stabilised following which a thorough general physical examination was done for rashes, lymphadenopathy, ascites, edema, facial puffiness, anasarca, hepatomegaly, splenomegaly. Baselines investigations were sent on OPD basis. Patients with fever and thrombocytopenia amongst them were explained regarding investigations including dengue viral infection. Once tested serologically positive for NS1 antigen, the patient's were explained about further investigation for liver function test. The blood sample was collected during intravenous cannulation done for regular fluid infusion for dengue fever.

Statistical analysis

The data was analyzed statistically using descriptive statistics namely mean, standard deviation, percentage wherever applicable. Appropriate parametric and non-parametric tests were used. All characteristics were summarized descriptively. For continuous variables, the summary of N, mean and standard deviation (SD) was used. For categorical data, the number and percentage were used in the data summaries and data was analyzed by Chi square test for association, comparison of means using t test, and diagrammatic presentation. Other suitable nonparametric methods of analysis also were used as per the need. If the $p<0.05$, then the results were considered to be statistically significant otherwise not statistically significant. Data was analyzed using SPSS software v.23 (IBM Statistics, Chicago, USA) and Microsoft office 2007.

RESULTS

The common belief that warning signals are present in most instances of dengue is challenged by the significant proportion of patients without any symptoms, highlighting the possibility of underestimating the severity of the disease. It is important to consider a range of symptoms for accurate and timely diagnosis. The association between hepatomegaly and dengue, particularly without warning signs, indicates its potential as a valuable clinical marker. In a similar view, the strong correlation seen between splenomegaly and dengue severity points to its function as a distinguishing factor. Consistent with findings from earlier research, elevated levels of AST and ALT are identified as potential biochemical indicators related with the severity of dengue. The group with elevated liver aminotransferases had a reduced survival rate, which highlights how crucial early detection of liver enzymes by a minimally invasive blood test is for good prognosis and reduced mortality and morbidity through early intervention, especially in a resource-limited setting.

The Table 1 indicates comparison of AST among dengue subjects with and without warning signs. The mean AST of study subjects without warning signs was 169.761 (SD=181.014) and the mean AST of study subjects with warning signs was 2555.250 (SD=2360.493). The mean AST of study subjects in two groups was compared using the Mann-Whitney U test. The result of Mann-Whitney U test indicates a significant difference in the mean AST of study subjects in two groups ($U=68.5$, $p<0.001$).

The Table 2 indicates comparison of ALT among dengue subjects with and without warning signs. The mean ALT of study subjects without warning signs was 104.054 (SD=110.264) and the mean ALT of study subjects with warning signs was 1446.00 (SD=1238.381). The mean ALT of study subjects in 2 groups was compared using Mann-Whitney U test. esult of Mann-Whitney U test

indicates a significant difference in mean ALT of study subjects in 2 groups (U=37.0, p<0.001).

The Table 3 indicates Association between outcome and dengue with and without fever. Out of 92 study subjects having dengue without warning signs, all 92 (100%) survived. While out of 8 study subjects having dengue with warning signs, 5 (62.5%) survived and 3 (37.5%) expired. The analysis using the chi-square test indicates a significant association between outcome and dengue with and without warning signs (chi-square=35.567, p<0.001).

Table 1: Comparison of AST among dengue subjects with and without warning signs.

Variables	N	Mean	SD	Mean rank	Mann-Whitney U	P value
Dengue without warning signs	92	169.761	181.014	47.240	68.5	<0.001
Dengue with warning signs	8	2555.250	2360.493	87.940		

Table 2: Comparison of ALT among dengue subjects with and without warning signs.

Variables	N	Mean	SD	Mean rank	Mann-Whitney U	P value
Dengue without warning signs	92	104.054	110.264	46.900	37	<0.001
Dengue with warning signs	8	1446.000	1238.381	91.880		

Table 3: Association of outcome with dengue with and without warning signs.

Outcome	Dengue without warning signs		Dengue with warning signs		Total		Chi square	P value
	N	%	N	%	N	%		
Survived	92	100	5	62.5	97	97	35.567	<0.001
Expired	0	0	3	37.5	3	3		
Total	92	100	8	100	100	100		

DISCUSSION

The revised recommendations of WHO in 2009 has divided the patients having dengue in three main categories, severe dengue, dengue without warning signs and dengue with warning signs.[6,7] The warning signs include persistent vomiting, abdominal pain or tenderness, lethargy, restlessness, clinical fluid accumulation or edema, increase in haematocrit values with a rapid decrease in platelet count, hepatomegaly of more than 2 cm and mucosal bleeding.[7]

The findings of the study reveal some noteworthy insights into the manifestation of dengue and its associated warning signs among individuals. The high percentage (92%) of dengue cases not exhibiting warning signs is a significant observation. This challenges the conventional perception that warning signs are prevalent in the majority of dengue cases. The absence of warning signs in a substantial proportion of patients suggests a potential underestimation of the disease's severity, emphasizing the need for vigilant monitoring and early detection methods beyond relying solely on warning signs. This finding is in contradiction to the findings obtained by Lamsa et al who found 234 (96.69%) patients out of 242 patients ailing with dengue to have warning signs.[8] Islam et al in a study conducted in Bangladesh also found that a higher number of patients reported with warning signs.[9] On the other hand, findings by Dhungana et al in Nepal supported those obtained from this study.[10]

Dengue and hepatomegaly

The association between hepatomegaly and dengue yields significant results. The analysis indicates a significant association between hepatomegaly and dengue with and without warning signs. The higher prevalence of hepatomegaly in subjects without warning signs (94.6%) compared to those with warning signs (75%) is an intriguing finding. The statistical significance suggests that hepatomegaly may serve as a valuable clinical marker for identifying dengue cases, regardless of the presence of warning signs. The concept of hepatomegaly was expanded to include "painful hepatomegaly" by Rathakrishnan et al and Romero-Vega et al.[11,12] Compared to the results of this investigation, Itha et al found that only 25% of their patients had hepatomegaly, while Rathakrishnan et al reported 15.1% and Wong et al reported as low as 11.8% of patients with hepatomegaly in their study group.[11,13,14]

Dengue and splenomegaly

The examination of splenomegaly in relation to dengue cases yields interesting results. Among subjects without warning signs, 54.3% had splenomegaly, while only 12.5% of those with warning signs exhibited splenomegaly. Significant association between splenomegaly and dengue between the two groups suggests that the presence of splenomegaly may serve as a distinguishing factor in differentiating the severity of

dengue cases. Wong et al reported only 2.36% and Rathakrishnan reported the lowest, that is 0.8% of patients having splenomegaly.[11,14] On the contrary, Itha et al. found no evidence of splenomegaly in their investigation; however, their limited sample size must be taken into account.[13]

Dengue and hepatic aminotransferases

The comparison of AST levels among dengue subjects with and without warning signs reveals a substantial difference. The mean AST in subjects with warning signs showed a sharp increase compared to AST levels in the group without warning signs. The significant difference between the two groups highlights the potential utility of AST as a biochemical marker associated with the severity of dengue. Similar to AST, the comparison of ALT levels indicates a significant difference between dengue subjects with and without warning signs. With the levels of ALT higher in the group having dengue with warning signs. These findings suggest that elevated ALT levels may be indicative of the severity of dengue cases. The finding of increase in serum liver enzymes was consistent with the findings obtained by Poudyal et al, Lamsal et al, Kuo et al and numerous other researchers.[8,13-17,19] According to Ferede et al, greater numbers of individuals (45.1%) had increased AST levels than did those with elevated AST levels (17.6%).[18] This finding has been discovered by several researchers as well.[18-20]

The analysis of outcomes among dengue subjects provides crucial insights. All 92 subjects without warning signs survived, while in the group with warning signs, 62.5% survived, and 37.5% expired. The survival rate was found to be lower than that by Itha et al, they reported a survival rate of 84%.[13] This underscores the prognostic value of warning signs in predicting the outcome of dengue patients.

Limitations

Considering the vast geographical area affected by dengue, this study covers a small population from Vijayapura and neighborhood places of Karnataka. This may underestimate the statistical measurements for a disease like dengue, a pandemic viral disease. There is a lack of previous cohort prospective research studies done for liver function tests in dengue infection.

CONCLUSION

The study provides valuable insights into the manifestation of dengue and the associated warning signs among patients, particularly in the context of the revised WHO recommendations in 2009. The common belief that warning signals are present in most instances of dengue is challenged by the significant proportion of patients without any symptoms, highlighting the possibility of underestimating the severity of the disease. The group with warning symptoms had a reduced survival rate, which highlights how crucial early diagnosis and monitoring are to better patient outcomes.

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