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Original Research Article

Profile of serum transaminases in patients with dengue infection in a tertiary care hospital

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ABSTRACT

Background: Although dengue virus is a non hepatotropic virus, liver injury due to dengue infection is not uncommon. Atypical manifestations with liver involvement have frequently been reported, ranging from mild elevations of aminotransferase levels to fulminant hepatitis. The aim of the present study is to study the serum transaminases level in various forms of dengue infection and correlate with severity.
Methods: An analysis of 151 serologically confirmed cases (0-14 yrs) of dengue from June 2017 to July 2017 at a tertiary care hospital, Dharwad was made to assess the frequency and degree of hepatic dysfunction in children with dengue infection by analyzing serum transaminase levels. Patients were classified according to WHO as dengue without warning signs, with warning signs and severe dengue. Patients were divided into primary and secondary dengue based on serology and serum transaminases levels were assessed in each of the above groups. Patients with normal aminotransferase levels were categorized into Grade A, those with atleast one of the enzymes raised to less than 3 times the reference range as Grade B, those with atleast one of the enzymes elevated more than 3 times but less than 10 times as Grade C and those with elevations more than 10 times as Grade D. $\chi 2$ test was applied to check statistical significance.
Results: During the study period, the total number of serologically confirmed cases of dengue were 151 among which dengue fever without warning signs were 38, with warning signs were 91 and severe dengue were 22. Serum transaminase levels were significantly raised in severe dengue ($\chi 2=14.228$, df=6, p=0.027).It was also found that transaminases were significantly higher in secondary dengue infection than primary dengue ($\chi 2=10.155$, df=3, p=0.017). Transaminases were significantly elevated in non-survivors ($\chi 2=16.958$, df=3, $p<0.001$).
Conclusions: Hepatic dysfunction was common in all forms of dengue infection, with AST rising significantly more than ALT. Transaminases were significantly elevated in severe dengue and secondary dengue infections. Patients with significantly high transaminases had a poor outcome.

Keywords: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Dengue infection, Hepatic dysfunction, Transaminases

INTRODUCTION

Dengue ranks among the most important mosquito-borne viral disease in the world. Dengue fever is an acute infectious disease caused by an arbovirus in the *Flavivirus* genus. It has four serotypes, and the mosquito *Aedes aegypti* is the vector. While dengue is a global concern, currently close to 75% of the global population exposed to dengue are in the Asia-Pacific region.

Dengue virus was isolated in India for the first time in 1945. Over the last few years, atypical manifestations of

dengue have been described, including involvement of the central nervous system, cardiac alterations, and elevations in aminotransferase levels, with reactive hepatitis. These manifestations have been observed during epidemics in Brazil.[1-3] The unusual clinical forms of this disease are frequently associated with more serious states, and they often result from multifactorial conditions, such as the use of hepatotoxic drugs, in addition to the direct aggression by the dengue virus.[4-7]

Hepatic involvement can be characterized by manifestations of acute hepatitis, with pain in the right hypochondrium, hepatomegaly, jaundice, and raised aminotransferase levels. In hepatitis, the levels of these enzymes reach a maximum on the ninth day after the onset of symptoms, and they gradually return to normal levels within three weeks. Although the liver is not the main target organ for this disease, histopathological findings, including centrilobular necrosis, fatty alterations, hyperplasia of the Kupffer cells, acidophil bodies and monocyte infiltration of the portal tract have been detected in patients with dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). 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.[8-14]

The present study was conducted with the primary objective of studying the serum transaminases level in various forms of dengue infection and correlate with the severity and outcome of the disease at a tertiary care hospital.

METHODS

Children between 0-14years admitted with the clinical diagnosis of dengue infection on the basis of history of fever and constitutional symptoms were subjected to dengue card test in the month of June and July 2017. The children with positive card test were considered serologically confirmed cases of dengue fever and were included in the study. They were categorized into primary and secondary dengue infection based on the serology. Those patients who tested positive either for NS1Ag or IgM or both were taken as primary dengue and those with NS1Ag or IgM and IgG positivity were taken as secondary dengue. Based on the WHO case definition, cases were classified as dengue fever without warning signs, dengue fever with warning signs and severe dengue. Cases who presented with or developed abdominal pain or tenderness or had vomiting or any bleeding manifestations or edema were taken as with warning signs and those with shock, plasma leak or any organ involvement were classified as severe dengue.

Those children with previous history of liver illness or abnormal aminotransferases prior to this illness were excluded from our study.

In the children falling in the study group, an analysis of serum transaminase levels was made in the critical phase of illness. Patients with normal aminotransferase levels were categorized into Grade A, those with atleast one of the enzymes raised to less than 3 times the reference range as Grade B, those with atleast one of the enzymes elevated more than 3 times but less than 10 times as Grade C and those with elevations more than 10 times as Grade D.

Data was collected using a proforma which had questions regarding symptoms, age, sex, weight, clinical presentation, dengue serology, salient laboratory parameters, serum transaminases and the outcome.

Descriptive data was expressed as percentage and presented in tables and graphs. Chi Square test was used to find out the association between the type of dengue illness and rise in aminotransferases. Statistical software used was SPSS 18 trial version.

RESULTS

The clinical and biochemical impact of dengue virus on serum transaminase levels was studied in 151 serologically confirmed cases of dengue infection in children aged 0-14yrs during an outbreak in the month of June and July 2017 in a tertiary care center, Dharwad, India.

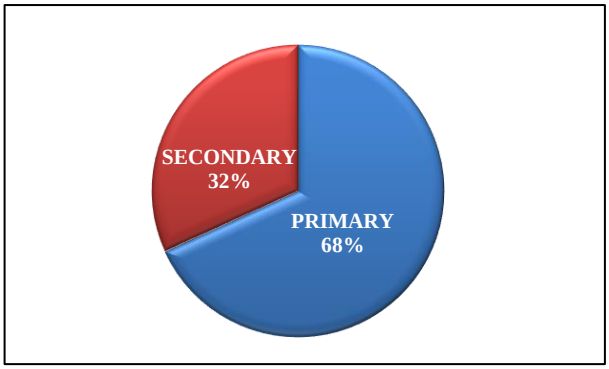

Figure 1: the number of primary and secondary dengue cases.

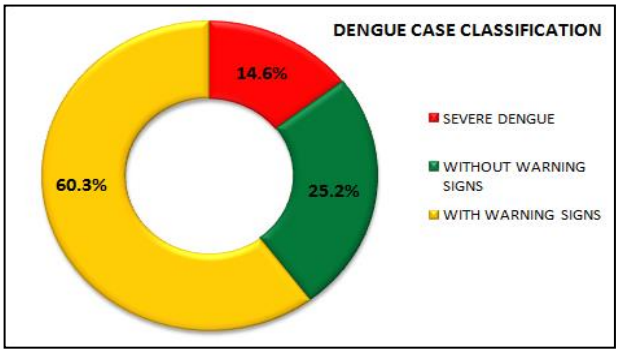

Figure 2: Dengue case classification according to WHO.

Of the 151 serologically positive children, 85 (56.3%) were boys and 66 (43.7%) were girls.

Based on the serology, those patients who tested positive either for NS1Ag or IgM or both i.e primary dengue cases were 103 (68.2%) and those with NS1Ag or IgM and IgG positivity that is secondary dengue infection were 48 (31.8%).

Table 1: Serum transaminase levels in the study population.

Serum transaminase levels	Frequency	Percent
Normal	22	14.6
>N - <3	61	40.4
3-10 Times	54	35.8
>10 Times	14	9.3
Total	151	100.0

As per WHO case definition, cases classified as per severity into without warning signs were 38 (25.1%), with warning signs were 91 (60.3%) and severe dengue were 22 (14.6%) cases.

Table 2: Comparison of pattern of rise in transaminase levels with primary and secondary dengue.

Infection	Normal	>1-3 times	>3-10 times	>10 times
Primary	21 (20.3%)	40 (38.8%)	35 (33.9%)	7 (6.7%)
Secondary	1 (2%)	21 (43.7%)	19 (39.5%)	7 (14.5%)

Out of the 151 cases, 22 (14.6%) had normal transaminase levels; 61 (40.4%) had raised aminotransferases upto 3 times the normal levels, 54 (35.8%) had levels raised 3-10 times the normal and 14 (9.3%) had enzymes raised more than 10 times the normal level.

Table 3: Elevated transaminase levels in various forms of dengue fever.

Case classification	Normal	<3 times	3-10 times	>10 times
Without WS	6 (15.7%)	16 (42%)	16 (42.1%)	0
With ws	12 (13.1%)	39 (42.8%)	33 (36.2%)	7 (7.6%)
Severe dengue	4 (18.1%)	6 (27.2%)	5 (22.7%)	7 (31.8%)
$\chi 2=14.228$, df=6, p=0.027 Significant				

Hepatic dysfunction in the form of raised transaminase levels was severe in secondary dengue cases with only 2% of them having normal transaminase levels and 40% having transaminases raised >3 times and around 14.5% having transaminases raised more than 10 times the normal as compared to 7% in primary dengue cases. It was found that AST was significantly raised than ALT.

Table 3 shows the pattern of rise in aminotransferase levels in various forms of dengue infection. Higher values of aminotransferases were noted in dengue with warning signs and severe dengue cases. Cases with warning signs and severe dengue had more severe rise in aminotransferase levels than those without warning signs and the difference was statistically significant (p=0.027).

Table 4: Correlation between adverse outcome and higher transaminase levels.

Outcome	Normal	<3 times	3-10 times	>10 times
Improved	22 (100%)	60 (98.3%)	53 (98.1%)	10 (71.4%)
Death	0	1 (1.6%)	1 (1.8%)	4 (28.5%)
Total	22	61	54	14
$\chi 2=16.958$, df=3, p<0.001 Significant				

Of the total 151 cases, mortality was seen in 6 (3.9%) cases. Among those who had poor outcome i.e 6 cases, 4 (66%) had serum transaminases raised more than 10 times the normal and one each (16.6%) had tansaminases raised more than 3 times and 3-10 times above normal levels. None of the patients who had normal transaminases expired and this difference is statistically significant.

Thus, in the present study it was noted that cases with poor outcome had significantly raised transaminase levels.

DISCUSSION

In the present study 103 children were cases of primary dengue infection and 48 were secondary dengue cases. Ninety one children presented with warning signs, 38 children had no warning signs and 22 children had severe dengue infection.

Biochemical liver dysfunction, in the form of increased transaminases was found in majority of the patients in our study that is 85.4% which is similar to the observations made in other studies.[15-17]

In the present study, the aspartate aminotransferase (AST) levels were found to be greater than alanine aminotransferase (ALT) levels similar to Souza LJ et al and. Kalayanarooj S et al.[18,19] This differs from the pattern in viral hepatitis. The exact cause of this is uncertain, but it has been suggested that it may be due to excess release of AST from damaged monocytes during dengue infection.[14]

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 severe dengue.[19] We noted a greater degree of hepatic injury in the severe dengue and with warning signs group of dengue fever (significantly higher values of AST and ALP) than in those belonging to without warning signs group, suggesting that the degree of liver injury may be related to the severity of dengue infection which is similar to observations made by Kalayanarooj S et al.

High aminotransferases were found to be significantly more severe in non-survivors as compared with survivors, thus detection of liver enzyme levels may be used as early prognostic markers in dengue infection.

CONCLUSION

In summary, raised transaminase levels is very common in all forms of dengue infection, with AST rising significantly more than ALT. Serum transaminase levels are significantly higher in patients with severe dengue, secondary dengue infection and in non-survivors. Therefore, preferentially high AST may serve as an early indicator of dengue infection and also acts as poor prognostic marker.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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