

Gastrointestinal Involvement in Dengue Fever Infection: A Study from the Western Region of Saudi Arabia

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ABSTRACT

Background: Dengue fever is prevalent in several areas in Saudi Arabia; however, information on the prediction of disease severity and progression to liver failure is lacking.

Aim: To identify the possible associations between liver chemistry and clinical presentation.

Methods: This was a retrospective chart review of patients admitted to Al-Noor Specialist Hospital, a tertiary facility with a large referral area. We identified patients with the ICD-10 codes for dengue fever and dengue hemorrhagic fever. Data collected included liver chemistry and other blood work for secondary liver diseases. Statistical analysis involved descriptive data and correlation data analyzed using Mann-Whitney and Kruskal-Wallis tests.

Results: A total of 535 patients met the selection criteria. There were 388 male patients (72.5%), 512 with dengue fever (95.7%), 21(3.9%) with dengue hemorrhagic fever, and two (0.4%) with dengue shock syndrome. Gastrointestinal symptoms were predominant in 312 patients (58.3%). Correlation analysis revealed that median serum levels of AST and ALT on admission significantly correlated with male sex. When the severe dengue disease group was analyzed separately, there were no significant differences in median serum levels of transaminases on admission and gender or symptom presentation.

Conclusions: Male patients presenting with dengue fever most often had associated elevated transaminase levels on admission and may benefit from early attention. Serum transaminase levels were not associated with particular symptom presentation.

Keywords: Liver failure; Liver; Liver function tests; Dengue; Severe dengue

INTRODUCTION

Viral hemorrhagic illness is a group of viral infections that occur in tropical and subtropical regions. Among them, dengue fever (DF) is reported in several areas of Saudi Arabia. DF shows multi-organ involvement; in this study, we paid particular attention to gastrointestinal involvement. Among the common acute viral infections in the liver, acute hepatitis A is associated with potential morbidity and mortality, including acute fulminant liver failure, followed by increasingly common cases of DF-mediated liver involvement. Fortunately, the incidence and seroprevalence of new cases of acute hepatitis A have decreased over the past twenty years^{1,2}. With diagnosis of more cases of DF, there is a growing interest in and vigilance regarding disease manifestation in several organ systems, including gastrointestinal involvement and the extent of disease severity. Since the first description and subtyping of DF in Saudi Arabia in 1994³, investigators have recognized it as an endemic febrile illness of interest for the public health. Liver and gastrointestinal involvement is noted in up to 66.7% of the infected patients⁴. Health services in several areas of the country detected DF in asymptomatic individuals, including blood donors⁵ and in symptomatic individuals, with higher prevalence among those who reside in areas of high risk where there is water collection, as well as in people in their twenties in the western and southern regions^{6,7,8}. *Aedes* mosquitoes are the vectors of transmission from larvae in stagnant water. The most common species in western Saudi Arabia is *Aedes aegypti*. Dengue multisystem involvement with severe complications has generated interest in mass

prevention and eradication of these viral epidemics. Findings of thrombocytopenia and generalized myalgia are ominous predictors of development of severe complications including acute fulminant liver failure^{9,10,11}. In our local region, information regarding the clinical course of dengue fever-related liver involvement and its correlation to serum transaminase levels is not available, as is the case for other endemic areas in the tropics. This study aimed to identify the hepatic manifestation of DF in a large cohort at a tertiary health center and to describe any possible associations among patient characteristics and the severity of liver disease caused by dengue fever infection. This will aid in the identification of early predictors of severity to provide expedited management.

METHODOLOGY

This was a retrospective chart review conducted at a large tertiary hospital (Al-Noor Specialist Hospital, Makkah) in the western region of Saudi Arabia with referrals coming from the surrounding western and southern areas of the country where DF is endemic. We reviewed admitted patients from January 2014–January 2016. Inclusion criteria included adult patients above 18 years of age with clinical presentations consistent with the WHO criteria for the diagnosis of dengue fever, confirmed by serology using ELISA and immunoglobulin M antibody to NS1 (nonstructural antigen) to DEN1 serotype. We retrieved medical records using ICD-10 classification of dengue fever (A90) and dengue hemorrhagic fever (A91), and were manually verified for diagnosis. Severe dengue disease (SDD) refers to dengue hemorrhagic fever (DHF) and

dengue shock syndrome (DSS) as described in the microbiology literature^{12,13}. We recorded demographic characteristics, clinical presentations (respiratory, neurologic, gastrointestinal, hematologic, and generalized flu-like illness) as well as ICU admission if clinical courses worsened. Treating physicians measured liver chemistries upon admission and we recorded peak levels. We also measured various markers in order to rule out secondary causes of chronic liver disease in the region, including hepatitis B surface antigen, hepatitis C total antibody-positivity as well as markers of metabolic liver diseases such as hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency and fatty liver.

We performed statistical analysis using SPSS. 22. We used descriptive data to express continuous variables as means and standard deviations. We used medians and ranges for skewed data. We performed correlation analysis using the Mann-Whitney U test for analysis of possible association between numerical values and clinical symptoms of interest in the general cohort. We considered a *p* value (two tailed) of less than 0.05 statistically significant.

We obtained approvals from the regional health authority and the hospital ethical boards for this retrospective study.

RESULTS

We retrieved a total of 535 cases that met selection criteria. There were 388 male patients (72.5%) (Table 1). Mean age was 33 years (range, 18–90 years). According to WHO classification of dengue fever, there were 512 patients with dengue fever (95.7%). Severe dengue disease included 21 (3.9%) patients with dengue hemorrhagic fever and two (0.4%) with dengue shock syndrome. There were no secondary causes of chronic liver diseases, including hepatitis B, hepatitis C, hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency or fatty liver. The presenting symptoms were predominantly gastrointestinal and hepatic in 312 patients (58.3%) followed by constitutional symptoms, including generalized flu-like illnesses with headache, retro-orbital pain, myalgia, and arthralgia (Table 1). The breakdown of gastrointestinal and hepatic symptoms is shown in Table 1 as well. The pattern of liver function tests at various stages of the illness is shown in Figure 1. Transaminases are presented with actual values rather than multiples to facilitate better representation.

Correlation analysis showed that median serum levels of AST and ALT on admission of patients with DF in general significantly correlated with male gender only (Table 2); there was no statistically significant association between median serum levels of AST and ALT on

admission and female gender. Furthermore, there were no statistically significant associations between median serum levels of AST and ALT on admission and other system manifestations, including respiratory, neurologic, bleeding, gastrointestinal and constitutional symptoms (Table 3). Despite the small numbers, but considering the importance of the severe dengue disease category, a subanalysis showed no statistically significant differences between median serum levels of transaminases on admission and gender nor clinical manifestations of bleeding (Tables 4 and 5).

Table 1: Demographic and clinical characteristic of the patients

Variable	Number (%)
Age (mean (SD), [range] in years)	33.26 (12.69) (18-90)
Gender	
Male	388(72.5)
Females	147(27.5)
Clinical Symptoms	
CNS	6(1.1)
Respiratory	7(1.3)
Gastrointestinal	312(58.3)
Bleeding	25(4.7)
Other	185(34.6)
CBC	
WBC x 10 ⁹ /L (mean (SD))	3.25(2.98)
HB gm/L (mean (SD))	14.18(2.01)
Hct% (mean(SD))	41.66(5.7)
Plateletx 10 ⁹ /L (mean (SD))	77.69(37.57)
AST U/L	
Admission (mean (SD), [range])	146.72(299.4)(14-4222)
High	433(80.9)
Peak	236.87+599.39(14-10482)
ALT U/L	
Admission (mean (SD), [range])	111.81(170.89)(3-1886)
High	398(74.4)
Peak	173.62+243.91(8-3184)
ALP U/L	
Admission (mean (SD), [range])	90.46(43.5)(34-394)
High	-----
Peak	91.93(43.91)(34-394)
Bilirubin-Total mg/dL	
Admission (mean (SD), [range])	0.525(0.535)(0-7)
High	-----
Peak	0.57(0.57)(0-7)
Bilirubin-Direct mg/dL	
Admission (mean (SD), [range])	0.189(0.27)(0-2.5)
High	----
Peak	0.22(0.39)(0-6)
INR	
Admission (mean (SD), [range])	1.93+0.24(1-2)
High	34 (6.4)
Peak	----

Qualitative data are presented as number and percentage . Quantitative data were presented as mean and standard deviation

Table 2: Association between serum Transaminases of the cohort and Gender:

Gender (n)	Serum AST		Serum ALT	
	Median (SD) ,	Range	Median (SD) ,	Range
Male (388)	85.5 (264.19)	(1-3743)	71(165)	(3-1730)
Female (147)	72 (378)	(15-4222)	54 (187)	(7-1886)
Total (535)	82 (299)	(1-4222)	66 (171)	(3-1886)
<i>p</i> value*	0.015		0.001	

*Mann-Whitney U test used for correlation, with significance at *p* value less than 0.05

Table 3: Association between serum transaminases on admission and the presenting clinical symptoms on hospital presentation:

Symptoms (n)	Serum AST		Serum ALT	
	Median (SD)	Range	Median (SD)	Range
CNS symptoms(6)	72 (1500)	(16-3743)	85 (685)	(13-1730)
Respiratory symptoms (7)	138 (199)	(24-506)	183(121)	(45-387)
GI symptoms (312)	84 (314)	(1-4222)	66 (187)	(7-1886)
Any bleeding(25)	117 (157)	(14-705)	72(110)	(4-404)
Other generalized symptoms(185)	75 (130)	(14-1030)	65 (92)	(3-619)
p value*	0.252		0.236	

*Mann-Whitney U test used for correlation, with significance at p value less than 0.05

Table 4: Association between serum Transaminases in the group of severe dengue disease and Gender:

Gender (n)	Serum AST		Serum ALT	
	Median (SD) ,	Range	Median (SD) ,	Range
Male (20)	178 (873)	(14-3743)	122 (412)	(4-1730)
Female (3)	129 (56)	(35-135)	72 (25)	(36-84)
Total (23)	134 (821)	(14-3743)	105 (399)	(4-1730)
p value*	0.411		0.315	

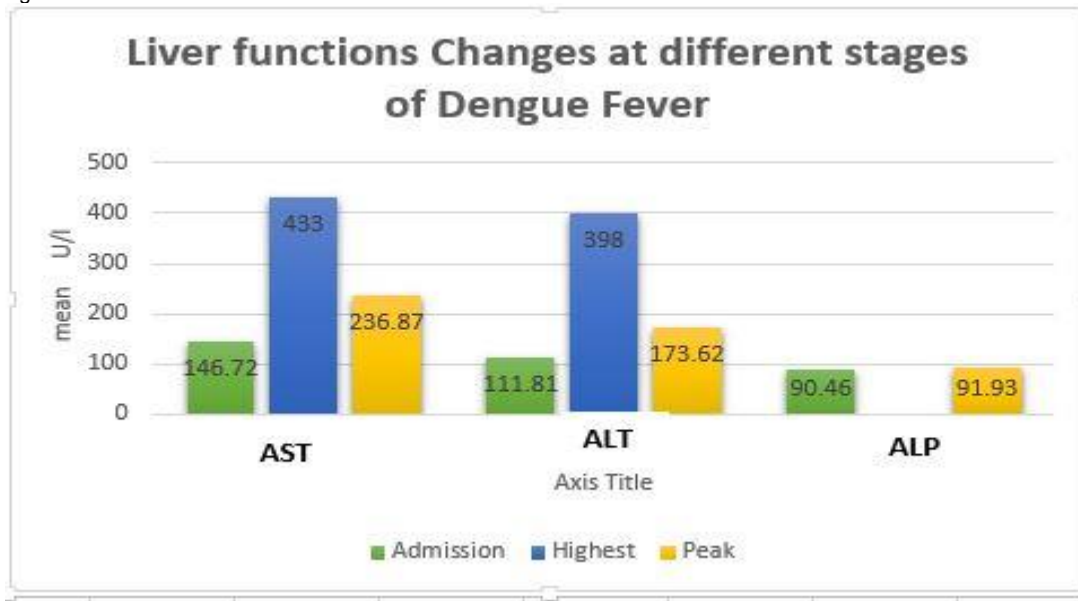
*Kruskal Willis H test used for correlation, with significance at p value less than 0.05

Table 5: Association between serum Transaminases in the group of severe dengue disease and clinical symptoms on hospital presentation:

Symptoms (n)	Serum AST		Serum ALT	
	Median (SD) ,	Range	Median (SD)	Range
Any bleeding (21)	129 (166)	(14-705)	84 (114)	(4-403)
p value*	0.072		0.072	

*Kruskal Willis H test used for correlation, with significance at p value less than 0.05

Fig. 1:



DISCUSSION

Infection with dengue fever virus may present on a spectrum from minor nonspecific symptoms that are unnoticed to major system presentations of variable severity. Liver involvement with dengue may occur either alone or against a background of underlying liver illness, as shown in several reports of chronic hepatitis B carriers and leptospirosis patients in whom full recovery was achieved with no residual consequences^{14,15}. Conversely, fulminant liver failure was reported in young patients from various areas of Asia due to *de novo* DF infections^{16,17,18,19}. Serum transaminases (ALT and AST) were significantly elevated with particularly elevation noted for AST in DF and

DHF.(20)(21, 22) Among the supportive therapies used for management of DF-induced fulminant liver failure is N-acetyl cysteine intravenous infusion, providing prompt responses^{23,24}. Nevertheless, a severe form of the illness may affect a group of individuals who are young, female and have high BMI. These cases showed that variability in incidence in various Asian countries of high endemicity does not show that the aggressive form of hepatic involvement is peculiar to any territory or specific demographic group. Predictive clinical manifestations for severe dengue disease in several large studies include gastrointestinal and hepatic manifestations: nausea, vomiting, gastrointestinal bleeding, abdominal pain,

hepatomegaly, ascites and elevated serum AST and ALT^{25,26}. In our study population, the common presentation of dengue fever was a less aggressive form with predominance of classic dengue fever syndrome (513 patients, 95.9%) and prevalent gastrointestinal manifestations. A similar study by Khan et al. in the same city (Makkah) reported similar findings²⁷ of common dengue fever; absence of systemic manifestations such as musculoskeletal pain, high serum AST and thrombocytopenia were associated with fewer complications related to DF infection.

Hepatocellular dysfunction in DF could be evaluated with precision using a liver biopsy; however, this method is invasive and its utility is limited. Alternatively, serum transaminases are used to evaluate causes of chronic liver diseases and to monitor its progression. When considering serum transaminases in the diagnosis and management of DF infection, especially with predominant gastrointestinal and liver involvement, it is essential to have a consistent reproducible method that allows prediction of development of advanced liver disease and hence to apply early measures of treatment. Elevated transaminases are associated with severe DF infection; however, they are not sufficiently able to differentiate or define degrees of severity when they are elevated more than 1000 IU/ml²⁸. These high levels are typically present during the critical and convalescent stages of severe DF^{29,30}. Parameters of interest in cases of severe DF that were studied in conjunction with serum transaminases include nausea, vomiting, bleeding manifestations, abdominal pain, jaundice, age of the patient, restlessness, lethargy, and physical signs such as hepatomegaly and abdominal tenderness^{31,32}. Laboratory parameters of interest are thrombocytopenia and elevated hematocrit. Elevated serum transaminases were significantly associated with the abovementioned gastrointestinal symptoms and with bleeding, as well as with thrombocytopenia and elevated hematocrit^{29,33}. There were weak correlations between serum levels of transaminases and the age of the patient and type of dengue fever infection³⁴. Our study showed a different trend of association from those studies, in which male gender was significantly associated with mean serum levels of transaminases as opposed to female gender and other system involvement. We may explain this by the presence of predominantly male cases in the cohort. Of note, predictors of admission to the intensive care unit for patients with DF included those with abdominal pain, jaundice, hepatomegaly and abdominal tenderness³⁰. The usefulness of this association may serve as a prediction for the group of patients who may benefit from earlier critical care. A retrospective analysis from Malaysia found that comorbidities associated with DHF contributed to mortality³⁵. In our study, there were two patients with dengue shock syndrome (0.4%) and 21 with dengue hemorrhagic fever (3.9%), however long follow-up was not available so as to provide survival data.

Limitations of our study include its retrospective nature and the lack of long follow-up to determine survival association. Most of the study analysis of the available data performed for the transaminases is shown in the literature; however, cholestatic enzymes (alkaline phosphatase and gamma-glutamyl transferase) did not contribute to disease

course or severity and did not constitute part of the assessment of hepatocellular injury; hence these values would not affect the assessment of the magnitude of acute hepatitis related to DF. Nevertheless, to the best of our knowledge, this study is among the first from the region to describe a relatively large cohort of patients affected with dengue fever compared to other studies from the Far East where high endemic disease burden is of similar magnitude and that describe the association between gastrointestinal and hepatic symptoms on the DF spectrum.

CONCLUSION

DF is prevalent in the western region of Saudi Arabia compared to the endemic areas of the world. Our study analysis showed common gastrointestinal symptom manifestation in the analyzed cohort. There was an association between serum ALT levels and patient gender. Further analysis showed no association among serum transaminase levels and symptom manifestation either for the mild form of DF (DF) or the severe forms (DHF or DSS).

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Conflicting Interest : None exists.

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