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Assessment of Dengue Fever Severity Through Liver Function Test

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Additional information is available at the end of the chapter

Abstract

Objective: To assess the utility of liver function tests (LFTs) for early recognition and prediction of severity of dengue fever in hospitalized patients. *Study Design*: An analytical study. *Place and duration of study:* Services Institute of Medical Science and Fatima Memorial Hospital, Lahore, from September to December 2010. *Methodology*: Admitted cases of dengue fever were divided into three groups: mild, moderate, and severe increases in aminotransferases. Elevation in LFTs was co-related with good or bad outcome i.e. (survival or complication free stay) or (death or complications). Results were analyzed in SPSS version 18. *Results*: Out of the 353 patients with mean age of 37.12 ± 15.45 years, 245 (69.4%) were males and 108 (30.6%) were females. Seventy five patients (21.2%) had mild elevation of aminotransferases (twofold increases), 265 patients (75.1%) had moderate increases (three to fourfold), and 13 (3.7%) had severe (>4 fold increase). Alanine transaminase (ALT) was statistically higher in patients with septicemia, hepatic, and renal failure (p-value ≤ 0.05). Aspartate transaminase (AST) was higher in almost all complications. Prolonged hospital stay was associated with raised LFTs and greater complications and mortality. AST was found to be twice as much raised as ALT. *Conclusion*: AST and ALT were statistically higher in patients with worse outcome thus can lead to early recognition of high risk cases.

Keywords: dengue fever, liver disease, liver function tests, severity

1. Definition of subject area

Dengue fever has emerged as a biggest global **pandemic** caused by a flavivirus with significant impact on the disease burden in population living in tropical countries with 1–2 epidemics every year [1].

1.1. Dengue virus

Dengue virus (DENV) has **four** serotypes (DEN 1–4). Currently, all the serotypes have diffused in tropical and subtropical regions of the world [2].

1.2. Mode of transmission

DENVs are transmitted via the female mosquito species **Aedes** *Aegypti* and less commonly by *Aedes Albopictus* [2].

1.3. Incubation period

Dengue virus has an incubation period of **3–10** days with average of 5–6 days [3].

1.4. Period of infectivity

Within first 5 days of illness, if Aedes mosquito feeds on patient blood, it will become infective [3].

1.5. Outcome of dengue infection

Majority of dengue infections are **asymptomatic**. Among symptomatic presentation is highly variable from mild **flu**-like illness to classical dengue fever (**DF)** (**bone-break** fever) and even some complicate into dengue hemorrhagic fever (**DHF**) and dengue shock syndrome (**DSS**), which are life threatening (**Table 1**) [4].

If total score >6, then patient has high chances of having dengue fever

- This scoring system carries
- *sensitivity = 90.7%*
- *specificity = 86.9%*
- *positive predictive value = 81.4%*
- *negative predictive value = 93.6%.*
- Chang et al. [5].

2. Description of study

Involvement of liver with deranged liver function tests (LFTs) is likely with dengue fever and which may include mildly raised in serum total bilirubin, increased alanine transaminase (ALT) and aspartate transaminase (**AST**), and decreased in serum albumin which can be a used as a prognostic indicator [6].

1	Epidemiology	Score
	Recent travel to Southeast Asia or four endemic dengue fever in Taiwan within 1 week	4
2	**Clinical symptom**	
	Skin rash	3
	Bleeding signs (Included petechia, gum bleeding, epistaxis, gastrointestinal bleeding, hemoptysis, hematuria, and menorrhagia)	3
	Fever	2
	Headache, retrobulbar pain, bone pain, myalgia	1
	GI symptoms (poor appetite, abdominal pain, diarrhea and nausea)	1
	Absence of cough and rhinorrhea	1
3	**Differential diagnosis**	
	Fever > 7 days	−8
	Identified infection focus (e.g., Eschar of scrub typhus and upper respiratory infection)	−10

Table 1. Diagnostic criteria for dengue fever.

3. Objectives of the study

The objectives of the chapter are as follows:

1. To evaluate such alterations in the liver function test as an early marker for severity and timely diagnosis of dengue fever complications and severity [7].

2. To identify patients who might develop severe complications.

3. To decrease the degree of in hospital stay by categorizing patients into mild, moderate, and high risk groups according to their raised transaminases (ALT and AST) levels [8].

4. Materials and methods

A study was conducted in different government as well as private tertiary care setups in Lahore from September 2010 to December 2010. The total 353 patients were included in the study. It was a simple **randomized** sample and the study design was a cross-sectional observational study.

4.1. Categorization of patients

Patients were divided into three groups and categorized to have mild, moderate, or severe liver dysfunction. Group I included patients who had twofold or lesser increase in liver enzymes; in

group II patients, liver function tests were between twofold and fourfold greater than normal; group III patients had liver function tests greater than fourfold above normal. The correlation of these groups with the development of complications, mortality, and number of days of hospital stay was studied. Good outcome was taken as survival and complication free pattern of disease, while bad outcome was taken as development of complication or mortality.

4.2. Results and conclusion

- The effects of dengue fever on liver are usually asymptomatic but can be atypical and have varied severity. From asymptomatic elevated transaminase levels to fulminant hepatic failure, the variable manifestations are a big challenge to the clinicians treating the condition (**Tables 2–4**).

Variables	Mean	Std. deviation	Minimum	Maximum
Age (years)	37.12	15.456	4	80
Duration of fever	5.49	2.64	1	35

Table 2. Descriptive statistics of demographical variables.

Complications	Severity of disease			Total $n = 85$
	Mild $n = 27$	Moderate $n = 38$	Severe $n = 20$	
DHF	12 (14. 11%)	11 (12.94%)	1 (1.17%)	24 (28.23%)
DSS	4 (4.7%)	4 (4.7%)	4 (4.7%)	12 (14.11%)
Hemorrhage	8 (9.41%)	18 (21.17%)	3 (3.52%)	29 (34.11%)
Septicemia	0 (0%)	2 (2.35%)	3 (3.52%)	5 (5.88%)
Hepatic failure	0 (0%)	1 (1.17%)	4 (4.7%)	5 (5.88%)
Encephalopathy	2 (2.35%)	1 (1.17%)	1 (1.17%)	4 (4.70%)
Respiratory failure	1 (1.17%)	1 (1.17%)	2 (2.35%)	4 (4.70%)
Renal failure	0 (0%)	0 (0%)	2 (2.35%)	2 (2.35%)
Total	27 (31.76%)	38 (44.70%)	20 (23.52%)	85

Table 3. Complications versus severity of disease.

The reversal of alanine transaminase and aspartate transaminase (ALT to AST) ratio observed in dengue fever as compared to that seen in other viral hepatitis can lead to an early diagnosis of these patients.

- Increasing trend in aminotransferases is associated with major complications and a bad outcome as compared to patients with mild or moderate hepatic dysfunction.

- Severe hepatitis and specifically raised alanine transaminase (ALT) levels are a poor prognostic indicator of outcome in dengue fever.

- The younger age group of patients was directly associated with severely raised levels of alanine transaminase (ALT) and thus contributing to a higher mortality.

4.3. Pathogenesis of DF, DHF, and DSS

Dengue virus presumably affects the reticulo-endothelial system of the body in skin, lymph nodes, spleen, marrow and liver [9].

DHF and DSS are caused by disorder of the immune system. In recovery phase (days 7–14) of first infection, another serotype is superinfected. Then antibodies against first serotype binds with new entrant serotype antigen leading to immune complex formation, their deposition on endothelium leading to widespread vessel wall injury, hemorrhages, and third spacing of fluid [4].

4.4. Dengue virus and liver

The dengue virus affects the liver but mostly, liver involvement is usually subclinical. But it can still lead to acute fulminant hepatic failure in dengue-affected countries. Dengue should be a differential in management of acute fulminant hepatic failure and as a triggering factor in patient with acute on chronic liver failure [6].

Despite being asymptomatic in majority of cases, clinical presentation like acute hepatitis and even acute fulminant liver failure may rarely appear as a complication.

4.5. Pathogenesis of liver injury

Hepatic dysfunction is a crucial feature seen in DENV infection. Hepatocytes and Kupffer cells are prime targets for DENV infection. Pathogenesis of hepatic injury in dengue is believed to be primarily a T cell-mediated process involving interaction between antibodies and the endothelium and a concomitant cytokine storm [7, 10].

4.6. Liver morphology

Liver biopsy and microscopy reveals fatty change (microvesicular) along with hepatocyte necrosis and hyperplasia. Additionally, there is mononuclear cell infiltration at the portal tract along with destruction of Kupffer cells and Councilman bodies [11].

Tests result	Mean	Std. deviation	Minimum	Maximum
TLC	4.7711	2.17496	1	20
ALT	100.29	102.14	11	1102
AST	234.17	136.09	21	1680
PT	16.71	3.59	10	60
APTT	34.40	1.650	19	50

Table 4. Descriptive statistics of different investigations.

Hepatocyte damage with necrotic changes mostly starts with midzonal area and then spreads to centrilobular area. As these particular areas are more sensitive to anoxic or immune-mediated injury [7, 8].

5. Clinical presentation with liver involvement in dengue fever

Clinical evidence suggests that dengue-related hepatic involvement incudes the presence of liver enlargement. Among the clinical features of hepatic involvement, patients have abdominal pain (18–63%) and nausea/vomiting (49–58%). Abdominal pain and anorexia are more common in DF than DHF [12].

Hepatomegaly can be seen in both DF and DHF but more common in DF. The incidence of hepatomegaly in the adult patients varies from 4 to 52%. Clinical jaundice has been found in only 1.7–17%, and hyperbilirubinemia has been found to be as high as 48% [13, 14].

5.1. Biochemical picture of liver (LFTs) in dengue fever

The most common abnormality has been raised transaminases levels. The raised aspartate transaminase (AST) levels are found around 63–97% of patients, whereas the elevated alanine transaminase (ALT) levels are found in 45–96% of patients [8].

Studies have shown in majority of cases that aspartate transaminase (AST) is usually more raised than alanine transaminase (ALT), more during the early infection, especially within first week and then declining to normal levels in next 3 weeks. Aspartate transaminase (AST) is more raised than alanine transaminase (ALT), the additional aspartate transaminase (AST) is released from damaged myocyte.

The reversal of alanine transaminase and aspartate transaminase (AST/ALT) ratio is helpful to differentiate it from other acute viral hepatitis like HAV, HBV, HCV, etc., where this is rarely seen except in alcoholic hepatitis [6].

The average levels of aspartate transaminase (AST) ranged from 93.3 to 174 U/L while alanine transaminase (ALT) from 86 to 88.5 U/L. The level of increase in hepatic transaminases can easily mimic acute viral hepatitis.

5.2. Role of transaminases as marker of severity of dengue fever

The median aspartate transaminase (AST) and alanine transaminase (ALT) values have been found to be higher for severer forms of dengue than for uncomplicated dengue fever [15].

This hints at a possible association between increased transaminase levels with increasing disease severity. Interestingly, the values of liver enzymes were noted to be higher in the febrile and the severer phases of dengue fever.

Aspartate transaminase (AST) has various sources including the heart, striated muscle, erythrocytes, etc., apart from the liver, whilst alanine transaminase (ALT) primarily is hepatic in origin. Therefore, rise in aspartate transaminase (AST) might not be a true reflection of hepatic

involvement. Moreover, patients with high levels of enzymes may be labeled as severe disease without any effect on the final outcomes [16].

Hypoproteinemia or hypoalbuminemia ranges from 16.5 to 76%. The heterogeneity in the population and severity of the disease may be responsible for such a wide range.

Coagulation abnormalities have been found in multiple studies. International normalized ratio (INR) > 1.5 have been found in 11% of patients, while abnormal prothrombin time (PT), partial thromboplastin time noted in 34–42.5% of the cases [17].

Increasing bleeding episodes have been seen with increasing alanine transaminase and aspartate transaminase (AST/ALT) levels, but correlation between PT and transaminase levels is not found to be strong during the recovery period, which means liver synthetic function like clotting factor production is usually well preserved.

Liver involvement comes commonly and with more severity in children as compared to adults [18]. Treatment is primarily supportive, and the prognosis is usually good. Differential diagnosis and hepatotoxic drugs should be avoided [19].

5.3. Suggestions

Liver function tests should be used as routine initial part of the investigative studies in a patient with suspected dengue fever.

Serial monitoring of liver function tests, especially alanine transaminase (ALT), should be done to identify high-risk cases.

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