

## The Utility of Liver Function Tests in Dengue

Dear Editor,

Dengue infection is endemic in many countries along the tropical and subtropical belt, with more than 100 million cases and 24,000 deaths annually worldwide.<sup>1</sup> Hepatic dysfunction is common in dengue infection, and is attributed to a direct viral effect on liver cells or as a consequence of dysregulated host immune responses against the virus. Other contributing factors include race, diabetes, hemoglobinopathies, pre-existing liver damage and the use of hepatotoxic drugs.<sup>2</sup> Although there are isolated case reports of fulminant hepatic failure, the derangements in the transaminases are usually mild and self-limiting. In our local context, liver function tests are performed almost routinely in patients with suspected dengue, even though these are probably indicated only in select patients.

We retrospectively analysed biochemical results of 127 serologically confirmed acute dengue cases admitted between November 2003 and December 2004 to Alexandra Hospital. The mean age was 33.0 years (range, 15 to 76) and 84 (66.1%) were male. All patients were IgM positive using the Panbio Dengue Duo Cassette (Brisbane, Australia; sensitivity 99%, specificity 98.6%). Thirty-four (26.8%) patients were positive for IgG antibodies to dengue, which is indicative of a prior dengue infection. One hundred and five patients had dengue fever with another 21 patients (16.5%) classified as having dengue haemorrhagic fever by World Health Organization (WHO) criteria (fever, thrombocytopenia (<100,000), blood hemoconcentration and haemorrhagic manifestations). One patient had dengue shock syndrome.

An average of 1.81 liver function tests were performed for each patient during hospitalisation and subsequent follow-up. 20.4% (26) patients had 3 or more liver function tests done (maximum 7). An elevation in aspartate aminotransferase (AST) level was seen in 90.6% and in alanine aminotransferase (ALT) in 71.7% (Table 1). Ninety (70.9%) patients had elevations of both AST and ALT. Abnormal levels of total bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) were observed in 13.4%, 5.5% and 44.1% of the patients, respectively. Low globulin level was observed in 14.2% and low albumin level in 16.5%. Mild-to-moderate elevations (up to 5-fold) in transaminases were common. The elevation of transaminases was 10-fold greater than the normal upper limit for AST and ALT in 10.2% and 9.5% of the patients, respectively. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were performed in 106 patients. Derangements were noted in

42.5% but these were typically mild, with aPTT being affected more than PT (PT 12.5+/- 2.4, PTT 37.2 +/-8.6). Thirteen patients had hepatitis serology performed, the indication being for elevated liver function tests. None had evidence of acute infection with one of the hepatitis viridae. One dengue fever patient was a known Hepatitis B carrier (HBsAg positive, HBe negative). He also consumed on average 2 pints of beer 3 times a week. His maximum AST levels were 94, ALT 73, ALP 72, GGT 83 and bilirubin 9 during admission. His liver function tests remained persistently elevated 2 months post-discharge.

Analysis showed that AST and ALT levels were significantly higher ( $P < 0.05$ ) in patients with any of the following clinical and laboratory features:

1. Patients with secondary dengue or dengue haemorrhagic fever.
2. Nausea or vomiting symptoms; bleeding manifestations or hepatomegaly on clinical examination.
3. Thrombocytopenia (<100 x 10<sup>9</sup> platelets/L) or an elevated haematocrit.

Clinically, 15 patients (11.8%) were noted to have mild hepatomegaly and 3 patients had mild splenomegaly. One patient had a palpable globular mass in the right hypochondrium but no confirmatory ultrasound of the hepatobiliary system was performed. No cases of clinical jaundice, fulminating hepatitis, liver failure or encephalopathy were observed. There was no dengue-related mortality in this study.

On discharge, most of the patients were given an outpatient appointment with our clinic. However, a significant number of patients, especially foreign workers, defaulted follow-up. In all, 39 (30.7%) patients had liver function tests repeated between 1 and 8 weeks post-discharge. In 14 patients, certain parameters such as bilirubin remained mildly abnormal. Further investigations such as liver ultrasound or a gastroenterology follow-up were usually planned. However, a significant proportion of patients again defaulted follow-up as they were asymptomatic and well.

Our study results correlated to those of previous authors, which showed that most dengue patients had some degree of mild-to-moderate liver involvement. In a Taiwan study, Kuo et al<sup>3</sup> reported similar results with elevations of AST and ALT in 93.3% and 82.2% of patients respectively. They noted that AST begins to increase from the 3<sup>rd</sup> day of illness, up to an average of 9.25 fold on the 6<sup>th</sup> day. After a peak on the 7<sup>th</sup> to 8<sup>th</sup> day, AST declines and normalises

typically by 3 weeks. ALT changes were noted to have a later onset and lower peak. In our study, AST level was higher than ALT in 75.6% (96) patients. This is postulated to be due to AST release from damaged monocytes. This can be used to differentiate dengue infection from acute hepatitis caused by Hepatoviridae A, B and C, where the AST/ALT ratio is reversed.<sup>4</sup> Patients with severe acute respiratory syndrome (SARS) have been found to have mild non-specific hepatitis. However, together with platelet count ( $>140 \times 10^9/L$ ) and total white count ( $>5 \times 10^9/L$ ), an AST  $<34$  IU/L in suspected SARS infection, can rule out dengue with 100% specificity.<sup>5</sup> Liver function tests may thus be useful in limited diagnostic situations.

In conclusion, dengue infection in adults typically runs a benign and self-limiting course. Transient mild-to-moderate transaminase elevation is common. Predictive factors for liver damage<sup>4</sup> have been identified including dengue haemorrhagic fever, secondary infection, thrombocytopenia, high blood concentration, female sex and children. Therefore, repeated liver function tests is unnecessary, except for cases with suggestive clinical and laboratory features. They should be taken from the 3<sup>rd</sup> up to the 8<sup>th</sup> day of illness. If clinically indicated, they can be repeated at least 3 weeks after discharge. Hepatitis serology is useful for patients with suspected hepatitis, or persistent liver function derangement on follow-up. Routine hepatobiliary ultrasound in acute dengue infection is not

recommended. Sonographic findings including gallbladder wall thickening, splenomegaly and ascites will spontaneously resolve.<sup>6</sup>

## REFERENCES

1. Gibbons RV, Vaughn DW. Dengue: an escalating problem. *BMJ* 2002;324:1563-6.
2. Seneviratne SL, Malavige GN, de Silva HJ. Pathogenesis of liver involvement during dengue viral infections. *Trans R Soc Trop Med Hyg* 2006;100:608-614.
3. Kuo CH, Tai DI, Chang-Chien CS, Lan CK, Chiou SS, Liaw YF. Liver biochemical tests and dengue fever. *Am J Trop Med Hyg* 1992;47:265-70.
4. Souza LJ, Alves JG, Nogueira RM, Gicovate Neto C, Bastos DA, Siqueira EW, et al. Aminotransferase changes and acute hepatitis in patients with dengue fever: analysis of 1,585 cases. *Braz J Infect Dis* 2004;8:156-63.
5. Wilder-Smith A, Earnest A, Paton N. Use of simple laboratory features to distinguish the early stage of severe acute respiratory syndrome from dengue fever. *Clin Infect Dis* 2004;39:1818-23.
6. Wu KL, Changchien CS, Kuo CH, Chiu KW, Lu SN, Kuo CM, et al. Early abdominal sonographic findings in patients with dengue fever. *J Clin Ultrasound* 2004;32:386-8.

Manzhi Wong,<sup>1</sup>MBBS, MRCS, Emily Shen,<sup>1</sup>MBBS, FRACP

<sup>1</sup> Department of General Medicine, Alexandra Hospital, Singapore

Address for Correspondence: Dr Wong Manzhi, 35 Jurong East Avenue 1 #10-02, Singapore 609774.

Email: manzhi@gmail.com

Table 1. Liver Function Tests in 127 Dengue Patients

	No.	Proportion of patients (%)	Mean	SD	Min	Max
Low albumin level ( $<35$ g/L)	21	16.53	38.89	6.07	6	51
Low globulin level ( $<23$ IU/L)	18	14.17	27.74	7.89	13	98
Elevated total bilirubin level ( $>22$ micromol/L)	17	13.39	16.20	17.61	5	189
Elevated alkaline phosphatase level ( $>122$ IU/L)	7	5.51	70.08	28.65	28	201
Elevated gamma-glutamyltransferase level ( $>50$ IU/L)	56	44.09	82.84	80.75	5	380
Aspartate aminotransferase level	115	90.6	163.18	184.58	16	1079
Normal ( $<36$ IU/L)	12	9.44				
1-5 fold elevation (36-175 IU/L)	80	62.99				
$>5$ fold elevation ( $>175$ IU/L)	35	27.56				
$>10$ fold elevation ( $>350$ IU/L)	13	10.24				
Alanine aminotransferase level	91	71.7	144.85	192.12	10	1237
Normal ( $<45$ IU/L)	36	28.35				
1-5 fold elevation (45-220 IU/L)	68	53.50				
$>5$ fold elevation ( $>220$ IU/L)	23	18.11				
$>10$ fold elevation ( $>440$ IU/L)	12	9.45				