Gastrointestinal Manifestations of Dengue Infection in Adults

E T Ooi, MRCP*, S Ganesananthan, FRCP*, R Anil, MRCP*, F Y Kwok, MBBS*, M Sinniah, FRCPath**

*Medical Department, **Virology Unit, Kuala Lumpur General Hospital, Jalan Pahang, 50586 Kuala Lumpur, Malaysia

SUMMARY

This is a retrospective study of the gastrointestinal symptoms, signs and laboratory parameters in adult dengue patients admitted to Kuala Lumpur Hospital from 1st December 2004 to 31st December 2004. Clinical and laboratory parameters that may predict the need for intensive care were investigated. Six hundred sixty-six patients with clinical and biochemical features consistent with dengue infection were identified. Patients were stratified into those who required intensive care and those who were managed in non high dependency wards. Serum alanine aminotransaminase (ALT) levels were normal in 22.8% of patients and 5.9% of patients had acute fulminant hepatitis. More patients with dengue haemorrhagic fever (DHF) had elevated ALT levels as compared to patients with classic dengue fever (DF) (p = 0.012). Patients with DF had a statistically significant lower mean ALT level as compared to patients with DHF. Abdominal pain (p=0.01) and tenderness (p < 0.001), gastrointestinal bleed (p< 0.001), jaundice (p< 0.001), hepatomegaly (p<0.001) and ascites (p<0.001) were predictors of need for intensive care. We conclude that gastrointestinal manifestations are very common in dengue patients. Presence of abdominal pain and tenderness, gastrointestinal bleed, jaundice, hepatomegaly and ascites can be used to triage patients requiring intensive care.

KEY WORDS:
Dengue, Gastrointestinal manifestations, Hepatitis, Intensive care

INTRODUCTION

Dengue is the most common and widespread arthropod-borne viral infection in the world today and is caused by a flavivirus spread by the *Aedes aegypti* mosquito. More than 2.5 billion people reside in areas that may be at risk for dengue infection[1]. It is estimated that each year 50-100 million cases of dengue fever occur out of which the potentially fatal dengue haemorrhagic fever (DHF) constitutes up to half a million cases[1].

Over the last few decades, there has been a dramatic increase in the incidence and geographical distribution of DHF,[2] and epidemics now occur frequently in some South-East Asian countries including Malaysia. In South East Asia the annual number of DHF cases has dramatically risen to more than 200,000 in the 1990s[3]. Malaysia has a diverse population comprising a Malay majority with ethnic Chinese, Indians and other minority groups making up slightly less than half the total population. Dengue fever was first reported in 1902 in Penang and has become a major public health problem in Malaysia[4]. Rapid industrial and economic progresses have brought massive infrastructure development, creating a man-made environment for breeding of Aedes mosquitoes. Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), dengue fever (DF), or dengue haemorrhagic fever (DHF) including dengue shock syndrome (DSS).

Atypical manifestations of dengue have been described, especially elevations in aminotransferase levels. Sixty five point two percent of patients with dengue infection were noted to have elevated aminotransferase levels in an epidemic in the city of Rio de Janeiro, Brazil in 2002 with 3.8% of patients suffering from acute fulminant hepatitis[5]. Some of the gastrointestinal clinical and laboratory parameters are associated with complications and poor outcomes[6]. We studied the gastrointestinal manifestations and liver involvement of dengue infection in adults during an epidemic of dengue fever in Kuala Lumpur and its suburbs. This study also aims to identify gastrointestinal symptoms, signs and laboratory parameters in patients who had a complicated clinical course and needed intensive care.

MATERIALS AND METHODS

We reviewed the medical records of all patients who were admitted to the Medical Wards of Kuala Lumpur Hospital with dengue infection from 1st December 2004 to 31st December 2004.

Case Definition[7]

Patients were included in the study if they had compatible clinical and laboratory states of acute febrile illness with two or more of the following manifestation:

- Headache
- Retro-orbital pain
- Myalgia
- Arthralgia
- Rash
- Haemorrhagic manifestations
- Leucopenia

and either supportive serology (Dengue IgM positive) or occurrence at the same location and time as other confirmed cases of dengue infection. DHF was classified and graded based on World Health Organization's definition[1].

This article was accepted: 12 November 2008
Corresponding Author: Ooi Ee Thiam, Department of Medicine, Kuala Lumpur Hospital, 50586 Kuala Lumpur, Malaysia
Email: ooieethiam@gamil.com

The gastrointestinal symptoms, signs and liver function tests were reviewed. The highest available ALT levels were taken for analysis. The reference level for serum ALT was 42 U/L or below. Acute hepatitis was graded according to the alterations in ALT levels; grade A – normal levels of ALT; grade B – elevated ALT but less than 4 times the upper limit of normal (ULN); grade C – elevated ALT between four 4 to 7 times the ULN; grade D – elevated ALT between 8 to 10 times the ULN; grade E – acute fulminant hepatitis, with ALT more than 10 times the ULN.

Patients were stratified into those who required intensive care and those who were managed in non high dependency wards. Criteria for admission to high dependency ward or intensive care unit were shown in Table I. Gastrointestinal parameters were compared between patients who required intensive care with those not needing intensive care.

Statistical analysis was done using chi-square test or Fisher's exact test for categorical variables, and t-test for continuous variables. Odd ratio was calculated by comparing the odds of patients requiring intensive care to the odds of not needing intensive care for each gastrointestinal parameter. Odd ratio was also calculated by comparing odds of having DHF to the odds of having DF for each gender and ethnicity (e.g. Malay vs. non-Malay).

RESULTS

Six hundred sixty-six patients with clinical and biochemical features consistent with dengue infection were identified. Two hundred and one patients had positive dengue IgM serology test, 22 patients had indeterminate dengue serology and 443 were clinical dengue without positive dengue IgM. The median age was 24 (range: 12-72) years with a male preponderance (n=433, 65%). Malays comprised 466 (70.0%), Chinese 82 (12.3%), Indians 55 (8.2%) and 63 (9.5%) were other races (Table II).

Two hundred and thirty cases (34.5%) had classic dengue fever and there were 436 cases (65.5%) of dengue haemorrhagic fever (Table II).

More male patients had DHF (p = 0.049, OR = 1.4, CI 1.00 – 1.94) while more Malays had DHF as compared to other ethnic groups (p=0.03, OR = 1.45, CI = 1.03-2.04).

Of the 666 patients, 28 needed intensive care with two deaths (Table III). A comparison of demographic characters showed that age and gender were not predictors for need of intensive care.

Patients presenting with abdominal pain (p = 0.01, OR = 2.91, CI = 1.26-6.7) and gastrointestinal bleed (p < 0.001, OR = 51.4, CI = 20.7-128.0) were more likely to develop severe disease and required intensive care compared to those who did not have abdominal pain or gastrointestinal bleed.

However, presence of nausea, vomiting and diarrhoea had no significant influence in the clinical course of disease and hence were not predictors of the requirement for intensive care.

Patients with jaundice (p<0.001, OR=34.5, CI=8.68-136.83)), hepatomegaly (p<0.001, OR=5.93, CI=2.74-12.82), abdominal tenderness (p<0.001, OR=20.7, CI=4.87-88.05) and signs of third space fluid loss such as ascites (p<0.001, OR=75.1, CI=21.23-265.51) or pleural effusion (p<0.001, OR=27.4, CI=11.20-66.95) were all more likely to require intensive care. (Table IV)

ALT levels were available for 627 patients (Table V). ALT levels were normal in 22.8% of patients (grade A); 51.8% had ALT levels between 1 to 4 fold of ULN (grade B); ALT levels were between 4 to 7 times the ULN in 13.9% of patients (grade C); 5.6% had ALT levels between 7 to 10 times ULN (grade D) and 5.9% of patients had acute fulminant hepatitis (grade E).

More patients with DHF had elevated ALT levels compared to patients with classic dengue fever (p = 0.012). However, there was no difference in severity of hepatitis between males and females.

Serum aspartate aminotransferase (AST) levels were not commonly checked in most of the patients; of the 22 patients who had both ALT and AST levels measured on admission, mean AST (319.1±346.8U/L) levels were higher than ALT (219.4±177.7U/L) levels, (95% confidence interval –232.7 to 33.3, p = 0.13).

The ALT decline was lowest at day 6±2 (range: 2-11) days, with the mean value for highest elevation in ALT of 140±166 (range:8-1394)U/L with 77.2% outside the normal range.

As shown in Table VI, patients with DSS had higher mean ALT levels compared to patients with DF (p<0.001), DHF grade 1 (p<0.001) and DHF grade 2 (p<0.005). Patients with DF had lower mean ALT levels compared to patients with DHF, grade 1 (NS) and grade 2 (p=0.006).

DISCUSSION

Acute hepatitis is a very common feature of dengue infection. Seventy seven point two percent of our patients presented with raised aminotransferase levels. However, the severity of hepatitis was mild to moderate in the majority of patients. Only 5.9% of the patients had acute fulminant hepatits with ALT levels more than 10 times of upper normal limits. Souza LJ *et al*,[5] reported an alteration in AST level in 63.4% and ALT in 45% of dengue patients. Kuo *et al*,[8] found that AST and ALT levels were abnormal in 93.3% and 82.2% of patients, respectively. However the increase in aminotransferase levels are usually mild to moderate. Acute fulminant hepatitis only occurred in 3.8% to 7.4% of patients,[5,8] and usually in patients with dengue haemorrhagic fever or DSS. Fulminant liver failure can occur due to hepatitis or focal necrosis of the liver causing hepatic encephalopathy and even death[9]. Extensive necrosis of hepatocytes was seen in 18 fatal cases of dengue infection with acute liver failure in Thailand and there was dengue antigen in liver tissue in 15 of them[10]. Viral antigen can be detected in hepatocytes, Kupffer cells and occasionally in acute inflammatory cells; suggestive of viral replication in the liver. Acute liver failure can also be seen as part of multi-organ failure which carries a poor prognosis. It has been

Table I: Criteria for admission to high dependency ward or intensive care unit

1. Patients showing signs of encephalitis ie confused, restless or a drop in Glasgow coma scale
2. Tachypnoea with respiratory rate ≥ 25/minute or P_aCO_2 ≤ 25mmHg, P_aO_2 < 60mmHg with F_iO_2 0.4
3. Systolic blood pressure < 90mm/Hg or mean arterial pressure (MAP) < 65mm/Hg for the last 4 hours despite fluid resuscitation
4. Urine output < 0.5mls/kg/hour for the last 4 hours despite fluid resuscitation
5. Metabolic acidosis with pH < 7.3 or bicarbonate of ≤ 18 mmol/L

Table II: Classification of dengue infection by ethnicity and gender

	DF* n=230 (34.5%)	DHF** Grade 1 n=267 (40.1%)	DHF** Grade 2 n=160 (24.0%)	DHF** Grade 3 n=7 (1.1%)	DHF** Grade 4 n=2 (0.3%)	Total n=666 (100.0%)
Malay	149 (32.0%)	195 (41.8%)	117 (25.1%)	4 (0.9%)	1 (0.2%)	466
Chinese	39 (47.6%)	27 (32.9%)	16 (19.5%)	0	0	82
Indian	27 (49.0%)	16 (29.1%)	11 (20.0%)	0	1 (1.8%)	55
Foreigners	15 (23.8%)	29 (46.0%)	16 (25.4%)	3 (4.8%)	0	63
Male	138 (31.9%)	177 (40.9%)	112 (25.9%)	4 (0.9%)	2 (0.5%)	433 (65.0%)
Female	92 (39.5%)	90 (38.6%)	48 (20.6%)	3 (1.3%)	0	233 (35.0%)

DF* = Classic dengue fever; DHF** = Dengue hemorrhagic fever

Table III: Comparison of demographic characteristics and gastrointestinal symptoms as predictors of requirement for intensive care.

Characteristics / Symptoms	N (666)	Intensive Care (n=28)	Without intensive care (n=638)	P values
Age (mean,year)	27.2±11.1	25.8±11.6	27.2±11.1	0.56
Male : Female	433 : 233	17 : 11	416 : 222	0.68
Nausea	425	16	409	0.54
Vomiting	429	20	409	0.54
Diarrhoea	237	14	223	0.11
Abdominal pain	315	20	295	0.01
GI bleed	29	15	14	< 0.001

Table IV: Comparison of gastrointestinal signs as predictors of requirement for intensive care

Characteristic / Signs	N (666)	Intensive Care (n = 28)	Without intensive care (n = 638)	P values
Jaundice	9	5	4	< 0.001
Hepatomegaly	119	15	104	< 0.001
Splenomegaly	2	1	1	0.08
Abdominal tenderness	272	26	246	< 0.001
Ascites	13	9	4	< 0.001
Pleural effusion	84	21	63	< 0.001
Maculopapular rash	196	6	190	0.40

Table V: Grading of severity of hepatitis based on serum alanine aminotransferase (ALT) levels

Grade of Hepatitis Total	A 143 (22.8%)	B 325 (51.8%)	C 87 (13.9%)	D 35 (5.6%)	E 37 (5.9%)	Total 627 (100%)
Sex						
Male	100	208	52	26	22	408 (65.1%)
Female	43	117	35	9	15	219 (34.9%)
Dengue (p = 0.012)						
Classic	66	103	28	9	9	215 (34.3%)
Hemorrhagic	77	222	59	26	28	412 (65.7%)
DHF Grade 1	48	142	30	16	12	248 (39.5%)
DHF Grade 2	27	78	28	10	13	156 (24.9%)
DHF Grade 3	1	2	1	0	3	7 (1.1%)
DHF Grade 4	1	0	0	0	0	1 (0.2%)

Grade A – normal levels of ALT
Grade B – elevated ALT but less than 4 times the ULN
Grade C – elevated ALT between four 4 and 7 times the ULN
Grade D – elevated ALT between 8 and 10 times the ULN
Grade E – acute fulminant hepatitis, with ALT more than 10 times the ULN

Table VI: Mean ALT Level in Each Class of Dengue Infection

Classification	ALT Level U/L(Mean±SD)
*DF	117.7±142.5
**DHF Grade 1	130.1±126.6
**DHF Grade 2	174.1±216.9
***DSS (DHF Grades 3 & 4)	343.5±386.9
Total	139.5±166.2

*DF = Classic dengue fever; **DHF = Dengue hemorrhagic fever;
***DSS = Dengue shock syndrome

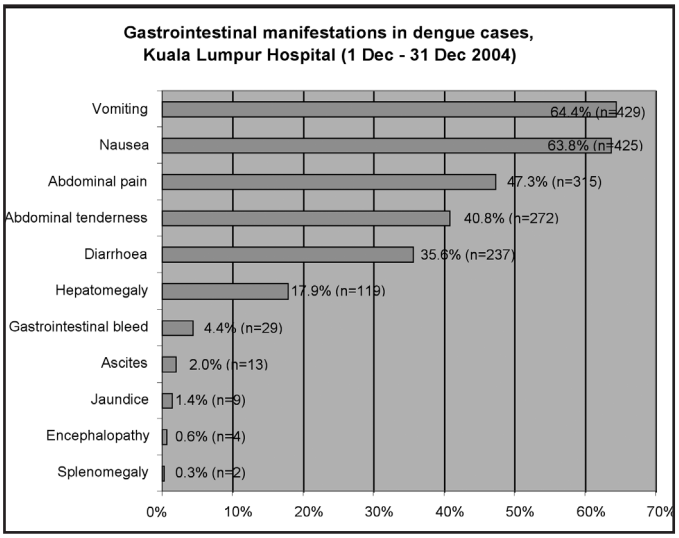

Fig. 1

shown that liver injury is an adverse prognostic factor for development of DHF. This increase usually happens within the first nine days of symptoms and normalizes in about two weeks[11].

Kuo et al and Souza LJ *et al* also noted that AST levels were significantly higher than ALT levels in dengue hepatitis. We found a similar pattern in our centre which did not achieve statistical significance as serum AST is not routinely measured.

Liver damage was more common and greater in patients with DHF. There were more patients with DHF (81.3%) with elevated ALT levels compared to patients with classic dengue fever, 69.3% (p = 0.012). The severity of hepatitis was greater in DHF. The mean ALT levels were significantly higher in patients with dengue shock syndrome (DHF grade 3; we were unable to analyse cases of DHF grade 4 as only two cases were available) compared to patients with classic DF. Wahid et al also found a similar pattern of dengue hepatitis. Indeed, liver injury is recognized as a predictive factor for development of DHF[11].

Gastrointestinal symptoms and signs are very common among dengue patients. More than half the patients presented with nausea (63.8%) and vomiting (64.4%). Forty seven point three percent of patients had abdominal pain and 35.6% had diarrhoea. Four point four percent of dengue infections were complicated by gastrointestinal bleed. Forty point eight percent of patients had tender abdomen while hepatomegaly was found in 17.9% of patients.

Among the 666 patients, 28 patients needed intensive care and two of them died. We studied the above symptoms and signs to look for predictors for need of intensive care. We found that abdominal pain and tenderness, gastrointestinal bleed, jaundice and hepatomegaly were all predictors for need of intensive care. Signs of plasma leakage such as ascites and pleural effusion, as expected, were also predictors of serious disease that needed intensive care. Symptoms of nausea and vomiting, though very common, were not associated with serious disease.

We also found that male and Malay patients were more likely to have dengue hemorrhagic fever compared to female and non-Malay patients respectively.

Although dengue infection is usually a self-limiting viral infection and only a small proportion of patients need intensive support, failure to identify this group of patients early may lead to a high risk of mortality. The main challenge of managing dengue infection during epidemics is in the burden of numbers on the existing human resources, hospital beds, laboratory and transfusion support. As mentioned, there were 666 adult dengue patients admitted to our hospital in just the month of December 2004, and without identifying and focusing on the high risk dengue patients, our resources will definitely be stretched.

As this is a retrospective study, there were a few potential biases during the retrospective data collection. The diagnosis of dengue infection was based on the definition from "Clinical Practice Guidelines 2003 - Management of Dengue Infection in Adults" published by the Ministry of Health Malaysia and Academy of Medicine Malaysia,[7] which include clinical dengue without presence of positive dengue serology. The dengue-specific IgM can be negative in tests during the first 5 days of illness, since it appears on or about 5th day. A repeat blood sampling and retest for dengue IgM would have established the diagnosis and this was carried out in a proportion of patient but this was not always possible due to logistic reasons. Efforts were made to review the disease pattern of each patient retrospectively so that only patients with clinical pattern consistent with dengue infection were included. The presence of symptoms and signs in this study was dependent on the proper documentation from the case records and complete physical examinations. There was also variation in the timing and frequency of blood investigations, especially for serum alanine-aminotransferase levels; therefore these levels may not be the actual peak levels for the patients.

In conclusion, dengue patients presenting with abdominal pain and tenderness, hepatomegaly, gastrointestinal bleed,

jaundice, signs of plasma leakage and very high serum aminotransferase levels should be given closer observation as they are likely to require intensive care.

REFERENCES

1. World Health Organization. Dengue haemorrhagic fever: diagnosis, treatment, prevention and control 2nd ed. Geneva: WHO, 1997.
2. Monath TP. Dengue: the risk to developed and developing countries. Proc Natl Acad Sci USA 1994; 91: 2395-400.
3. Gibbons RV, Vaughn DW. Dengue: an escalating problem. BMJ 2002; 324: 1563-66.
4. Skae FM. Dengue fever in Penang. BMJ 1902; 2: 1581-82.
5. Souza LJ, Alves JG, Nogueira RM, *et al*. Aminotransferase changes and acute hepatitis in patients with dengue fever: analysis of 1585 cases. Braz J Infect Dis 2004; 8(2): 156-63.
6. Narayanan M, Aravind MA, Ambikapathy P, *et al*. Dengue fever – clinical and laboratory parameters associated with complications. Dengue Bulletin 2003; 27: 108-15.
7. Clinical Practice Guidelines. Management of Dengue Infection In Adults, Ministry of Health Malaysia, Academy of Medicine Malaysia. December 2003.
8. Kuo CH, Tai DI, Chang-Chien CS, *et al*. Liver biochemical tests and dengue fever. Am J Trop Med Hyg 1992; 47(3): 265-70.
9. Nguyen TL. The impact of dengue hemorrhagic fever on liver function. Res Virol 1997; 148: 273-77.
10. Bruce LI, Khin SAM, Ananda N, *et al*. Acute liver failure is one important cause of fatal dengue infection. Southeast Asian J Trop Med Public Health 1990; 21: 695-96.
11. Kalayanarooj S, Vaughn DW, Nimmannitya S, *et al*. Early clinical and laboratory indicators of acute dengue illness. J Infect Dis 1997; 176(2): 313-21.