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*World J Clin Cases* 2017 July 16; 5(7): 258-306



**MINIREVIEWS**

- 258 New device to implement the adenoma detection rate  
*Zippi M, Hong W, Crispino P, Traversa G*
- 264 Screening of celiac disease in Down syndrome - old and new dilemmas  
*Pavlovic M, Berenji K, Bukurov M*
- 270 Practical approach to the patient with acute neuromuscular weakness  
*Nayak R*

**ORIGINAL ARTICLE****Retrospective Study**

- 280 Feasibility of initial endoscopic common bile duct stone removal in patients with acute cholangitis  
*Yamamiya A, Kitamura K, Ishii Y, Mitsui Y, Nomoto T, Yoshida H*

**SYSTEMATIC REVIEWS**

- 286 Diagnostic performance of high resolution computed tomography in otosclerosis  
*Kanzara T, Virk JS*

**CASE REPORT**

- 292 Post traumatic dural sinus thrombosis following epidural hematoma: Literature review and case report  
*Pescatori L, Tropeano MP, Mancarella C, Prizio E, Santoro G, Domenicucci M*
- 299 Rare case of cryptogenic brain abscess caused by *Raoultella ornithinolytica*  
*Luongo M*
- 303 Is dengue emerging as important cause of acute liver failure in endemic regions?  
*Singh L, Singh A, Agarwal M, Mishra S*

## Contents

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The primary task of *WJCC* is to rapidly publish high-quality Autobiography, Case Report, Clinical Case Conference (Clinicopathological Conference), Clinical Management, Diagnostic Advances, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Clinical Practice, Meta-Analysis, Minireviews, Review, Therapeutics Advances, and Topic Highlight, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, geriatrics and gerontology, hematology, immunology, infectious diseases, internal medicine, obstetrics and gynecology, oncology, ophthalmology, orthopedics, otolaryngology, pathology, pediatrics, peripheral vascular disease, psychiatry, radiology, rehabilitation, respiratory medicine, rheumatology, surgery, toxicology, transplantation, and urology and nephrology.

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## Is dengue emerging as important cause of acute liver failure in endemic regions?

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### Abstract

Dengue virus infection continues to be major public health problem in large part of world. The epidemiology of dengue viral infection is becoming increasingly complex and has substantially changed over almost past six decades not only in terms of prevalent strains and geographical locations but also in terms of disease severity and atypical presentations. Though liver is the most common organ affected but is generally asymptomatic. We present a case of infant with severe dengue who died of fulminant hepatic failure and showed pan lobular necrosis on post mortem liver biopsy. The case is being presented to highlight life threatening complication of dengue in young children, and dengue viral infection as a cause of acute liver failure in endemic areas. Thus dengue fever should also be considered as one of the differential diagnosis in children presenting with fever and fulminant hepatic failure in endemic regions.

**Key words:** Dengue viral infection; Acute liver failure; Panlobular hepatic necrosis; Hepatomegaly; Transaminitis

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**Core tip:** Dengue infection has more severe manifestation in young children and it should be considered as a cause of acute liver failure in children residing in endemic area.

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## INTRODUCTION

Dengue virus (DENV) infections continue to be a major public health problem in large parts of the world<sup>[1]</sup>. It is one of the most important causes of febrile illness in endemic regions. DENV affects various organs during the period of viremia including liver and brain. Liver is the most common organ affected but is generally asymptomatic. Liver involvement ranges from derangement of liver enzymes, increased bilirubin to clinical jaundice and acute liver failure rarely. DENV is known to cause severe manifestation in infants. Virus virulence factor and detrimental host response are responsible for severe manifestations of dengue.

We present a case of infant with severe dengue who died of fulminant hepatic failure and showed pan lobular necrosis on post mortem liver biopsy. The case is again a reminder of life threatening complication of dengue in young children, and DENV as a cause of acute liver failure in endemic areas.

## CASE REPORT

A 3-mo-old male, presented, with jaundice and frank bleeding from multiple sites (gastrointestinal, nasal, skin). Child was relatively asymptomatic 1 wk back then developed high grade fever with running nose. On 3<sup>rd</sup> day of illness, child had one episode of seizure followed by altered sensorium which persisted beyond postictal period. He was documented to be afebrile for 2 d before developing frank bleeding, abdominal distension and worsening of sensorium. On examination, child was sick looking with pallor, deep icterus and rapid pulse. Abdominal examination revealed hepatomegaly with liver 8 cm below the costal margin with sharp border and mild tenderness.

The differential diagnosis of acute infective viral hepatitis, complicated malaria, leptospirosis, severe dengue was kept and investigations ordered. Baseline investigations are shown in Table 1.

Child met the criteria for acute liver failure defined by the Pediatric Acute Liver Failure study group as there was no past history of chronic liver disease, his coagulopathy was not corrected after giving vitamin K and he was in hepatic encephalopathy with deranged PT/INR. Child was managed with supportive care (vitamin K, fresh frozen plasma infusion for coagulopathy), broad spectrum antibiotic, monitoring for electrolyte abnormality and hypoglycaemia and management of raised intracranial pressure. Despite these measures, there was progressive deterioration in clinical condition with requirement for mechanical ventilation. Child succumbed to the illness, 12 h after admission due to massive bleed and refractory shock, in the setting of fulminant hepatic failure.

The post-mortem liver biopsy showed multilobular and pan lobular hepatic necrosis with predominant involvement of centrilobular and midzonal regions with relative sparing of zone 1 (Figure 1). Thus, final diagnosis of severe dengue fever<sup>[1]</sup> with acute liver failure was made.

## DISCUSSION

Dengue has recently emerged as the most rapidly spreading arboviral disease with an estimated 390 million dengue infections annually<sup>[2]</sup>. The pattern of dengue fever in Indian subcontinent has changed substantially in the last 60 years shifting from sporadic epidemic disease to an endemic one. With the endemicity, the disease severity has changed and atypical presentations like acute liver failure, myositis, hemophagocytic syndrome myositis are increasingly being reported<sup>[3]</sup>.

Dengue fever has a spectrum of clinical manifestations ranging from self-limited illness to fulminant course resulting in death. Younger age is a risk factor for severe manifestation of dengue. Virus virulence factor and detrimental host response are responsible for severe manifestations of dengue. Pathogenesis of the different manifestations of dengue virus infections in humans is still an area of research. The spectrum of clinical manifestation of dengue involves relatively benign subclinical infection or dengue fever to life-threatening dengue haemorrhagic fever, and dengue shock syndrome (DSS). Differential targeting of specific vascular beds may cause localized vascular hyperpermeability seen in DSS. Hepatic involvement is usually subclinical but dengue virus is known to have hepatotoxic effect. Derangement of liver enzymes and jaundice may be seen and rarely it may cause acute liver failure. In presence of detrimental host response like young age as in our case, the rare manifestations of dengue are increasingly being recognized in endemic areas.

With considerable decrease in the prevalence of hepatitis B due to universal immunization and hepatitis A due to improved sanitation dengue has emerged as an important cause of acute liver failure in children especially during epidemics<sup>[4]</sup>.

Hepatic involvement in dengue fever presents with liver enlargement and elevated transaminases<sup>[5,6]</sup>. In most of the studies, elevation in AST is more than ALT. The increased AST/ALT ratio seen in dengue fever is rarely observed in Hepatitis A, B or C viruses induced acute hepatitis<sup>[7]</sup>. The mortality rate is reported to be 50% to 66% in childhood dengue infection associated ALF<sup>[8]</sup>.

The pathogenesis of hepatic injury in dengue infection remains elusive however it is believed to be multi factorial and various factors implicated include direct viral injury, dysregulated immune response and hypoxic/ischemic injury. The frequent use of acetamino-

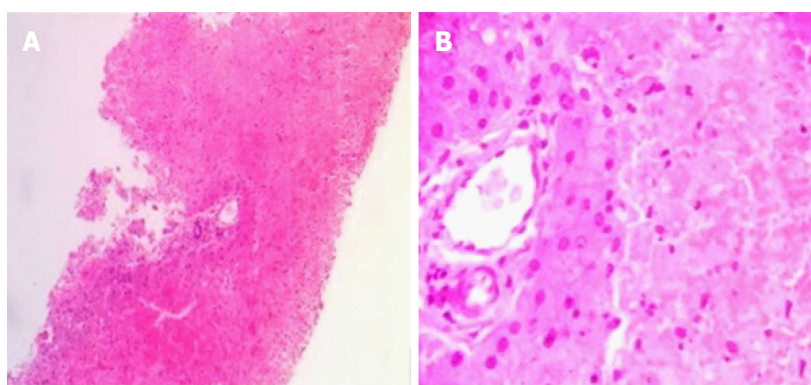
**Table 1** Baseline investigation of the infant with acute liver failure caused by Dengue infection

Investigation	Result	Reference range
Hb	8.4 g/dL (haematocrit 25.9%)	10.0-13.2 g/dL
Total leukocyte count	14000/mm <sup>3</sup>	6-17.2 × 10 <sup>3</sup> /uL
Differential count	Neutrophil (N) 68, Lymphocyte (L) 25	N 15-45, L 47-77
Platelet	98 × 10 <sup>3</sup> cells/mm <sup>3</sup>	1.5-4.5
Peripheral smear	No malarial parasite, no atypical cell, microcytic hypochromic picture	
ALT	3853 IU	13-45 IU/L
AST	20861 IU	9-80 IU/L
Total bilirubin	8.28 mg/dL	< 1.2 mg/dL
Direct bilirubin	4.59 mg/dL	< 0.2 mg/dL
Total protein	4.02 g/dL	
Alkaline phosphatase	171 IU	80-280 IU
Prothrombin time	56.4 s	11.5-15.3
Control	12.4 s	
CRP	90 mg/L	0-5 mg/L
Renal function test	Urea 121.6 mg/dL Creatinine -0.3	7-20 mg/dL 0.2-0.4 mg/dL
Infective etiology work up	LDH antigen for malarial parasite - negative Chikungunya PCR - negative Hepatitis A IgM, anti hepatitis E IgM - negative Hepatitis B surface antigen - negative Hepatitis C IgM - negative Dengue NS-1 antigen and IgM antibody - positive (serum capture enzyme linked immunosorbent assay) Leptospira IgM - negative	

ALT: Alanine transaminase; AST: Aspartate transaminase.

**Table 2** Differential diagnosis in cases presenting with fever and acute hepatic failure<sup>[12]</sup>

	Acute viral hepatitis	Complicated malaria	Leptospirosis	Dengue associated ALF
High grade fever	Absent	Present	Present	Present
Haematocrit	Normal	Normal	Falls	Raised
Platelet	Normal	Decreased	Normal	Decreased
SGOT	Raised	Normal	Normal	Raised
SGPT	Raised	Normal	Normal	Raised
SGOT/SGPT	Raised	Normal	Normal	Markedly raised
Hypoalbuminemia	Not seen in acute viral hepatitis may be seen in acute on chronic cases	Absent	Absent	Present especially in DHF due to plasma leakage <sup>[11]</sup>
Renal function test	Deranged	Normal	Normal	Deranged in DHF and DSS due to hypotension
Plasma leak	Absent	Rare	absent	Present
Peripheral smear	-	Malaria Parasite	-	-



**Figure 1** Liver biopsy showing multilobular and pan-lobular hepatic necrosis (A, HE × 200); Higher magnification shows relative sparing of zone 1 hepatocytes (B, HE × 400).

phen in dengue may add to liver injury in susceptible individual<sup>[9]</sup>.

Liver biopsy in fatal cases of dengue points to Hepatocytes and Kupffer cells as prime targets for dengue virus infection<sup>[10]</sup>.

Several hepatic histological changes have been reported in dengue infection<sup>[9]</sup>. This includes fatty change (micro vesicular), Kupffer cells hyperplasia, and destruction, hepatic necrosis, Councilman bodies and infiltrates at the portal tract consisting of mainly

mononuclear cells. The midzonal area is most commonly involved followed by the centrilobular area. This may be due to higher susceptibility of the hepatocytes in midzonal area to anoxia but preferential targeting of the midzonal hepatocytes by dengue virus may also be a possibility.

The magnitude of liver involvement in acute phase of dengue may be missed as DENV hepatic involvement and its manifestations peaks around day 6-7 of illness<sup>[11]</sup>.

The possible pointers to hepatic involvement in early phase include extreme nausea and vomiting with laboratory tests showing very high levels of AST with rise in serum bilirubin and alkaline phosphatase. Such presentation should raise the suspicion of impending liver failure (Table 2).

Primary dengue infection may lead to pan lobular hepatic necrosis. In dengue, endemic regions, dengue fever should be one of the differential for fever with fulminant hepatic failure in children.

## COMMENTS

### Case characteristics

A three-month-old child with fulminant hepatic failure.

### Clinical diagnosis

Child was clinically diagnosed as dengue induced acute liver failure with evidence of coagulopathy and encephalopathy.

### Differential diagnosis

The differential of acute liver failure in such young infant will be infective or metabolic causes. For the indexed patient infective causes were considered as the first possibility. Malaria, chikungunya, leptospirosis, hepatitis A and E were ruled out.

### Laboratory diagnosis

Dengue NS1 Ag and IgM were positive by serum capture enzyme linked immunosorbent assay.

### Pathological diagnosis

Panlobular hepatic necrosis caused by dengue virus infection.

### Treatment

Child received vitamin K, fresh frozen plasma, broad spectrum antibiotic and 3% NaCl for raised intracranial pressure.

### Related reports

Please provide other contents related to the case report to help readers better

understand the present case.

## Experiences and lessons

Dengue may have fulminant course in young children. The prognosis will be worse in presence of pan lobular necrosis.

## Peer-review

The main highlight of the case is presence of dengue induced pan lobular necrosis in such a young infant. The main limitation of the report is inability to explain reasons behind such fatal complication of dengue virus in such patients.

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