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Management of hepatic manifestations of dengue fever

Saima Majid Mattoo[1*], Maryam Nazir Ahmad[1], Reem Imadeldin Hamad[2], Imadeldin Ahmed[3], Rajesh Gupta[3], Noble Thomas[4]

[1] Specialist Physician, Department of Internal Medicine, Sharjah Kuwait Hospital, United Arab Emirates
[2] Medical Student, Ajman University, United Arab Emirates
[3] Consultant Physician, Department of Internal Medicine, Sharjah Kuwait Hospital, United Arab Emirates
[4] Consultant Physician, Department of Gastroenterology, Sharjah Kuwait Hospital, United Arab Emirates
Corresponding Author: Saima Majid Mattoo

Abstract

Background: Dengue is a mosquito-transmitted viral infection that causes symptoms such as fever, headaches, joint pain, nausea, vomiting, and retroorbital pain. In more severe instances, it can progress and cause liver involvement, ranging from mild transaminitis to acute liver failure. [1]

Case presentation: We present a case series of three Asian males who presented with similar symptoms of fever and body ache for few days. They were diagnosed with dengue virus based on lab results showing severe thrombocytopenia and a positive PCR test.

Upon admission, all the patients were vitally stable, alert, and oriented, though dehydrated. Their physical examination showed no major abnormalities except for dehydration. Initial lab results showed a severely low platelet count and elevated liver function tests (high AST, ALT), indicating liver dysfunction. Coagulation parameters and C-reactive protein were also elevated.

Management included IV fluids and symptomatic treatment. During hospital stay, patients deteriorated further with worsening liver function, leading to acute hepatic failure, treated with N-acetylcysteine.

Despite complications, their platelet count and liver functions gradually improved with supportive care, and all three patients were discharged in a stable condition.

Conclusion: Early evaluation and treatment of hepatic manifestations in dengue fever improves patient outcome.

Keywords: Dengue fever, hepatitis, transaminitis, hepatic failure

Introduction

Dengue is a mosquito-borne virus and is the most common cause of arthropod-borne viral infections worldwide. The virus is transmitted by several species of Aedes mosquitoes, predominantly Aedes aegypti, Ae. polynesiensis, Ae. scutellarin, and Ae. albopictus. Dengue fever can be caused by one of four serotypes: DEN-1, DEN-2, DEN-3, and DEN-4. It is a single-stranded RNA (ssRNA) virus with positive-sense RNA (5' to 3') that belongs to the Flaviviridae family, and its RNA can be directly translated into proteins.

The symptoms of dengue can vary in severity, typically appearing three to four days after infection. The illness usually lasts between five and seven days and can have a biphasic pattern, remittent course, or low-grade presentation. Liver involvement can start as early as the first 5 days of illness. It can either settle spontaneously, or progress to acute liver failure, also referred to as dengue related acute liver failure. [1]

Acute hepatic failure linked to dengue fever has been documented, primarily in children, with a few isolated cases reported in adults. Risk factors for acute liver failure include individuals under 40 years of age, elevated liver enzyme levels within the first five days of illness, those with lymphocytosis and low platelet count at the time of presentation, severe hepatitis at the first contact and a MELD score higher than 15 (Model for end stage liver disease). [1]

This paper discusses dengue fever related hepatic manifestations that were seen during rainy season in May-June 2024 with a focus on three patients who developed acute liver failure and were treated successfully.

Case Report

Case presentation

We report three cases of dengue infection in Asian patients - two males aged 41 and 46 years and one female aged 26years -who presented with almost similar clinical symptoms of fever, myalgia and reduced oral intake of several Days duration. Dengue infection was confirmed by positive polymerase chain reaction testing in all cases. Initial investigations revealed severe thrombocytopenia, elevated transaminases, deranged coagulation parameters, and raised inflammatory markers.

On admission, patients were hemodynamically stable, conscious, and oriented. Clinical examination was unremarkable apart from evidence of dehydration. They were managed with intravenous hydration and supportive care. Their hematological and biochemical parameters were monitored regularly.

Despite initial optimal supportive management, all three patients demonstrated progressive worsening of hepatic function, characterized by rising liver enzymes levels, raising concern for acute dengue associated liver injury. Hepatitis-B and C serology was negative for all three patients. Given the continued deterioration in liver function tests despite supportive measures and the risk of progression to severe hepatic injury, intravenous N-acetylcysteine was initiated as adjunctive therapy. Following initiation of N-

acetylcysteine, serial biochemical monitoring demonstrated stabilization and then a gradual sustained improvement in transaminase levels in all three patients, suggesting a temporal association between treatment and recovery of hepatic function.

Following treatment, liver function tests showed gradual and sustained improvement in all 3 patients. Concurrently platelet counts improved as part of the natural course of dengue infection. All patients experienced favorable clinical outcomes without major complications and were discharged in stable condition with appropriate outpatient follow up in infectious disease clinic.

Table 1: Patient 1: Male -41 years

	On admission	**Follow up in ward**	**On discharge**	**On followup in opd**
Platelet (/mcL)	28,000	34,000	84,000	196,000
Creatinine(umol/L)	Normal		Normal	
ALT(IU/L)	159	404	162	118
AST(U/L)	262	816	154	65
CRP (mg/L)	47.6	Not available	Not available	Not available
Ferritin (ng/ml)	4587	Not available	Not available	Not available
Hepatitis serology (Hep B sAg, Hep C Ab)	Negative	-	-	-

Patient 2: Male-46 years

	On admission		**On discharge**	**On followup in opd**
Platelet (/mcL)	19,000	12,000	243,000	403,000
Creatinine(umol/L)	Normal		Normal	
ALT (IU/L)	292	1018	192	117
AST(U/L)	303	2353	129	63
CRP (mg/L)	11.3	Not available	Not available	Not available
Ferritin (ng/ml)	6454	Not available	Not available	Not available
Hepatitis serology (Hep B sAg, Hep C Ab)	Negative	-	-	-

Patient 3: Female -26 years

	On admission		**On discharge**	**On follow-up in opd**
Platelet (/mcL)	114,000	96,000	147,000	484,000
Creatinine(umol/L)	Normal		Normal	
ALT (IU/L)	634	698	389	165
AST(U/L)	544	564	127	26
CRP (mg/L)	9	Not available	Not available	Not available
Ferritin (ng/ml)	6298	Not available	Not available	Not available
Hepatitis serology (Hep B sAg, Hep C Ab)	Negative	-	-	-

Laboratory work of all patients showed a general trend of initial thrombocytopenia, increasing trend of transaminases followed by decrease, normal to borderline CRP and high ferritin (acute phase reactant). Radiology was generally unremarkable apart from mild serositis associated with dengue fever.

Discussion

Background

As per data published by World health organization (WHO) in December 2025, the year 2024 saw the highest burden of dengue in the world in history. There were 7718585 confirmed cases, of which 52738 were classified as severe. 11,201 deaths were reported due to dengue fever. [2]

In a retrospective analysis of 1664 patients admitted at a certain facility in India between 2016 and 2021, incidence of dengue hepatitis was seen to be 11.9% (199 patients). Of these 199 patients, 36% had severe dengue and 4% developed acute liver failure. Overall mortality in patients with dengue hepatitis was 17%, mostly attributable to multi organ dysfunction. Mortality in patients with acute liver failure was 37%. [3]

In another meta-analysis done on 26,389 dengue patients from 21 studies, the overall mortality of patients developing acute liver failure with dengue was 47%. [4]. These numbers highlight the importance of early recognition of hepatic manifestations of dengue fever, and the need for early intervention wherever required.

Pathogenesis

Hepatic involvement of dengue fever can present in various forms, ranging from mild elevation of hepatic enzymes (alanine aminotransferase-ALT and Aspartate amino transferase –AST), to fulminant hepatic failure. Associated with this spectrum are other manifestations like abnormal coagulation, represented by an abnormal international normalized ratio (INR) and hepatic encephalopathy, represented by altered consciousness. [5, 22]

Plasma leakage is the most widely accepted explanation of organ involvement in dengue fever. This is achieved through dysfunctional endothelial cell junctions, coupled with cascade of various nonspecific inflammatory markers including interleukins, tumor necrosis factor, nitric oxide, vascular endothelial growth factor, and complement. [6]

The liver forms the site of viral replication in the body. This exposes the liver to risk of direct injury from the virus. Once the dengue virus enters the liver and begins to multiply, it interferes with the normal function of the endoplasmic reticulum and mitochondria, causing oxidative stress and cell death, which worsens the damage to the liver. Liver injury itself causes release of further cytokines into the blood stream, which can in turn lead to further multi organ damage. [7]

Histopathological analysis of damaged hepatocytes shows features of apoptosis and necrosis. Sudden deposition of fat globules in hepatocytes is seen as well, which triggers even further inflammatory response in the form of markedly increased reactive oxygen species, which leads to severe oxidative damage. Death of hepatocytes causes afflux of macrophages, monocytes, neutrophils and lymphocytes. Their aim is to remove damaged cells and control the viral infection. However, all these cells by their individual cytokine response inducing capabilities, end up causing further direct damage to hepatocytes. These responses include the production of tumor necrosis factor alpha, reactive oxygen species, perforin-induced mechanism, and Kupffer cell activation. All these pathways lead to increased vascular permeability and disruption of hepatic function. [7, 10]

Part from causing increased vascular permeability, hyperactivated Kupffer cells also lead to sinusoidal congestion through their hyperplasia. These cells tend to consume platelets and red blood cells, thus causing thrombocytopenia, development of microvascular thrombi within hepatic sinusoids, sinusoidal overload, increased intra hepatic pressure and reduced delivery of blood and oxygen to hepatocytes. The overall ability of the liver to function is affected as fewer nutrients reach the salvable hepatocytes. [6, 7]

In patients with secondary dengue infection, the preexisting antibodies may form complexes with the dengue virus, leading to easier uptake into macrophages. This may explain why some dengue strains are faster spreading, since uptake into macrophages also increases their rate of replication. [8, 9]

Clinical Presentation

Dengue fever associated with hepatic dysfunction has been reported from multiple areas in South Asia, tropical and subtropical regions. [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] In 2024, a systematic review of previously published cases of dengue fever with liver involvement was published, in which 2552 papers were identified, and 167 of these were included in the study. [5]. This review analyzed the multiple ways hepatic involvement is demonstrated in dengue fever. Patients may present with nonspecific symptoms including nausea, vomiting, abdominal pain, occasionally jaundice and hepatomegaly on radiology. Liver appears enlarged and echogenic due to hepatocellular necrosis and inflammation. [5]. In addition, perihepatic fat stranding, acalculous cholecystitis, retroperitoneal fat stranding, and mild ascites have been reported while examining CT scan of such patients. Bilateral pleural and pericardial fluid, highlighting the presence of overall serositis, indicating severity of disease, may also be noted [13, 21].

Another retrospective observational study done in North India and published online in 2023 reviewed 170 patients of dengue fever with hepatic involvement and proposed to classify patients as having dengue fever, warning dengue and severe dengue depending on the extent of liver involvement, which was judged by rise in liver enzymes. [11, 20] Normal values were considered to be <40IU/L for Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), <128 IU/L for alkaline phosphatase (ALP) and <61IU/L for gamma glutamyl transferase (GGT). In addition, total bilirubin was considered normal when <20.52 µmol/L, total protein >65g/L and albumin >34 g/L. Patients with normal values indicating lack of liver injury were considered to be having dengue fever. Patients with abnormal values were considered to be having evidence of liver injury, with severe injury indicated by AST/ALT ratio >3 times upper limit of normal (hepatocellular injury) or ALP/GGT >2 times upper limit of normal (cholestatic injury) or both (mixed liver injury). Elevation of bilirubin at any point in time was taken as a marker for liver injury. Isolated presentation with cholestatic jaundice has been documented as a precursor for testing for dengue fever in an otherwise afebrile patient [21].

Other significant biochemical markers were leukocytosis, deranged international normalized ratio (INR) and rapidly reducing platelets counts to below 100,000/ µL. These changes corresponded to warning signs like severe vomiting, mucosal bleed, abdominal pain/tenderness, restlessness, and hepatomegaly. [18]

Patients with severe dengue exhibited additional signs including shock, severe bleed (especially with platelet count<20,000/µL, multiorgan involvement (especially with AST/ALT>1000 IU/L), impaired sensorium and organ failure. Elevated CRP was shown to have high association with severity of the disease. The higher the CRP, the more severe the disease [11].

In another review published recently, liver involvement was classified as Dengue induced severe hepatitis (DISH) and Dengue related acute liver failure (D-ALF). (12). Patients with underlying liver disease including Metabolic associated steatotic liver disease (MASLD), Metabolic associated steato hepatitis (MASH), Alcoholic liver disease, metabolic –alcoholic liver disease (Met-ALD) and cirrhosis were found to be having more prevalence of hepatic complications when infected by dengue virus. (12). Co infection with hepatitis A was found rarely, which complicated the clinical picture and prolonged the disease course. This finding is important since both diseases affect people living in poor sanitation areas with water stagnation especially after rainy season, leading to prevalence of both these diseases within the same time frame [24, 25].

Prognostic Features

MELD score (Model for end stage liver disease) has been found to be the single most important tool for assessing prognosis of acute liver failure in dengue fever patients and for predicting mortality [14, 15, 17]. This score considers whether patient needs dialysis, creatinine level, total bilirubin and INR value. The final value is calculated according to the equation (0.957x (Serum creatinine) + 0.378x (Serum bilirubin) + 1.120x(INR) + 0.643) x10. If the patient is on dialysis, creatinine is automatically set to 4. [26]. The score is interpreted as follows:

MELD score	Mortality
<9	1.9%
10-19	6%
20-29	19.6%
30-39	52.6%
>40	71.3%

An initial MELD score >15 has been seen to carry increase incidence of progression to acute liver failure from DISH (dengue induced steato hepatitis).

Another significant marker for prognosis is the baseline INR level. An initial INR of >1.5 predicted death from DISH with a sensitivity of 81.8% and specificity of 86.8%. (15)

pH and lactate levels have also been studied as independent factors for assessing prognosis of patients with acute liver failure in dengue fever. Overall progression of acute liver failure in patients with deranged pH and lactate levels on admission was seen to be 0.35%. Mortality in patients progressing to acute liver failure was assessed to be >50%. [14]

Treatment Strategies

As in all cases of dengue fever, the first line of management is conservative. Management of fluid status plays a vital role in patient management [27]. Transfusion with fresh frozen plasma and cryoprecipitate has been recommended in case of patients with severe coagulopathy and bleeding tendencies [17]. Multiple medications have been tried in the past as possible treatment options for dengue fever including chloroquine, lovastatin, balapiravir and celgosivir [27]. None of these have found to be successful so far.

Multiple case reports, case series and reviews have discussed successful use of N acetyl cysteine in treatment of non-acetaminophen induced liver failure, especially liver failure associated with dengue fever [23, 27, 28, 29, 30]. N acetyl cysteine was initially introduced as a mucolytic agent about 36 years ago. Its use for acetaminophen overdose was first recognized in 1974 [31]. It was noticed that acetaminophen overdose leads to loss of glutathione stores in the liver, which causes increased liver injury. N acetyl cysteine functions by replenishing hepatic glutathione stores as well as scavenging free radicals. These actions prevent toxic injury of the liver and restore blood flow to the liver [27, 28, 29]. Since the pathophysiology of dengue fever involves replication of dengue virus in the liver leading to cell death and oxidative stress, formation of free radicals and depletion of glutathione stores, it only makes sense to use a drug countering all these effects.

N acetyl cysteine can be started as soon as liver injury is noted in a patient with dengue fever. There are various schools of thought regarding the appropriate dose. A case series published in 2021 recommends use of 100gm/hr for 3-5 days [28]. Another report review based in Sri Lanka and published in 2010 recommends use of loading dose of 150mg/kg over 15 minutes, followed by 12.5 mg/kg/hr over 4 hrs, followed by 6.25 mg/kg/hr over 72 hrs. [29]. Yet another case report based in Sri Lanka advises giving N acetyl cysteine only if patient goes into hepatic encephalopathy. The dose recommendation is 150mg/kg in 100ml normal saline over 1 hr, followed by 50mg/kg in 200ml normal saline over 4 hrs, followed by 150mg/kg in 500ml normal saline over 24 hrs for 3 days [30]. Dextrose supplementation was used to prevent hypoglycemia in all these cases.

Regardless of the dosing regime, N acetyl cysteine has proven beneficial in treatment of acute liver failure in dengue fever. Ease of use and the relative nontoxic nature of the drug has made its use widely prevalent. In a case series, use of N acetyl cysteine was shown to have a mortality rate of only 3.3% [28] as compared to >50% without treatment in patients with acute liver failure. Despite these claims, N acetyl cysteine is yet to be formally introduced into any major treatment guidelines for management of hepatic failure in dengue fever.

Limited studies are available with regards to plasma exchange as a treatment modality for dengue related acute liver failure [19]. A systematic review published in 2025 showed that out of 713 cases included, only 9 were candidates for plasma exchange. This limitation in sample size precludes recommending plasma exchange as a regular modality of treatment for the most severe cases of dengue associated liver failure [19].

Liver transplant is the last resort in patients not improving with the preexisting modalities.

Conclusion

Despite advances in medical science and availability of a vaccine for dengue fever, its prevalence remains a matter of concern for all the nations concerned. Research has confirmed it to be a disease affecting multiple organ systems. The liver has the tendency to be especially severely affected due to the hepatotropic nature of the virus. In such a scenario, the addition of any new modes of treatment is welcome news. N acetyl cysteine is one such drug which can act as a scavenger for liver changes during dengue fever and help in overall improvement in patient condition. Based on our clinical experience, and supported by ample evidence from medical literature, we support the use of N acetyl cysteine for treatment of patient with dengue associated acute liver injury.

Author Contributions

Dr Saima Majid Mattoo- Study design, Data analysis, Conceptual development
Dr Maryam Nazir Ahmed- Study design, Data analysis, Conceptual development
Dr Reem - Data acquisition, Conceptual development
Dr Rajesh Gupta-Data analysis
Dr Imadeldin Ahmed- Data analysis
Dr Noble Thomas- Data analysis

Ethics Committee

Ethical committee approval is attached.

Conflict of Interest

This study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent

Written consent was taken from the patients.

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