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Dengue induced acute liver failure: A meta summary of case reports

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Abstract

BACKGROUND

Dengue fever is the most common cause of viral hemorrhagic fever, with more than 400 million cases being reported annually, worldwide. Even though hepatic involvement is common, acute liver failure (ALF) is a rare complication of dengue fever.

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AIM

To analyze the demographic profile, symptomology, hospital course and outcomes of patients presenting with ALF secondary to dengue infection by reviewing the published case reports.

METHODS

A systematic search was performed from multiple databases including PubMed, *Reference Citation Analysis*, Science Direct, and Google Scholar. The search terms used were "dengue" OR "severe dengue" OR "dengue shock syndrome" OR "dengue haemorrhagic syndrome" OR "dengue fever" AND "acute liver failure" OR "hepatic failure" OR "liver injury". The inclusion criteria were (1) Case reports or case series with individual patient details and (2) Reported acute liver failure secondary to dengue infection, published in English language and on adult humans. The data were extracted for patient demographics, clinical symptomatology, clinical

interventions, hospital and intensive care unit (ICU) course, need for organ support and clinical outcomes.

RESULTS

Data from 19 case reports fulfilling the predefined inclusion criteria were included. The median age of patients was 38 years (inter quartile range: Q3-Q1 26.5 years) with a female preponderance (52.6%). The median days from diagnosis of dengue to development of ALF was 4.5 days. The increase in AST was higher than that in ALT (median 4625 U/L *vs* 3100 U/L). All the patients had one or more organ failure, with neurological failure present in 73.7% cases. 42.1% patients required vasopressor support and hepatic encephalopathy was the most reported complication in 13 (68.4%) cases. Most of the patients were managed conservatively and 2 patients were taken up for liver transplantation. Only 1 death was reported (5.3%).

CONCLUSION

Dengue infection may rarely lead to ALF. These patients may frequently require intensive care and organ support. Even though most of these patients may improve with supportive care, liver transplantation may be a therapeutic option in refractory cases.

INTRODUCTION

Dengue is the most common cause of viral hemorrhagic fever, globally. It is endemic in many tropical countries, but in the last few years, cases have also been frequently reported from non-endemic regions[1,2]. As per the current estimates, worldwide, more than 5 billion people are at risk of getting affected with dengue, and more than 400 million cases are being reported annually[2].

Traditionally, dengue was classified as non-classical dengue fever (DF), classical DF, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS)[3]. However, the modified dengue classification by the World Health Organisation divides it into three categories: dengue without warning signs, dengue with warning signs and severe dengue. Patients with severe capillary leak, hypotension, severe bleeding or severe organ involvement are all classified as severe dengue[4].

Classically, dengue patients present with fever and rash and in severe cases with bleeding and shock. Liver injury is commonly reported in patients with dengue, and various phases of liver dysfunction have been described as secondary to dengue infection. In most patients, the liver enzymes have transient mild elevation[5]. Marked elevation of transaminases by more than ten times has also been described, and termed as dengue–induced severe hepatitis (DISH), which may occur in 4-15% of the dengue cases[5-7]. However, the progression of DISH to acute liver failure (ALF) is rare and is reported in less than 1% of cases[5].

Patients with liver involvement generally present with gastrointestinal symptoms like nausea, vomiting, abdominal pain and anorexia, along with yellowish discoloration of the eyes and skin. Hepatomegaly has been reported to be present in 4-79% of the patients[7-10]. However, in patients with severe disease, the presence of complications or multiple organ involvement may complicate the clinical picture. Patients with severe dengue may frequently require intensive care unit (ICU) admission and usually a multi-organ support[11]. Such patients have significant morbidity and mortality. Further, there is a substantial difference in mortality rates between DISH and ALF secondary to dengue, making it essential to recognize it early and institute supportive care[5].

As ALF secondary to dengue is rare and there is a dearth of data from large trials, we aimed to analyze the demographic profile, symptomology, hospital course and

outcomes of patients presenting with ALF secondary to dengue infection by reviewing the published case reports and case series.

MATERIALS AND METHODS

For the present meta-summary, a systematic search was performed from multiple databases including, PubMed, *Reference Citation Analysis* (RCA), Science Direct, and Google Scholar. The search terms used were "dengue" OR "severe dengue" OR "dengue shock syndrome" OR "dengue haemorrhagic syndrome" OR "dengue fever" AND "acute liver failure" OR "hepatic failure" OR "liver injury". The inclusion criteria were (1) case reports or case series with individual patient details, and (2) reported acute liver failure secondary to dengue infection. Further, it was filtered for the literature published in English and on adult (> 18 years) humans. We excluded 1) conference abstracts; 2) case reports or series that did not have individual biochemical data. All reports published till 30th September 2023 were included. The authors manually screened the results to include only the relevant literature and removed the duplicate articles.

All the selected case reports and case series were evaluated. The data were extracted for patient demographics, clinical symptomatology, clinical interventions, hospital and ICU course, need for organ support and clinical outcomes. A datasheet for evaluation was further prepared.

Statistical analysis

Excel and Microsoft Office 2019 were used to analyze the prepared datasheet. Categorical variables were presented as frequency and percentage. For continuous variables, mean [standard deviation (SD)] or median [interquartile range (IQR)] were calculated, as appropriate. SPSS (version 25.0, IBM SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For tabulation and final documentation, Microsoft (MS) Office software (MS Office 2019, Microsoft Corp, WA, USA) was used.

RESULTS

The present meta-summary was performed using the PRISMA 2009 checklist (Figure 1). Eventually, data from 19 case reports fulfilling the predefined inclusion criteria were included in the analysis (table 1)[12-30]. The median age of patients was 38 years (IQR: Q3-Q1 26.5 years) with a female preponderance (52.6%), as shown in table 2. Most cases were reported from India (7, 36.8%) and Sri Lanka (5, 26.3%). The median days from diagnosis of dengue to development of ALF was 4.5 days. The baseline laboratory reports and hospital course are given in Table 3. The increase in aspartate aminotransferase (AST) was higher than that in alanine aminotransferase (ALT) (median 4625 U/L *vs* 3100 U/L). All the patients had one or more organ failure, with neurological dysfunction being most commonly reported in 14 patients (74%). The most common organ support required was cardiac, with 42.1% requiring vasopressors to maintain blood pressure. Most patients recovered with supportive therapy and two patients had undergone liver transplantation. The patients reported to require ICU stay had a median ICU stay of 6 days. 42.1% of patients required vasopressor support. Hepatic encephalopathy was the most commonly reported complication in 13 (68.4%) cases. Only one death was reported (mortality rate 5.3%).

DISCUSSION

Dengue infection may rarely lead to ALF. In the present meta-summary, all the patients had severe dengue, with 79% being diagnosed with DSS. The rise in AST was more than ALT, along with an increase in other liver function parameters. The median INR value was 2.13, and the most common reported complication was hepatic encephalopathy (68.4%). Only 1 death was reported in our cohort of patients.

Dengue infection commonly leads to deranged liver functions, but ALF is rarely reported. Liver injury in patients with dengue may be multifactorial. The direct cytopathic effect of dengue virus may lead to liver injury. Further, the cytokine storm associated with severe dengue fever may cause immune-mediated hepatic injury and

may progress to ALF. Severe hypotension associated with DSS, may also lead to hepatic hypoperfusion and contributes to liver injury. Additionally, frequent use of hepatotoxic drugs (paracetamol, nonsteroidal anti-inflammatory drugs, antibiotics) may contributes to liver injury (Figure 2). [5,6,31]

Even though DEN-1 and DEN-3 types of dengue virus have been shown to have more prominent liver tropism, all 4 serotypes (DEN-1 to DEN-4) have been shown to affect the liver and may cause fulminant hepatitis[32-34]. Most of the cases in our summary were reported from the Indian subcontinent (India 37% and Sri Lanka 26%). This is reasonable as these are tropical countries, where dengue is endemic and all four serotypes are prevalent. In India alone, more than 63,000 dengue cases were reported in 2022[35].

The median days to develop ALF from the diagnosis of dengue was 4.5 days. This is consistent with the previous reports which have shown that there is a gradual increase in transaminase levels which peak around seven days of illness[5]. Even though the increase in transaminases is the most common liver function abnormality associated with dengue fever, there may be derangement of other parameters including, bilirubin, alkaline phosphatase and INR levels, especially in severe disease. This was also evidenced in our report, where we observed higher median levels of bilirubin (5.5 mg/dL), alkaline phosphatase (191 IU/L) and INR (2.13).

Transaminases are more frequently raised in patients with severe forms of dengue. Even the level of increase in transaminases depends on the severity of dengue[36,37]. As per a recent meta-analysis, AST may be raised in 75% of cases of DF as compared to 80% of patients with DHF. Similarly, ALT was raised in 52% of patients with DF and 54% of patients with DHF[38]. The increase in AST levels is greater as compared to ALT levels. It can partly be due to release of AST from the muscular injury secondary to dengue[39]. In most cases, the transaminase levels return to their baseline by day 21 of

illness, with ALT levels taking longer duration to normalize due to their longer half-life[5]. Again, the coagulopathic derangement is also dependent on the severity of dengue. Greater increase in INR has been reported in patients with DSS (1.53) as compared to DHF (1.27), while it remained normal in patients with DF[9].

The treatment of ALF associated with dengue fever is largely supportive. Although no specific treatment is recommended, there is increasing interest in using intravenous N-acetylcysteine (NAC) for managing such cases. Even in our cohort, 6 (31.6%) patients were administered NAC for ALF, albeit in different doses and wide variation of duration[12,15,16,17,20,30]. NAC is the recommended antidote for managing ALF secondary to paracetamol overdose[40], but is increasingly been used in managing non-paracetamol related ALF[41]. In ALF secondary to dengue infection, small case series have shown improved survival with early NAC administration in patients with grade 1 and 2 encephalopathy[6,42]. The exact mechanism of action remains unknown, but it is postulated that NAC administration may help restore hepatic anti-oxidants, scavenge oxygen free radicals and improve oxygen delivery due to its vasodilatory effect[6,41,42].

As dengue induced ALF is rare, the data regarding utility of NAC has been extrapolated from studies in acetaminophen and non-acetaminophen induced ALF. Earlier reports suggested that NAC may be more useful in preventing rather than treating hepatic injury and hence, it was recommended to start NAC early (within 8-12 h) of acetaminophen overdose[43]. However, it is difficult to determine the exact time of hepatic insult in patients with non-acetaminophen induced liver failure and hence, it is recommended to initiate NAC in patients with significant acute liver injury as soon as ALF is detected[44]. Further, it may not be beneficial in later stages of the disease, when liver injury is advanced[42,45]. Hence, NAC may be a useful adjunct in managing patients with severe liver injury, if initiated early. Further, large scale studies need to be performed to evaluate its efficacy, dose and duration of therapy in patients with ALF secondary to dengue infection.

Among the other therapies, corticosteroids have also been shown to be beneficial. Corticosteroids may improve outcomes in patients with severe dengue, but their role in ALF secondary to dengue has not been evaluated[46]. Further, most of these patients may require organ support in the form of renal replacement therapy, invasive mechanical ventilation or vasopressors. Therapies like cytokine filtration, plasma exchange and molecular adsorbent recirculating system have also been used in patients with severe ALF. However, large scale data is missing to recommend their routine use[20,25].

Although liver transplantation is considered as the ultimate therapeutic intervention in patients with ALF, it may be challenging in ALF secondary to dengue due to presence of hemodynamic instability, high risk of bleeding and underlying organ dysfunction. Hence, till date it has been successfully conducted in only a few cases[15,18].

Outcome of dengue patients with liver involvement depends on the severity of liver injury. Most patients with mild increase in transaminases show complete recovery and even those with DISH, have low reported mortality rates of less than 1%. However, ALF secondary to dengue is associated with high mortality rates ranging from 58.8-66.7%[5,47]. In our cohort, only one death was reported, which may be attributed to selective reporting[23].

Strength and limitations

The present meta-summary compiled 19 case reports of ALF secondary to dengue infection from across the world, and is first of its kind. Moreover, we included those case reports and series which had individual patient details to compare patient demographics, clinical course, and outcomes. However, the included studies were only case reports without any control arm. As these reports were heterogeneous, they are

prone to high risk of bias and missing data, which may affect the generalizability of the results.

CONCLUSION

Dengue infection may rarely lead to ALF. These patients may frequently require intensive care and organ support. There is no specific therapy, but intravenous NAC therapy, if initiated early, maybe beneficial. Even though most of these patients may improve with supportive care, liver transplantation may be a therapeutic option in refractory cases. Early recognition is important for institution of supportive care, prognostication and timely referral for liver transplantation.

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