



Case Report

Two Liver Transplant Center's Experience of Dengue-Associated Acute Liver Injury

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Abstract

Background: Acute liver failure is an uncommon, but often fatal, complication of dengue virus infection in adults. Aims: In this study, we aimed to evaluate the occurrence of a major adverse event to propose a management strategy. **Methods:** The files of seven patients hospitalised for dengue virus infection and severe acute liver injury from 1997 to 2013 were reviewed. **Results:** High levels of serum aminotransferases, bilirubin, and severe coagulopathy were observed. All patients had ingested acetaminophen during the last 3-5 days. Among them four had grade 0-I encephalopathy when N-acetylcysteine was administered intravenously. Two of them showed mediolobular liver necrosis, as observed in dengue virus-infected patients. One of these two patients developed severe metabolic acidosis and grade 4 encephalopathy despite continuous administration of N-acetylcysteine for 2 days but survived because of orthotopic liver transplantation. The two others had documented features of acetaminophen hepatotoxicity, with acute liver failure in one of them, but both survived. The remaining 3 patients developed acute liver failure with grade IV encephalopathy, hypotension, and renal failure. They died after protracted shock and medio- or panlobular liver necrosis despite administration of delayed N-acetylcysteine. **Conclusions:** In cases of dengue-associated severe acute liver injury, acetaminophen administration is contraindicated, and N-acetylcysteine should be immediately administered with or without encephalopathy. Liver transplantation is the only therapeutic alternative for persistent acute liver failure, despite N-acetylcysteine.

Keywords: Dengue; Acute Liver Failure; Acetaminophen; N-Acetylcysteine; Liver Transplantation

Abbreviations: ALF, Acute Liver Failure; APAP, Acetaminophen; AST, Aspartate Aminotransferase; DENV, Dengue Virus; ICLU, Intensive Care Liver Units; IgM, Immunoglobulin M; IgG, Immunoglobulin G; IV-NAC, Intravenous (IV) N-Acetylcysteine; OLT, Orthotopic Liver Transplantation; PT, Prothrombin Time; sALI, Severe Acute Liver Injury; sAT, Serum Aminotransferase; SD, Severe, Dengue; ULN, Upper Limit Of Normal; WHO, World Health Organization.

Introduction

Dengue Virus (DENV) is endemic to most tropical areas and is responsible for more frequent infectious diseases worldwide. The prevalence of DENV infection worldwide is estimated to range from 50 to 100 million cases annually [1]. Acetaminophen (APAP), the only drug recommended (at a maximal daily dose of 4 g) by the World Health Organization (WHO) [1], has been used by a large percentage of patients since the first hours and days of the illness [2,3]

In patients hospitalised for dengue, Serum Aminotransferase (sAT), especially Aspartate Aminotransferase (AST) activity, is mildly raised in 63 to 97% of patients [2,4]; serum bilirubin is uncommonly slightly increased [3], and jaundice is exceptional [2]. In 2009, the WHO defined Severe Dengue (SD) [1,5] as the presence of severe plasma leakage, severe haemorrhage, or severe organ impact, including sAT activity above 1,000 UI/L [1]. Acute Liver Failure (ALF) is exceptional in hospitalised adults with dengue, with prevalence lower than 1% in three studies [2,6,7] from Southeast Asia, and its annual incidence ranges between 5 and 9% of all ALF cases in two Asian countries endemic for DENV [8,9].

In this study, we aimed to: (i) evaluate which characteristics were associated with Severe Acute Liver Injury (sALI) in patients hospitalised for severe DENV infection in two French referral liver units; (ii) describe the course and outcome of this major complication, including ALF and death; and (iii) emphasise therapeutic measures aimed at preventing DENV-associated fatal ALF in infected patients.

Patients and Methods

Definitions

Definitions of illnesses due to DENV are issued by the WHO [1]. The criteria for circulatory shock were those recommended by experts [10]. ALF is defined as an acute liver disease complicated by coagulopathy and encephalopathy within 24 weeks of illness onset in a patient without a recognized underlying chronic liver

disease [11]. We defined sALI as cases of acute liver disease complicated by severe coagulopathy, but without encephalopathy [12,13].

Patients

From 1997 to 2013, files of seven adults hospitalized in the Intensive Care Liver Units (ICLU) of Hôpital Beaujon (Clichy) and Hôpital Paul-Brousse (Villejuif), France, for sALI and/or ALF with SD, were recorded and analysed.

Diagnostic of DENV-infection

Diagnosis of dengue infection was based on commonly used methods [14].

Histology

Standard liver histology was available for six patients, and each slide was reviewed by two independent pathologists specializing in liver diseases.

Ethical considerations

Written permission to publish their clinical data was obtained from the patients or next-of-kin, and the ethical committee of Guadeloupe approved this study.

Statistical analyses

Data were collected using Microsoft Excel 8.0 file. Statistical analyses were performed using the EPI INFO version 3.5.4. Dichotomous data were compared using the χ^2 test ($\alpha=5\%$) or Fisher's exact test, when appropriate. Quantitative data were compared using Student's t-test. The exact Poisson confidence intervals were then calculated. Data are expressed as median and range; differences were considered significant at $P<0.05$.

Results

Overall presentation

From 1997 to 2013, seven French adults (four males and three females, two with diabetes mellitus, and three alcohol drinkers) were admitted to the emergency unit of a university hospital 3-6 days after the abrupt onset of fever, which persisted on admission. Five patients resided in the French Caribbean Islands and two in metropolitan France but had travelled to Southeast Asia and returned to France a week earlier.

The anamnesis of recently ingested drugs and the patients' clinical and biochemical features are summarised in (Table 1). During the past 3-5 days, all patients sustained severe anorexia and had ingested APAP, in five of them at the recommended daily dose, but in fact in three of them at unintentional relative overdose compared to their body weight. Initially, on the first admission, six had normal arterial blood pressure, five had cutaneous and mucous

bleeding, and two had grade I-II encephalopathy. Within 8-48 hours after admission, five patients developed progressive encephalopathy grades III-IV. Finally, the seven patients had Prothrombin Time (PT) ratio lower than 50% compared to the control and elevated serum bilirubin and were transferred to an ICLU with liver transplantation facilities (four to Hôpital Beaujon and three to Hôpital Paul-Brousse).

	SURVIVORS (n=4) (cases 1 to 4)	DEATHS (n=3) (cases 5 to 7)
Age (years) / male sex	31 [26-68] / 1	53 [21-63] / 3
Consumption of APAP (patients) - daily recommended dose - unintentional overdose in mg/kg	2 / 4 3 / 4	3 / 3 0 / 3
First admission to emergency unit - duration of fever at admission (days) - initiation of IV-NAC (patients) - shock or hypotension (patients) - encephalopathy (grade I-II) - AST (IU/L) - ALT (IU/L) - total serum bilirubin (µmol/L) - PT ratio (%) - serum creatinin (µmol/L)	5-6 4 / 4 1 / 4 2 / 4 6174 [1,700-11,730] 5440 [735-10,880] 29 [17-52] 31 [16-64] 103 [82-400]	3-4 0 / 3 0 / 3 0 / 3 14,700 [350-27,410] 6620 [214-7,490] 59 [7-94] 68 [38-83] 193 [98-341]
Admission to intensive care liver unit - time elapsed since first admission (hours) - administration of IV NAC (patients) - shock or hypotension (patients) - encephalopathy (grade III-IV) - AST (IU/L) - ALT (IU/L) - total serum bilirubin (µmol/L) - PT ratio (%) - serum creatinin (µmol/L)	8 [2-12] 4 / 4 1 / 4 2 / 4 5,405 [3,010-11,730] 3,011 [1,115-10,880] 30 [22-113] 28 [18-43] 99 [82-489]	48 [48-68] 3 / 3 3 / 3 3 / 3 17,000 [8,693-19,413] 5,054 [4,502-5,700] 57 [33-92] 23 [16-25] 317 [220-415]

Dengue infection. For six patients with fever for five days, the diagnosis of dengue was based on positive serology (presence of DENV-specific antibodies Immunoglobulin M (IgM) and Immunoglobulin G (IgG)) by capture enzyme-linked immunosorbent assays [14]. In two patients (including one without available serology) with fever of less than 6-days duration, the diagnosis of dengue was based on the detection of the viral genome using reverse transcriptase-polymerized chain reaction [14]. According to the levels of dengue-specific IgG, secondary infection was diagnosed in six patients (including five with ALF) and primary infection in one patient with sALI.

The seven patients were negative for serum markers of acute hepatitis A, B, C, D, and E. Similarly, serum markers for autoimmunity were absent.

Patient outcomes were associated with a delay in the administration of IV NAC since the first admission to the hospital.

Patients' outcome after early administration of intravenous (IV) N-acetylcysteine (NAC) (**Figure 1A**)

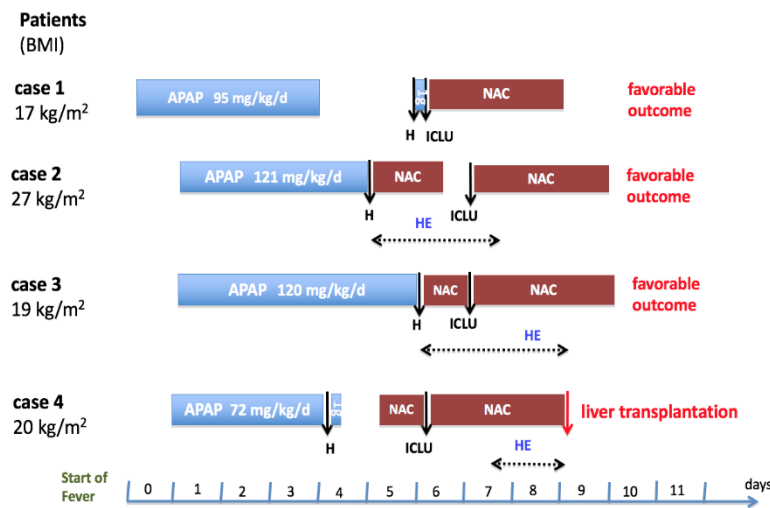


Figure 1A: Patients' outcome after early administration of intravenous N-acetylcysteine. The dose of APAP, the administration of IV-NAC and the outcome are detailed. **Abbreviations:** BMI, Body Mass Index; D, Day; APAP, Acetaminophen; IV-NAC, Intravenous N-Acetylcysteine; H, Hospitalization; ICLU, Intensive Care Liver Unit; HE, Hepatic Encephalopathy

In four patients, IV-NAC perfusion was initiated within the first 6 h after their first admission when grade 0-1 encephalopathy and median total serum bilirubin 29 $\mu\text{mol/L}$ [17-52] were present (early IV-NAC) (Table 1). This early administration of IV NAC was probably explained by a decrease in median PT ratio to 31% [16-64]. Subsequently, IV-NAC was maintained until PT ratio reached 50% of control.

In two patients, dengue-associated hepatic mediolobular necrosis without centrolobular necrosis was diagnosed based on liver histology. These patients ingested less than 4 g/day of APAP for 3-4 days and had no detectable APAP in the blood. They both survived. One of these two patients had severe evolution with transient arterial hypotension on the first admission. He subsequently developed acute respiratory failure and grade 4 encephalopathy. His arterial pressure was stabilised by low doses of catecholamines, but he had a PT ratio persistently lower

than 20% of the control, an acute renal failure, and a metabolic acidosis (lactic acid, 8.9 mmol/L) despite early administration of IV-NAC. Emergency orthotopic liver transplantation (OLT) was performed on the third day in the Hôpital Paul-Brousse ICLU. In addition to massive mediolobular necrosis, liver explant histology revealed moderate macrovesicular steatosis (Figure 2). Five years later, the patient recovered a normal life while receiving chronic immunosuppression. On the other hand, APAP hepatotoxicity was diagnosed in two other patients who survived. One patient developed sALI with non-inflammatory centrolobular liver necrosis (Figure 3). He had ingested the recommended dose of 4 g daily of APAP for 4-5 days but was a teetotaler patient. The other patient was a social alcohol consumer who had ingested 6 g of APAP daily for 4 days; his APAP blood concentration was 50 mg/L on the first admission, and he survived ALF with coma, but no liver histology was obtained.

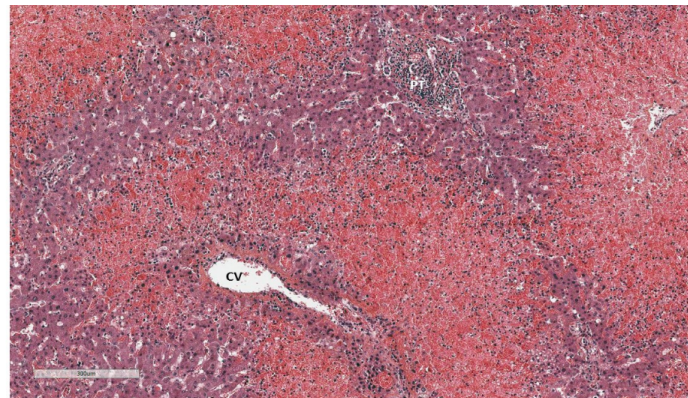


Figure 2: Mediolobular coagulation necrosis of most of the liver lobule except a rim of hepatocytes around portal tract. **Abbreviations:** PT, Portal Tract; CV, Central Vein

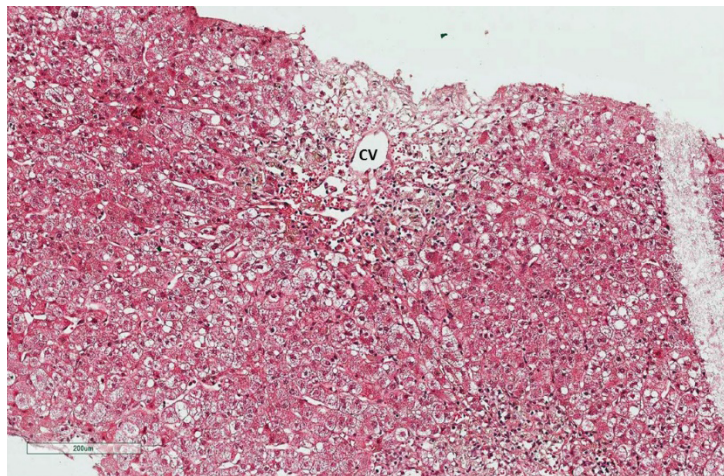


Figure 3: Acetaminophen toxicity: inflammation and necrosis around centrolobular vein. **Abbreviation:** CV, Central Vein Patients' outcome after delayed administration of IV-NAC (Figure 1B)

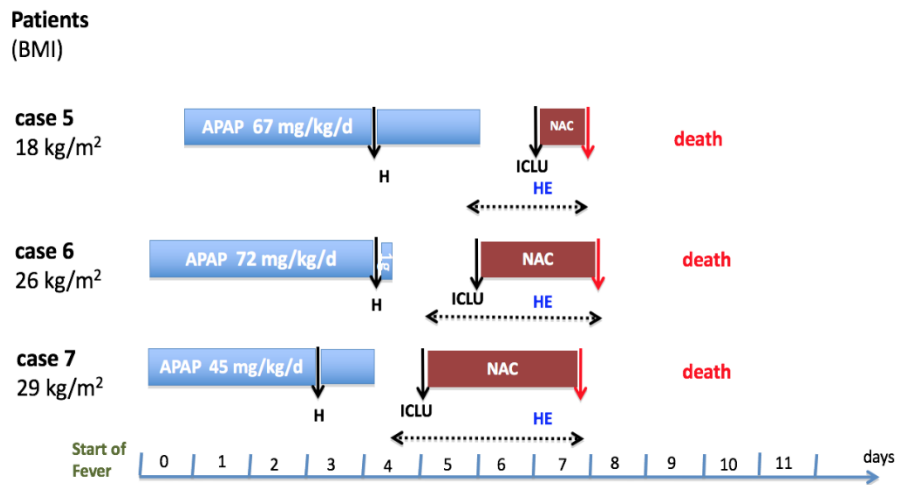


Figure 1b: Patients’ outcome after delayed administration of IV NAC. The dose of APAP the administration of IV-NAC and the outcome are detailed. **Abbreviations:** BMI, Body Mass Index; D, Day; APAP, Acetaminophen; IV-NAC, Intravenous N-Acetylcysteine; H, Hospitalization; ICLU, Intensive Care Liver Unit; HE, Hepatic Encephalopathy

In three other patients, IV-NAC was not administered on first admission when median PT ratio was 68% of control, median serum creatinine 193 $\mu\text{mol/L}$, and no sign of encephalopathy was present (delayed IV-NAC) (Table 1). All had ingested 3-4 g of APAP daily in the last 3 days and had no detectable APAP in the blood. Prior to the first admission, one of these three patients was challenged again with APAP (6 g in 48 hours) in a primary care centre, although sAT activity was more than 10 times that of ULNV. In these 3 patients, IV-NAC was initiated only upon arrival to ICLU, 48 to 72 hours later, while all of them had grade 4 encephalopathy, refractory shock, a median serum creatinine level of 317 $\mu\text{mol/L}$, severe coagulopathy, and mechanical ventilation. In ICLU, three patients died within 72 h. The distribution of liver necrosis was panlobular in 2 patients and mediolobular in the third one.

Discussion

The dengue virus is widespread in the Caribbean Islands, and large recent epidemics have been reported. In this study, we aimed to retrospectively evaluate and analyse the occurrence of the rare but often fatal complication of DENV infection, sALI. Only seven cases were readily documented over a period of 16 years. Fortunately, the first main point is that this event is very rare despite the large liver involvement in DENV infection, according to the reported epidemiological data of Asia [2,7-9]. However, analysing the files of the seven patients identified in our study, we found that 3 of them (43 %) died. The remaining patients developed sALI and ALF in three patients who required emergency OLT for one

patient. The second main finding of this study was that the time of introduction of IV NAC treatment was crucial. Indeed, all the three patients who died received the IV-NAC 48h after their admission to the hospital and developed of grade 4 encephalopathy (Table 1), contrary to the four patients (57%) who survived. Moreover, when we compared our results with those of previously reported series of at least four patients [2, 7, 8, 15-19], according to early or late administration of IV-NAC, we found survival rates of 65% (13 out of 20 patients) and of 39%, respectively (13 out 33). Therefore, in accordance with the controlled trial by Lee et al. [20], our findings, although obtained in a limited number of patients managed in two different institutions, support the view that early administration of IV-NAC is beneficial in adults with dengue-associated ALF before the installation of grade 4 encephalopathy and, obviously, in patients with sALI without encephalopathy. The risk of “too early” treatment must be preferred to that of “too late” administration of IV-NAC.

Various etiological factors may have contributed to the uncommon dengue-associated ALF in our six patients. Mediolobular necrosis, likely the most frequent liver lesion in patients with dengue-associated sALI or ALF, often occurs after plasma leakage [5]. This latter lesion, observed in three of our patients, was previously described in children who died from SD [21] but also in adults with severe, fatal, or non-fatal [22] dengue. Hypotheses involving virus-associated immunological mechanisms have been raised [23]. However, since mediolobular cell necrosis was also observed in severe cases of heatstroke [24] and in a patient who developed ALF early after a session

of therapeutic total-body hyperthermia, it can be hypothesised that high-grade hyperthermia might contribute, at least in part, to hepatic injury in patients with sALI, ALF, and SD [21]. It is noteworthy that we report the first case of emergency OLT in a patient with SD and medial lobular liver necrosis-associated ALF. We emphasise that our patient was hospitalised for ICLU with transplantation facilities 60 h before surgery, when OLT was not yet indicated. The decision to perform OLT was based on the significant aggravation of the patient's condition despite early and continuous administration of IV-NAC, as attested by the progression to grade IV encephalopathy, worsened results of liver function tests, severe coagulopathy, acute renal failure, and refractory lactic acidosis.

Another important aspect is the role of APAP. Indeed, in the first week after the abrupt onset of fever, almost all patients with dengue fever ingest prescribed or nonprescribed APAP [3,6]. Therefore, APAP hepatotoxicity is very likely a possible factor that may contribute to dengue-associated sALI or ALF. In a previous prospective study of DENV-infected patients in Thailand, a positive correlation was found between oral consumption of more than 8 g of APAP and increased sAT activity (exceeding 3 times the ULN). Thus, the authors recommended a reduced daily dosage of APAP of 3 g/day [25]. APAP hepatotoxicity has only been assessed recently and has been reported in a few cases [8]. Although severe APAP hepatotoxicity (i.e. with sALI or ALF) seems to be more prevalent in children [26] than in adults, it occurred in two patients in our series. In a retrospective study from Sri-Lanka, Kumarasena et al. found a 39% risk of ALF in adults with SD and sAT activity above 1,000 UI/L (approximately 30 times the ULN) [27]. Consequently, an empiric strategy of early IV-NAC infusion, the recognised antidote against APAP hepatotoxicity [28], could be a therapeutic option for adults affected by dengue with such an increased sAT activity (even with no obvious features of APAP hepatotoxicity), especially when associated with at least two of the following three features: persistent nausea and vomiting, increased serum alkaline phosphatase, and serum bilirubin levels (27). In addition, as suggested earlier, intrahepatocytic replenishment of reduced glutathione, secondary to the administration of NAC, might inhibit, at least in part, dengue virus production [29].

Another issue is hepatic injury. Two of our patients who died and received delayed administration of IV-NAC beyond the development of encephalopathy grade 4 showed massive panlobular liver necrosis, a common post-mortem lesion following protracted liver ischaemia secondary to prolonged shock [30]. However, no acute liver lesions can predict such pejorative evolution. Of note, however, in one of the patients who died, APAP was administered (6 g in 2 days) before admission to the hospital, while sAT activity was already increased >10 times the ULN, which might have also contributed to the fatal evolution. Therefore, it is reasonable

to assume that in some patients, dengue-associated sALI or ALF results from several liver injuries linked to the dengue virus itself, hyperthermia, and some degree of APAP hepatotoxicity.

In conclusion, this retrospective study presents the first case of OLT in DENV-associated ALF despite the small number of patients. Our findings allowed us to propose the following measures aimed at preventing DENV-associated sALI and ALF. First, beyond 3 days of fever, medical counselling is strongly recommended for the early diagnosis of dengue, immediate adequate rehydration, and possible recognition of sALI. Second, during epidemics, the daily intake of APAP, occurring frequently in febrile and anorectic adults, should be reduced to a maximum dose of 3 g/day, instead of 4g/day, and notably, patients with low body mass index must not exceed 60 mg/kg. Third, to obviate the risk of hidden and accelerated development of severe hepatotoxicity, APAP should be fully withdrawn in patients with sAT activity > 10 times the ULN. Fourth, when sAT activity increases between 30 and 40 times the ULN, together with elevated serum bilirubin levels, we recommend immediate infusion of IV-NAC in addition to the withdrawal of APAP ingestion. Finally, in patients admitted early in ICLU and in whom the condition rapidly deteriorates despite the infusion of IV-NAC, OLT, which can be performed in an emergency, is the sole alternative to life-saving surgery.

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