International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Experience Using Intravenous N-Acetylcistein in Severe Dengue Induced Acute Liver Failure; A Rare Case Report

Garba Sandhi Wusana Despriyatmoko[1], Diatrie Anindyajathi[2]

[1]General Practitioner, [2]Department of Child Health Bhayangkara Tk.I Pusdokkes Polri Hospital, East Jakarta, Indonesia.
Bhayangkara Tk.I Pusdokkes Polri Hospital, East Jakarta, Indonesia.
sandhigarba@gmail.com*

1. Introduction

Dengue is one of the common harmful mosquito borne-viral disease which belongs to the Flaviviridae family[1]. There are different dengue virus serotypes causing dengue disorders, including, asymptomatic infection, dengue fever, undifferentiated fever, fatal and severe dengue hemorrhagic fever. Aedes aegypti mosquito (main-urban-vector) and Aedes albopictus female mosquitos are the known vector for transmission of dengue virus from an infected person to others by biting[2]. Dengue a growing public health concern approximately four billion people in 130 countries identified at risk of infection. As of 30 april 2024, 7.6 million dengue cases have been reported to WHO in 2024, including 3.4 million confirmed cases, over-16000 severe cases, and over-3000 deaths[3]. Incidence of hepatic dysfunction in children with dengue is quoted to be as high as 90%. Acute liver failure (ALF) can rarely occur, less than 1% of cases and is associated with poor outcome with mortality rate of up to 50%[4]. N-acetylcysteine (NAC), which is used for the treatment of nasal congestion disorder and paracetamol overdose toxicity, could be used as a definitive therapy for dengue virus induced ALF[5]. We report a case of a 12-years-old boy with severe dengue induced acute liver failure in whom intravenous (iv) NAC was used-successfully.

Case

We report a case of a 12 year old boy weighing 67kg heighing 155cm, admitted to hospital with chief complaint of fever for the past 2 days, high fever with nosebleeds, decreased appetite, nausea, vomiting with every meal, diarhea 5 times a day without mucus and blood, abdominal pain, and dizziness. History of seizures, epilepsy, and other chronic diseases were denied. Basic immunisation history was complete. Physical examination on admission was compos mentis, Glasgow coma scale (GCS) E4V5M6, blood pressure (BP) 90/60mmHg, pulse 100 beats/minutes, respiratory rate (rr) 23 beats/minutes, temperature 37,7˚C, and SpO2 98% on room air. Specifically, there was no area of abdominal tenderness and no rash noted, Extremities get a warm impression with CRT <2 seconds. Investigations at the emergency room revealed leukocyte 8720ul, hematocrit 46% and thrombocyte 148000ul. The patient was diagnosed as dengue fever without warning sign, based on clinical and supporting

examinations. On the fourth day of hospitalisation, the patient had no diarrhea. The measured temperature is 37.5ºC. The general condition is stable. The complete blood count showed a decrease in platelets from the previous one. On the fifth day of hospitalisation, the patient decrease of consciousness, severe abdominal pain, bleeding via Naso Gastric Tube and shortness of breath. GCS E3V4M5 BP 80/60 mmHg pulse 104 beats/min rr25 beats/min temperature 37.2˚C SpO2 88% nasal canula 1lpm, cool peripheries, capillary refill time >2second, he was resuscitated 10ml/kg of normal saline and transferred to Pediatric's Intensive Care Unit. Laboratory investigation showed a rising hematocrit of 55%, worsening transaminitis (Aspartat transaminase (AST) 1146U/l and alanine transaminase (ALT) 664U/l) and new onset disseminated intravascular coagulopathy (platelets 12000ul, prothrombin time (PT) 90,8s, international normalized ratio (INR) 9.36 and partial thromboplastin time (APTT) "no coagulation". Intravenous (iv) NAC started at 150 mg/kg for 1 hour and then 10 mg/kg/hour for 20 hours,10 mg vitamin k iv and dexametason are given. Diagnosis progressed from severe dengue induced severe hepatitis to severe dengue induced acute liver failure.

His liver function continued to deteriorate and liver enzymes reached peak values of AST 1474 U/l and ALT1794 U/l on days 8 of illness, intravenous NAC still was continued dose 10mg/kg/hour for 5 days. On the days 11 of hospitalization, the general condition was stable with compos mentis consciousness GCS E4V5M6, vital sign within normal limit. A marked improvement in liver enzymes was noted: AST dropped to 189,5U/l and ALT 618,7 U/l, and three days later AST dropped to 71,7 U/l and ALT 280,8 U/l. Coagulopathy improved markedly as well. APTT normalized at 31.8 s, and PT normalized to
11.1 s. He did not have hypoglycaemia during the course of illness. Investigations to exclude other infectious causes of ALF such as human immunodeficiency virus serology, HBsAg, Anti HCV were negative.

He wãs transferred out of PICU after 6 days and discharged home after 14 days of hospitalization. On discharge, liver enzymes were only mildly elevated, AST 71,7 U/l and ALT 280,8 U/l, with normal platelet 162000/l, leukocyte 10000 and haematocrit 45%. The patient was treated as an outpatient with curcuma 2x1 caplet and paracetamol 3x500mg if necessary.

The patient had no complaints during outpatient control at the pediatric health polyclinic on day 18. Blood pressure 100/60 mmHg, pulse 74x/minute, respiration 16x/minute, temperature 36ºC, oxygen saturation 99% on room air. Liver enzymes was noted: AST dropped to 45,4U/l and ALT 115,8 U/l The patient continued to take curcuma 2x1 caplets.

Relevant laboratory investigations in relation to day of illness

		Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 11	Day 14	Day 18
Hemoglobin (mg/dL)		14,6	15,5	19,7	16,9	13,2	12,4		14,5	12,9
Hematokrit (%)		42	46	55	47	39	37		45	40

Platelets (10^3 ul)		114000	56000	12000	34000	57000	118000		162000	149000
Leukosit (10^3 UL)		4380	3870	8130	15400	6970	8690		10000	10970
PT				90,8			15.1		11.1	
APTT				NO COAGULATION			31.7		31.8	
INR				9,36						1.02
SGOT/AST				1146			1474	189.5	71.7	45.4
SGPT/ALT				664			1794	618.7	280.8	115.8

2. Discussion

Dengue virus is one of the most devastating mosquito-borne viral pathogens in humans. It is endemic throughout tropical and subtropical countries, particularly in Southeast Asia and Western Pacific regions, with an estimated 390 million infections annually[6]. Over the past five decades, Indonesia has been affected by dengue, a febrile illness caused by dengue virus. The tropical climate of the country facilitates the breeding of Aedes mosquitoes, the main vector of dengue. The co-circulation of all four DENV serotypes (DENV-1, -2, -3 and -4) is commonly detected in many regions in Indonesia, which contributes to cycles of epidemic and interepidemic years, while a seasonal pattern of transmission is observed annually. DENV-1 was the predominant serotype circulating in Indonesia from 2009 to 2012, and from 2013 onwards, multiple dengue serotypes began to dominate in multiple different areas[7,8]. Dengue infection has a range of clinical manifestations. According to the WHO classification in 2009, dengue is classified as dengue fever (with or without warning signs) and severe dengue fever which includes severe plasma lekage, severe haemorrhage and severe organ impairment[9]. Liver involvement is a common manifestation of dengue fever. Elevation of liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occur in 88% and 69% of cases respectively[9]. In majority of patients liver enzyme elevation do not cause hepatic dysfunction, but 4–7% of patients develop significant acute hepatitis with tenfold or more rise of aminotransferase levels and termed as dengue–induced severe hepatitis (DISH), which may occur in 4%-15% of the dengue cases. However, the progression of DISH to ALF is rare and is reported in less than 1% of cases. It carries a mortality rate of 50% due to complications such as encephalopathy, severe bleeding, renal failure and metabolic acidosis[10]. There are several mechanisms of severe liver involvement in dengue infection. i.e. hypoxic injury, direct viral invasion, immune mediated injury and secondary bacterial sepsis[11,12,13]. Liver injury can develop in prolonged dengue shock with plasma leakage but it is known to occur in dengue patients without evidence of plasma leakage[14].

Dengue infection may rarely lead to ALF, Hepatic involvement in DF is common and it is usually mild with transaminases of less than 5-fold increase[15] . A significant elevation of transaminases by more than 10-fold is rare[16,17]. ALT and AST are considered as indicators of liver cell injury as they are

released into the circulation following liver cell injury[18]. Although ALT is also found in low concentrations in skeletal muscle, brain and intestinal tissue, it is predominantly considered to be a liver specific enzyme[18]. In contrast, AST is released following damage to liver, cardiac and skeletal muscle[18]. We found that the rise in AST was more prominent than the rise in ALT levels in patients with SD, which probably suggests that other sources apart from the liver could also be contributing to the rise in serum AST levels[18]. Importantly, the mean AST levels rose more than twofold from day 4 to day 6 of onset of illness[19], The natural history of liver involvement in dengue is such that peak elevations in liver enzymes occur on days 7–8 of illness[20]. Our patient has his peak elevation of liver enzymes during this described period.

ALF is classically defined as severe liver injury in a patient without a previous history of liver disease who develops encephalopathy within 8 weeks of the initial symptoms. The etiology of ALF in children varies with age, with viral hepatitis (41%), drugs (10%) and unknown causes (47%) being the most common in children >1 year of age. ALF in dengue infection is more common in children <15 years of age and is asso- ciated with dengue serotype 3 infection. PALFSG entry criteria for child with acute liver failure include; acute onset liver disease with no evidence of chronic liver disease, biochemical evidence of severe liver injury, coagulopathy not corrected by vitamin k: PT≥15 or INR≥1.5 with encephalopathy or PT≥20 or INR≥2 with or without encephalopathy[21].

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 severe dengue, 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. 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. 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 63000 dengue cases were reported in 2022. The median days to develop ALF from the diagnosis of dengue was 4.5 day. This is consistent with our case report which have shown that there is a gradual increase in transaminase levels which peak around eight days of illness. 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 (2.72 mg/dL) and INR (9.36). 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. 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. 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. the coagulopathic derangement is also dependent on the severity of dengue. Greater increase in INR has been reported in patients with DSS as compared to DHF [22].

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[22]. NAC is the recommended antidote for managing ALF secondary to paracetamol overdose, but is increasingly been used in managing non-paracetamol related ALF. 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[22].

The mechanism of action of NAC in patients who recovered from dengue-induced ALF could be associated with its ability to increase antioxidant defense system, its free radical scavenging activity, and its vasodilatory activity that increases blood flow to the liver[25]. As reported by Chandrasena et al (2019), the antioxidant enzymes such as glutathione peroxidase and glutathione reductase have been reduced during acute dengue infection. Thus, the antioxidant activity of NAC could be due to increasing plasma antioxidant levels such as glutathione peroxidase and glutathione reductase which results in reducing oxidative stress[26]. NAC showed antiviral activity by reducing infectivity in HepG2 cells infected DENV, suppressing DENV replication, and reducing oxidative damage. NAC could also reduce the infectivity of dengue virus at its entry, replication, post translation, RNA synthesis and exocytosis in a dose-dependent manner. Additionally, the drug up-regulates the expressions of pattern recognition receptors including, retinoic acid-inducible gene I and melanoma differentiation-associated gene 5 in DENV-infected mice[27]. As dengue induced ALF is rare, the data regarding utility of NAC has been extrapolated from studies in acetaminophen and non-acetaminophen induced ALF[22].

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. 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. Further, it may not be beneficial in later stages of the disease, when liver injury is advanced. Hence, NAC may be a useful adjunct in managing patients with severe liver injury, if initiated early. In this case report, a loading dose of 150 mg/kg and a daily dose of 10 mg/kg for 5 days were used[23].

Among the other therapies, corticosteroids have also been shown to be beneficial. Corticosteroids in ALF are the mainstay of treatment and are highly effective. Carefully selected individuals with low grade hepatic ensephalopathy may also benefit from corticosteroid therapy[24]. Corticosteroids may improve outcomes in patients with severe dengue, but their role in ALF secondary to dengue has not been evaluated. The rhizomes of Curcuma longa L. (CL) have been widely used in herbal medicines worldwide. It has been shown to possess prophylactic effects against oxidative stress. When administered orally, it led to reduced impairment of liver functions by the preservation of intracellular GSH-Px, which could explain the hepatoprotective effect, decreased MDA concentration, and increased SOD and GSH-Px concentrations, as a result of its antioxidant nature. It also prevented lipid peroxidation-induced liver damage, by its radical scavenging nature. With the evidence of normal histological findings for all treated groups, it suggests that CL does not have any toxic effects on the liver and kidneys at a dose 100 mg/kg/day/orally for six consecutive days. The results revealed that CL exhibited an antioxidative stress effect in the liver and kidneys as indicated by the low levels of ALT and creatinine. In response to antioxidant enzymes, especially that of the 3rd-day treatment group, an increase in SOD and GSH-Px indirectly caused an alleviation of oxidative stress, leading to a much lower level of MDA. It was

concluded that treatment with CL at 100 mg/kg b.w./per day for three consecutive days demonstrated the highest efficacy in abating oxidative stress in rats[29].

Keywords: acute liver failure, dengue, N-Acetylcysteine

3. Conclusion

Dengue fever could be induced ALF, laboratory investigation biochemical enzyme liver and coagulant factor should be performed to identify acute liver injury. NAC could be used as a definitive therapy in dengue virus induced ALF. Corticosteroids may improve outcomes in patients with severe dengue induced ALF. Curcuma at 100 mg/kg b.w./per day for three consecutive days demonstrated the highest efficacy in abating oxidative stress in acute liver injury.

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