THERAPEUTIC PLASMA EXCHANGE AND SINGLE-PASS ALBUMIN DIALYSIS IN A 10-MONTH-OLD GIRL WITH DENGUE SHOCK SYNDROME IN THAILAND: A CASE REPORT

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Abstract. Dengue infection may have a variety of presentations ranging from asymptomatic to severe multiorgan involvement and rarely, severe liver involvement. We present a case of a 10-month-old female who developed dengue shock syndrome and acute liver failure. She underwent continuous venovenous hemofiltration (CVVH), single pass albumin dialysis (SPAD), and therapeutic plasma exchange (TPE) because she had volume overload and acute liver failure and the molecular adsorbent recirculating system is limited in our center. She was discharged after 72 days of hospitalization. At follow-up, she had no residual symptoms and her liver function had returned to normal. Acute liver failure may occur with dengue infection in children.

Keywords: dengue infection. plasma exchange. dialysis. liver failure

INTRODUCTION

Dengue infection is a mosquito-borne viral disease endemic in Southeast Asia (WHO, 2020). In Thailand in 2015, there were 144,952 reported cases of dengue infection (Department of Disease Control, 2019). Dengue infection in Thailand is associated with the rainy season and has a peak incidence in July and August (Department of Disease Control, 2019). In Thailand the incidence of dengue infection is highest among children aged 5-14 years and young adults aged 15-24 years (Department of Disease Control, 2019). Children aged <1 year are more likely to develop severe dengue infection than adolescents (Mena Lora *et al*, 2014). Dengue infections can range from mild to severe. Liver involvement by dengue infection may present as elevated serum transaminases, hyperbilirubinemia, hypoalbuminemia and coagulopathy (Arora *et al*, 2015). Studies from India (Kumar *et al*, 2008) and Thailand (Poovorawan *et al*, 2006) have reported dengue infections among children causing acute hepatic failure in 18.5% and 34.3% of reported cases, respectively. The pathogenesis of hepatic dysfunction in dengue infection is multifactorial (Dalugama and Gawarammana, 2017). Proposed etiologies of hepatic dysfunction in dengue infection include a viral effect

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on the hepatocytes, a dysregulated host immune response (Ahmed *et al*, 2015), immunologic injury (Cabrera-Hernandez *et al*, 2007), and hypoxic injury due to reduced hepatic perfusion during shock (Khongphatthanayothin *et al*, 2013). The management of dengue infection is still debated.

Case presentation

In October 2017 a 10-month-old Thai girl was referred from a provincial hospital to a tertiary care hospital in lower northern Thailand with a 4-day history of fever and vomiting. She had previously been healthy. Her mother and her family had no previous history of dengue infection. Her vital signs at the provincial hospital were: a temperature of 37.6ºC, a pulse rate of 160 beats/minute, a blood pressure of 84/57 mmHg and a respiratory rate of 50 breaths/minute.

A complete blood count from the provincial hospital gave the following results: a total leukocyte count of 9,000 cells/mm^3, 30% neutrophils, 67% lymphocytes, a hematocrit of 35.1% and a platelet count of 21,000/mm^3. A dengue nonstructural protein 1 antigen (NS1) was positive. The international normalized ratio (INR) was 3.68, and the activated partial thromboplastin time (APTT) was 90 seconds with an aspartate transaminase (AST) level of 9,651 U/l and an alanine aminotransferase (ALT) level of 2,091 U/l. A chest radiograph showed a right pleural effusion.

She had a history coffee ground vomitus and had received a packed red blood cell transfusion, vitamin K, and fresh frozen plasma. She had developed hypoglycemia, treated with intravenous glucose. She had also been given intravenous fluid to stabilize her hemodynamic status. She was intubated because she had dyspnea. Before transfer she had been diagnosed with having dengue hemorrhagic fever with coagulopathy due to hepatic failure.

On examination after transfer to the tertiary care hospital, her body weight was 7.3 kg; her temperature was 37.8ºC, her pulse rate was 154 beats/minute, her respiratory rate was 42 breaths/minute and her blood pressure was 98/48 mmHg. She was lethargic. There were fine crepitations in the lungs bilaterally. Her abdomen was distended due to ascites. She had hepatomegaly (the liver edge was 5 cm below the right costal margin). A skin examination revealed generalized petechiae in all 4 extremities and she had muscle spasticity.

Her initial complete blood count after transfer to the tertiary care hospital revealed a hemoglobin of 9.9 g/dl, a hematocrit of 32.3%, and a total leukocyte count of 11,170 cells/mm^3 with 28% neutrophils, 49% lymphocytes and a platelet count of 14,000/mm^3. The prothrombin time (PT) was 20.8 seconds with an international normalized ratio (INR) of 1.71, and the activated partial thromboplastin time (APTT) was 39.1 seconds.

Her blood urea nitrogen (BUN) level was 9.5 mg/dl, the creatinine level was 0.33 mg/dl, the total protein level was 4.1 g/dl, the albumin level was 2.8 g/dl, the globulin level was 1.3 g/dl, the total bilirubin level was 2.29 mg/dl, the direct bilirubin level was 1.5 mg/dl, the aspartate transaminase (AST) level was 34,822 U/l, and the alanine aminotransferase (ALT) level was 4,842 U/l. Her calcium level was 9.56 mg/dl, the magnesium level was 2.2 mg/dl, the phosphorus level was 2.7 mg/dl, the sodium level was 132 mmol/l, the potassium level was 3.5 mmol/l, the chloride level was 99 mmol/l, and the

bicarbonate level was 13 mmol/l. Her serum ammonia (NH_3) level was 108 μmol/l, her lactate level was 122.9 mg/dl and her c-reactive protein (CRP) level was 1.7 mg/l. The dengue IgM antibody was positive.

She presented to the tertiary level hospital with hematemesis, and received a platelet concentrate transfusion of 10 ml/kg, fresh frozen plasma, leukocyte poor packed red cells (LPRC), vitamin K, intravenous sodium bicarbonate to correct severe metabolic acidosis, and intravenous cefotaxime to cover for a potential bacterial infection. She had spasticity controlled with intravenous Levetiracetam. The next day, she was given cryoprecipitate, fresh frozen plasma, LPRC, tranexamic acid, and NovoSeven Coagulation Factor VIIa due to bleeding. She was also given albumin because of hypoalbuminemia.

A repeat liver function test showed: a total protein level of 4 g/dl, an albumin level of 2.7 g/dl, a globulin level of 1.3 g/dl, a total bilirubin level of 3.01 mg/dl, a direct bilirubin level of 2.29 mg/dl, an AST level of 40,746 U/l and an ALT level of 5,068 U/l. Her serum calcium level was 9.56 mg/dl, her magnesium level was 2.2 mg/dl, her phosphorus level was 2.7 mg/dl, her sodium level was 137mmol/l, her potassium level was 3.1 mmol/l, her chloride level was 104 mmol/l, and her bicarbonate level was 18 mmol/l. Continuous venovenous hemodialysis (CVVHD) was started with a dialysate flow of 300ml/hour. The dialysate fluid contained 2-4% albumin, and was conducted for 6-9 hours/session (single pass albumin dialysis (SPAD) mode). The fluid loss rate was 90-130 ml/hour. To remove volume and bilirubin after blood component replacement in order to maintain hemodynamic stability, a normal saline flush was given at 50-100 ml/hour without anticoagulant followed by CVVH throughout the day. The CVVH priming blood line was 100 ml of 5% albumin with a machine temperature of 36.5ºC. The blood flow rate was 5.5-6.5 ml/kg/minute, pre-dilution and post-dilution each in the order of 50%, fluid loss rate was 90-110 ml/hour, and normal saline flush at 50-100 ml/hour without anticoagulant; manual substitution fluid depended on the current patient electrolytes and corrected for electrolyte imbalances. The antibiotic was changed to meropenem and vancomycin.

The patient was kept on CVVH for 10 days with 5 cycles of SPAD. A sputum Gram stain showed Gram negative bacilli; so the antibiotics were changed to tigecycline and colistin.

After SPAD, she was bolused with a dose of N-acetylcysteine (NAC) at 300 mg/kg followed by 100 mg/kg daily for 6 days. She was also given therapeutic plasma exchange (TPE) for 3 days using fresh frozen plasma and albumin replacement.

The sputum culture grew out *Stenotrophomonas*; so levofloxacin was added to the antibiotic regimen. She was also received pentaglobin for 3 days. She was also given antifungal treatment.

DISCUSSION

The patient presented in this report was in the leaking phase of dengue infection and had typical fever for 4-5days prior to transfer to our hospital. On admission she had elevated liver enzymes and coagulopathy. Her coagulopathy was corrected to prevent bleeding. We used a blood transfusion to maintain hemodynamic stability and a urine output of at least 1 ml/kg/hour. However, the

fluid intake was greater than the output; thus, resulting in volume overload. Finally, the patient was managed with renal replacement therapy using CVVH to remove the fluid and serum ammonia. Serum ammonia levels play a major role in causing hepatic encephalopathy and cerebral edema (Back *et al*, 2011). CVVH also removes other toxic substances, such as lactic acid, in acute liver failure (Cardoso *et al*, 2018).

Newer treatment of acute liver failure includes using the molecular adsorbent recirculating system (MARS) leading to a rapid reversal of biochemical abnormalities and encephalopathy (Penafiel *et al*, 2006). The use of MARS has been limited in developing countries because of its technical difficulties and high cost. However, SPAD is an extracorporeal albumin dialysis, which has been proposed as an alternative.

Clinicians can reduce plasma bilirubin levels using SPAD (Sponholz *et al*, 2016). SPAD dialyzes blood against albumin-rich dialysate that is discharged after a single pass through the dialyzer. In a study by Boonsrirat *et al* (2009), treatment with SPAD significantly improved total bilirubin, conjugated bilirubin, urea, and creatinine levels.

In our study, SPAD had no effect on bilirubin levels. The bilirubin levels peaked on the 26th day of admission (Table 1). This delay in the peak bilirubin level might have occurred due to cholestasis resulting from hepatocyte damage. Serum ammonia levels decreased to below 100 μmol/l when the patient was placed on CVVH and SPAD treatment. The serum ammonia levels decreased to normal (<43 μmol/l) by the 12th day of hospitalization.

In this patient, the AST and ALT levels peaked on the first day of admission at tertiary care hospital, thereafter, the AST and ALT levels declined (Table 1). This is in contrast to Fernando *et al* (2016) who reported liver injury peaked around Days 6 and 7 of illness. During hemodialysis, substances with a molecular weight <500 Da are usually removed (Mirrakhimov *et al*, 2016). Hemofiltration has been reported to remove substances with a molecular weight <40 kDa (Mirrakhimov *et al*, 2016). AST and ALT have molecular weights of 45 kDa (Hayashi *et al*, 1990) and 114 kDa (Ndrepepa and Kastrati, 2019), respectively. CVVH with SPAD decreased AST and ALT levels in this patient. However, both AST and ALT may also have decreased along the clinical course of the disease.

Plasmapheresis has been reported to decrease total bilirubin and transaminase levels (Singer *et al*, 2001). TPE has been reported to significantly decrease bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), PT, and INR levels (Maheshwari *et al*, 2020). TPE may also remove some toxic substances from the patient's plasma (Bobati *et al*, 2017). Singer *et al* (2001) reported post-exchange coagulation values improved significantly from pre-exchange values. Treatment of coagulopathy results in an increase in fibrinogen and factors II, V, IX and VII (Singer *et al*, 2001). In our study, PT and INR decreased after 3 cycles of TPE. Plasmapheresis also resulted in a decrease in TB and transaminase levels. However, there was a rebound increase in TB levels between plasmapheresis sessions (Table 1).

It is also important to be aware of the risks of TPE, such as infections, hypocalcemia, and other adverse reactions (Lu *et al*, 2019).

We used N-acetylcysteine (NAC) in our patient to manage dengue

Table 1
Selected laboratory results over the time of study.

Laboratory result	Day of hospitalization														
	1		2[a,b]	3[a,b]	4[a,b]	5[a,b]	8[b]		9[b]	10[b]	11	20	26	41	70
	0h*	8h**,[a,b]					After TPE1	Before TPE2	TPE2	TPE3					
Hct (%)	32.3	33.1	29.7	31.1	27	30.2	33.2	30.9	35.4	28.9	32.3	28.6	33.5	35.8	40
WBC ($\times 10^3/mm^3$)	11,170	4,530	5,090	7,100	6,910	5,910	7,870	7,930	9,860	6,910	7,340	15,350	10,100	23,000	10,020
Plts ($\times 10^3/mm^3$)	14,000	26,000	104,000	181,000	137,000	125,000	151,000	133,000	127,000	90,000	97,000	153,000	161,000	177,000	270,000
TB (mg/dl)	2.29	3.01	4.23	5.93	7.16	9.10	7.89	14.42	16.28	14.35	15.72	22.01	25.99	10.47	1.05
DB (mg/dl)	1.50	2.29	2.53	2.90	3.93	4.50	3.04	5.88	7.54	7.15	8.47	16.35	21.49	9.12	0.86
AST (U/l)	34,822	40,746	14,789	5,918	2,919	1,865	338	527	414	219	173	87	177	301	58
ALT (U/l)	4,842	5,068	2,288	1,357	931	691	176	305	262	146	120	20	31	163	36
PT (seconds)	20.80	38	17.6	15.5	20.5	18.4	16.10	20.7	23.2	20.10	19.8	15.3	16	14.9	NA
INR	1.71	3.04	1.46	1.62	1.69	1.53	1.34	1.71	1.90	1.66	1.64	1.28	1.34	1.25	NA
BUN (mg/dl)	9.5	12	6.2	3.7	3.5	3.9	12.1	21.1	25.6	14.6	30.3	54.4	NA	NA	10.4
Cr (mg/dl)	0.33	0.37	0.2	0.22	0.23	0.24	0.32	0.49	0.47	0.17	0.31	0.28	NA	NA	0.16
NH_3 (μmol/l)	108	NA	65	49	95	81	125	NA	243	74	62	NA	NA	NA	NA

Hct: hematocrit; WBC: white blood cell count; Plts: platelets; TB: total bilirubin; DB: direct bilirubin; AST: aspartate transaminase; ALT: alanine aminotransferase; PT: prothrombin time; INR: international normalized ratio; BUN: blood urea nitrogen; Cr: creatinine; NH_3: ammonia; 0h*: on admission; 8h**: 8 hours after admission; TPE 1: therapeutic plasma exchange cycle 1; TPE2: therapeutic plasma exchange cycle 2; TPE3: therapeutic plasma exchange cycle 3; a: single pass albumin dialysis (SPAD); b: continuous venovenous hemofiltration (CVVH); mm^3: cubic millimetre; mg/dl: milligram per deciliter; U/l: unit per liter; μmol/l: micromole per liter.

associated severe liver disease (Lim and Lee, 2012; Nabi *et al*, 2017). An important complication of acute liver failure is abnormal oxygen transport and utilization (Lim and Lee, 2012). As a result, the oxygen extraction ratio and oxygen consumption decreases, leading to anaerobic metabolism and lactic acidosis (*Bihari et al*, 1985; Holt, 1999). NAC acts as a vasodilator and improves antioxidant defenses by scavenging reactive oxygen species (Lim and Lee, 2012). In our patient, after NAC use, the transaminases decreased and the PT and INR improved.

Though uncommon, dengue infection can lead to acute liver failure in a minority of cases in children. SPAD has been suggested as an alternative replacement therapy in liver failure but in our study made no significant impact. The decision to use TPE should be individualized since there are no standard recommendations for its use in dengue infection. Further studies are needed to determine if there is indeed a role for TPE or SPAD in dengue infected patients with severe liver involvement.

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