Case Report

Therapeutic plasma exchange as a treatment of a dengue encephalopathic patient

Aphisit Thongthaisin[1], Jettawan Siriaksorn[2], Siwaporn Boonyasuppayakorn[3] and Phandee Watanaboonyongcharoen[1,2]

[1]Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University; [2]Transfusion Medicine Unit, King Chulalongkorn Memorial Hospital; [3]Department of Microbiology, Faculty of Medicine, Chulalongkorn University

Abstract:

Introduction: *Dengue virus is a global burden affecting about 390 million people annually. Neurological complications were found in a broad range of 0.5-21% of dengue-infected patients. Dengue encephalopathy and encephalitis have a fatality rate of 22%. There is currently no specific treatment. Therapeutic plasma exchange is recommended as one of the possible alternative treatments. However, to our knowledge, there has been no published record of therapeutic plasma exchange in severe dengue patients. Here, we present a dengue encephalopathy case successfully treated with therapeutic plasma exchange.* ***Case report:*** *A 39-year-old male with no known underlying disease presented at the Emergency Department with hematemesis for one hour. A diagnosis of dengue infection with acute liver failure and upper gastrointestinal tract bleeding was given. He developed alteration of consciousness and focal to generalized tonic-clonic seizure. He was diagnosed of dengue encephalopathy because he had impaired consciousness, seizure, hepatic failure, and normal CSF. The Blood Bank was consulted for the therapeutic plasma exchange and was done for a total of three times. Thereafter, the patient's Glasgow coma score improved. The patient did not convulse again. His platelet count reached 136,000/mm^3 and was eventually discharged. On follow-up, he had not convulsed again and had no fever.* ***Conclusion:*** *We report a case of dengue encephalopathic patient successfully treated with therapeutic plasma exchange which decreased the levels of the inflammatory cytokines and pathological antibodies from the plasma. The patient improved dramatically after the first therapeutic plasma exchange.*

Keywords : ● *Therapeutic plasma exchange* ● *Dengue encephalopathy* ● *Apheresis*

J Hematol Transfus Med. 2021;31:79-85.

Received 21 December 2020 Corrected 25 January 2021 Accepted 2 February 2021

Correspondence should be addressed to Aphisit Thongthaisin, MD, Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University 1873 Rama IV Road, Pathum Wan, Bangkok, 10330 Tel. 062-532-2463 Email: aphisitthongthaisin@gmail.com

รายงานผู้ป่วย

การรักษาผู้ป่วย dengue encephalopathy ด้วย therapeutic plasma exchange

อภิสิทธิ์ ทองไทยสิน[1] เจตวรรณ ศิริอักษร[2] ศิวะพร บุณยทรัพยากร[3] และ พรรณดี วัฒนบุญยงเจริญ[1,2]

[1]ภาควิชาเวชศาสตร์ชันสูตร คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย [2]ธนาคารเลือด โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย [3]ภาควิชาจุลชีววิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

บทคัดย่อ

บทนำ *ไวรัสเดงกีเป็นสาเหตุของโรคไข้เลือดออกทั่วโลกปีละ 390 ล้านคน พบภาวะแทรกซ้อนทางระบบประสาทได้ใน 0.5-21% ในผู้ติดเชื้อไวรัสเดงกี Dengue encephalitis และ encephalopathy มีอัตราป่วยตายร้อยละ 22 ปัจจุบันยังไม่มีวิธีรักษาที่จำเพาะ therapeutic plasma exchange เป็นวิธีการรักษาหนึ่งที่เป็นไปได้ อย่างไรก็ตาม ณ ปัจจุบันยังไม่มีรายงานผู้ป่วยติดเชื้อเดงกีรุนแรงที่ได้รับการรักษาด้วย therapeutic plasma exchange บทความนี้รายงานการรักษาผู้ป่วย Dengue encephalopathy รายหนึ่งด้วย therapeutic plasma exchange ที่ประสบความสำเร็จ* ***รายงานผู้ป่วย*** *ผู้ป่วยชายอายุ 39 ปี ไม่มีโรคประจำตัวมาที่ห้องฉุกเฉินด้วยอาการอาเจียนเป็นเลือดมา 1 ชั่วโมง ได้รับการวินิจฉัยเป็นโรคไข้เลือดออกร่วมกับภาวะตับวายเฉียบพลันและภาวะเลือดออกในทางเดินอาหารส่วนบน ผู้ป่วยมีอาการซึมลงตามมาด้วยอาการชักเฉพาะที่ ต่อมามีอาการชักทั้งตัว ผู้ป่วยได้รับการวินิจฉัยว่าเป็น Dengue encephalopathy เนื่องจากมีอาการซึม อาการชัก ภาวะตับวาย และการตรวจน้ำไขสันหลังปกติ ธนาคารเลือดได้รับการปรึกษาเพื่อทำ therapeutic plasma exchange เป็นจำนวน 3 ครั้ง ภายหลังการทำพบว่าแบบประเมินความรู้สึกตัวของกลาสโกวมีคะแนนดีขึ้น ผู้ป่วยไม่มีอาการชักอีก จำนวนเกล็ดเลือดเพิ่มขึ้นเป็น 136,000/mm^3 และได้รับการจำหน่ายออกจากโรงพยาบาลได้ ในการตรวจติดตามอาการผู้ป่วย พบว่าไม่มีอาการชักอีกและไม่มีไข้* ***สรุป*** *บทความนี้ได้รายงานการรักษาผู้ป่วย Dengue encephalopathy รายหนึ่งด้วย therapeutic plasma exchange ที่ประสบความสำเร็จ ซึ่ง therapeutic plasma exchange สามารถลดปริมาณ inflammatory cytokines และแอนติบอดีที่ทำให้เกิดโรคจากพลาสมาผู้ป่วยได้ ทำให้ผู้ป่วยมีอาการดีขึ้นอย่างรวดเร็วหลังจากการรักษาครั้งแรก*

คำสำคัญ : ● *การแลกเปลี่ยนพลาสมาเพื่อการรักษา* ● *เดงกีเอนเซฟาโลพาธี* ● *อะเฟอรีซิส*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2564;31:79-85.

Introduction

Dengue virus is a global burden affecting about 390 million people annually[1]. This mosquito-borne flavivirus consists of four serotypes (DENV1-4) cocirculating in the tropical areas. Its structure contains a positive-sense, single- str anded RNA genome, encapsidated in an icosahedral capsid (T = 3), and enveloped by ER-derived phospholipids and two viral proteins called membrane (M) and en velope (E)[2]. Most dengue infection is asymptomatic, or a self-limited fever with myalgia, headache wi th retroorbital pain, fatigue, and sometimes accompanied by nausea and vomiting. Severe dengue manifestations, although accounted for 1-7%[3], cause a serious burden with hypovolemic shock from plasma leakage or massive blood loss, acute renal failure, and neurological complications.

Neurological complications were found in a broad range of 0.5-21% of dengue infected, admitted patients during 1994-2008 in Thailand, Vietnam and Brazil[4] and were frequently associated with infections of DENV2 and DENV3 serotypes[5,6]. Dengue encephalopathy and encephalitis are defined as two common characteristics found in central neurological involvement (Table 1)[4] and have a fatality rate of 22%[7].

There is currently no specific treatment for dengue encephalopathy and encephalitis; therefore, supportive treatments including antiepileptics for seizures and cerebral decongestant are the keys to improve the clinical outcomes[8]. Therapeutic plasma exchange is recommended as one of the possible alternative treatments. However, to our knowledge, there has been no published record of therapeutic plasma exchange in severe dengue patients. Moreover, the treatment of dengue encephalopathy using therapeutic plasma exchange is not listed as an indication in the American Society for Apheresis (ASFA)'s Guidelines on the Use of Therapeutic Apheresis in Clinical Practice[9]. Here, we present a dengue encephalopathy case successfully treated with therapeutic plasma exchange.

Case report

A 39-year-old male with no known underlying disease presented at the Emergency Department with hematemesis for one hour. One day prior to the admission, he had fever with chills with no organ specific symptoms. He took acetaminophen (500 mg) once and reported that it alleviated his fever. He denied hematochezia or melena. He had a history of heavy alcohol drinking for 20 years. Vital signs showed body temperature of 37.8 ˚C and per rectal examination showed yellow feces. Other physical examinations were normal. Nasogastric intubation was done and showed fresh blood. Laboratory investigations showed hemoglobin 16.5 g/dL (13-17), platelet count 4,000/mm^3 (150,000-450,000), prothrombin time 17.9 sec (10.1-13.1), partial thromboplastin time 48.1 sec (20.9-31.1), international

Table 1 Definition of dengue encephalopathy and encephalitis

Encephalopathy	Encephalitis
At least one of the followings:	Dengue CNS involvement, and presence of dengue virus RNA, IgM, or NS1 antigen in CSF, and CSF pleocytosis without other neuroinvasive pathogens
Impaired consciousness, neck stiffness, focal neurological signs, or seizure	
AND	
Presence of the following dengue-associated complications:	
hepatic failure, metabolic acidosis, severe hyponatraemia, prolonged shock, disseminated intravascular coagulation, or brain haemorrhage AND	
Normal CSF	

normalized ratio 1.48, aspartate aminotransferase 2,489 IU/L (5-35), alanine aminotransferase 657 IU/L (0- 40), alkaline phosphatase 163 IU/L (40-120), dengue non-structural protein 1 antigen positive by immunochromatography test and dengue immunoglobulin M and immunoglobulin G negative by immunochromatography test. A diagnosis of dengue infection with acute liver failure with upper gastrointestinal tract bleeding was given. He was treated with intravenous octreotide 50 μg/hour and pantoprazole 8 mg/hour and was given two units of leukocyte poor platelet concentrate and four units of fresh frozen plasma. He was admitted to intensive care unit and underwent esophagogastroduodenoscopy one day later which showed no stigmata of recent hemorrhage. Dexamethasone 5 mg every 6 hours was started to decrease platelet destruction from immunopathological process. Two days after admission, he developed alteration of consciousness with Glasgow coma score of E1V1M4 and was intubated. CT scan showed a 1.8x1.3x1.8 arachnoid cyst at right paramedian aspect of posterior cerebellum causing pressure effect to adjacent calvarium and right cerebellar hemisphere and no evidence of acute large territorial infarction or intracranial hemorrhage. Three days after admission, his laboratory investigation showed albumin of 3.2 g/dL (3.5-5.0) which is an evidence of plasma leakage, so he was diagnosed with dengue hemorrhagic fever. Four days after admission he developed focal to generalized tonic-clonic seizure for one minute. After the seizure, his Glasgow coma score was E1VTM4. Levetiracetam 500 mg every 12 hours was started and lumbar puncture was performed. Cerebrospinal fluid analysis showed white blood cells count of three and dengue genome was negative by PCR. He was given the diagnosis of dengue encephalopathy because he had impaired consciousness, seizure, hepatic failure, and normal CSF. He also developed fever of 38°C, consistent with an infiltration at left upper lung shown in chest X-ray. Sputum gram stain showed many gram negative rods. Meropenam 1 g every 8 hours was started.

Blood bank was consulted for therapeutic plasma exchange because the acute disseminated encephalomyelitis (ADEM) is in ASFA Category II, or apheresis is accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment[9]. Moreover, therapeutic plasma exchange is considered secondary treatment for post-dengue ADEM[10] caused by immunopathological responses. Medications at that period included meropenam 1 g every 8 hours, levetiracetam 500 mg every 12 hours, thiamine 500 mg every 8 hours and pantoprazole 80 mg (8 mg/hour). There was a case report that therapeutic plasma exchange reduced serum levetiracetam level to 83% of the baseline level[11]. However, the dose was not adjusted and the patient did not receive any pre-medications. Therapeutic plasma exchange was performed for a total of three times using the double lumen catheter as the venous access. Sodium citrate was used as anticoagulant with anticoagulant (AC) ratio of 18:1. The first time was done two days later using the fresh frozen plasma as the replacement fluid because the patient also had coagulopathy. Total blood volume of the patient was calculated using Nadler's formula as 4,272 mL (The patient's height was 166 cm and weight was 61.8 kg.). The plasma volume of the patient was 2,880 mL and the plasma volume exchange was performed with 3,000 mL fresh frozen plasma. His vital signs were stable and there was no complication. The patient's Glasgow coma score improved to E4VTM6. One day later the patient was extubated and underwent another round of therapeutic plasma exchange using 3,000 mL fresh frozen plasma as the replacement fluid. His vital signs were stable and there was no complication. His sputum culture result showed *Acinetobacter baumannii* which was susceptible to meropenam, ceftazidime and ciprofloxacin, so his antibiotics was switched to ciprofloxacin 400 mg every 12 hours. Proton pump inhibitor was also changed to omeprazole 40 mg every 12 hours. One day later the patient underwent the final round of therapeutic plasma exchange using 3,000 mL fresh

frozen plasma as the replacement fluid. His vital signs were stable and there was no complication. His laboratory data before and after the procedures is shown in Table 2. He was then transferred to a general medical ward. The patient did not convulse again. Four days later, his platelet count reached 136,000 /mm^3 and was eventually discharged nine days later. On follow-up five days later, he had not convulsed again and had no fever. The patient's clinical course is shown in Figure 1.

Table 2 Laboratory data before and after the therapeutic plasma exchanges

	Hb (g/dL)	Hct (%)	WBC (/μL)	PMN (%)	Lymph (%)	Mono (%)	Platelets (/μL)	Ca (mg/dL)	PT (sec)	PTT (sec)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
Before 1st TPE	10.7	32.6	8,550	80.3	5.4	14.1	80,000	8.6	16.9	28.2	307	351	78
After 1st TPE	12.1	34.4	8,380	81	5.4	13.3	72,000	8	16.6	27.6	174	320	92
After 2nd TPE	12	34.5	10,770	80.2	8.0	11.1	58,000	7.9	15.1	29.1	82	148	77
After 3rd TPE	11.1	32.3	15,880	82	6.1	9.7	53,000	8.3	15.4	29.7	78	115	79

Discussion

There is currently no specific treatment for dengue encephalopathy. We report a case of dengue encephalopathy patient successfully treated with therapeutic plasma exchange. This case was selected for therapeutic plasma exchange treatment as post-dengue ADEM fits in ASFA category II which is accepted as a second-line therapy as earlier discussed[9,10]. Dengue infection, especially by a second heterotype infection, activates the immune-mediated pathological responses including excessive pro-inflammatory cytokines released including IL2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-18, monocyte chemoattractant protein-1 (MCP-1), macrophage migration inhibitory factor (MIF), transforming growth factor-β, TNF-α, and IFN-γ[12]. Moreover, the infection also stimulates the production of cross-reactive autoantibodies via molecular mimicry of viral antigens nonstructural protein (NS) 1, precursor membrane protein (prM), and envelope protein (E)[12]. Autoantibodies against platelets, endothelial cells, and coagulatory molecules, such as plasminogen, leading to platelet dysfunction, endothelial cell apoptosis, coagulation defect, and macrophage activation[12]. Therapeutic plasma exchange is therefore an ultimate solution to remove inflammatory cytokines and pathological antibodies from the plasma[13]. ASFA guideline recommended 1- 1.5 plasma exchange volume every other day with 5% albumin as fluid replacement for a total of 3-6 treatments in the case of ADEM[9]. This patient underwent daily therapeutic plasma exchange

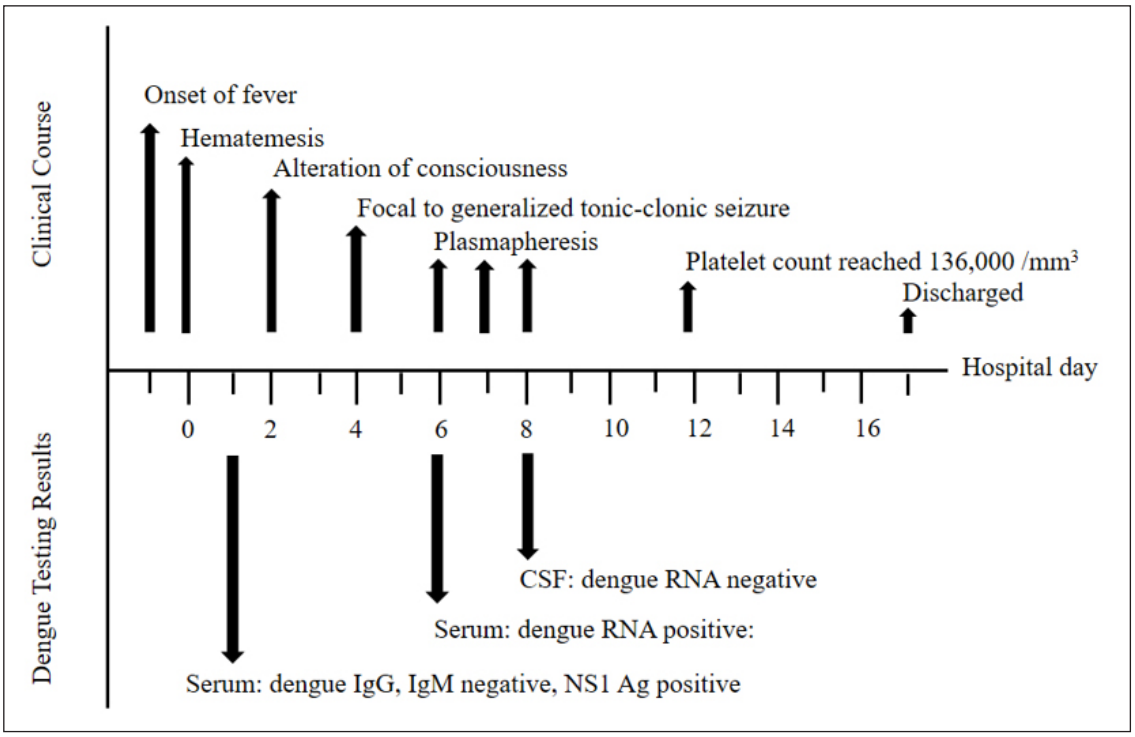

Figure 1 The timeline of the patient's clinical course: The hospital day in the x-axis indicate the day after the patient's admission. Serum dengue NS1 antigen was positive on hospital day 1. The patient developed focal to generalized tonic clonic seizure on hospital day 4. Therapeutic plasma exchange was performed on hospital day 6, 7 and 8. The patient's platelet count reached 136,000/mm3 on hospital day 12. The patient was discharged on hospital day 17

with plasma exchange volume of 1.0 for three days which removed 3,000 mL of the patient's plasma and replaced with 3,000 mL of fresh frozen plasma because he had coagulopathy. The procedures took approximately 2 hours to perform. There was no complication after the procedures. The patient improved dramatically after the first therapeutic plasma exchange because his Glasgow coma score improved from E1VTM4 to E4VTM6, he did not convulse again, and he was extubated one day later. His aspartate aminotransferase and alanine aminotransferase decreased from 307 IU/L and 351 IU/L before the procedures to 78 IU/L and 115 IU/L after the third procedure, respectively. He was successfully discharged nine days after completing the third therapeutic plasma. Further studies should include the following parameters; percentage of clearance of anti-plasmin and anti-platelet, to objectively measured the effectiveness of therapeutic plasma exchange in dengue encephalopathic patients.

Conclusion

A 37-year-old man with dengue encephalopathy was treated with the therapeutic plasma exchange for a total of three times. He improved dramatically after the first treatment. Therefore, a severe case of dengue encephalopathy can be considered for treatment with therapeutic plasma exchange and the excellent clinical outcome is expected.

References

1. *Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496:504-7.*
2. *Zhang W, Chipman PR, Corver J, Johnson PR, Zhang Y, Mukhopadhyay S, et al. Visualization of membrane protein domains by cryo-electron microscopy of dengue virus. Nat Struct Biol. 2003;10:907-12.*
3. *Endy TP, Chunsuttiwat S, Nisalak A, Libraty DH, Green S, Rothman AL, et al. Epidemiology of inapparent and symptomatic acute dengue virus infection: a prospective study of primary school children in Kamphaeng Phet, Thailand. Am J Epidemiol. 2002;156:40-51.*

4. *Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. Lancet Neurol. 2013;12: 906-19.*
5. *Varatharaj A. Encephalitis in the clinical spectrum of dengue infection. Neurol India. 2010;58:585-91.*
6. *Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LT, Raengsakulrach B, et al. Neurological manifestations of dengue infection. Lancet. 2000;355:1053-9.*
7. *Cam BV, Fonsmark L, Hue NB, Phuong NT, Poulsen A, Heegaard ED. Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. Am J Trop Med Hyg. 2001;65:848-51.*
8. *Verma R, Sahu R, Holla V. Neurological manifestations of dengue infection: a review. J Neurol Sci. 2014;346:26-34.*
9. *Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based Approach from the Writing Committee of the American Society for Apheresis: the seventh special issue. J Clin Apher. 2016;31:149-62.*
10. *Wan Sulaiman WA, Inche Mat LN, Hashim HZ, Hoo FK, Ching SM, Vasudevan R, et al. Acute disseminated encephalomyelitis in dengue viral infection. J Clin Neurosci. 2017;43:25-31.*
11. *Hau Man TH, Shek-Kwan CR, On-Kei CA, Lam CPW. Effect of plasmapheresis on serum levels of clobazam, levetiracetam and topiramate. Epilepsy Behav Case Rep. 2017;8:66-8.*
12. *Wan SW, Lin CF, Yeh TM, Liu CC, Liu HS, Wang S, et al. Autoimmunity in dengue pathogenesis. J Formos Med Assoc. 2013;112:3-11.*
13. *Reeves HM, Winters JL. The mechanisms of action of plasma exchange. Br J Haematol. 2014;164:342-51.*