European Review for Medical and Pharmacological Sciences 2021; 25: 3002-3006

Successful mild brain hypothermia therapy followed by targeted temperature management for pediatric hemorrhagic shock and encephalopathy syndrome

Y. FUJITA[1], G. IMATAKA[1], J. KIKUCHI[2], S. YOSHIHARA[1]

[1]Department of Pediatrics, Dokkyo Medical University, Tochigi, Japan
[2]Department of Emergency and Critical Care Medicine, Dokkyo Medical University, Tochigi, Japan

Abstract. – OBJECTIVE: Hemorrhagic shock and encephalopathy syndrome (HSES) is the most severe form of acute encephalopathy that progresses rapidly, often resulting in death or severe neurological sequelae. We report the case of a 4-year-old girl with HSES with shock and impaired consciousness.

PATIENT AND METHODS: Blood test results showed hypercytokinemia, and the 4-year-old patient was immediately admitted to the intensive care unit. Within 4 h of symptom onset, she received mild brain hypothermia therapy with a target body temperature of 35°C. Methylprednisolone pulse, high dose immunoglobulin, and large doses of circulatory drugs were administered.

RESULTS: After 72 h of brain hypothermia therapy, targeted temperature management with a target body temperature between 36°C and 37°C was continued for 96 h. The patient was diagnosed with HSES based on acute encephalopathy with shock, hypercytokinemia, low platelet count, coagulation disorder, renal damage, and intestinal bleeding. Magnetic resonance imaging results revealed no signs of any specific acute encephalopathy. She was discharged without neurological sequelae 28 days after symptom onset.

CONCLUSIONS: Mild brain hypothermia therapy initiated in the early stages followed by targeted temperature management may be an effective way to improve neurological outcomes in children suffering from HSES.

Key Words:
Brain hypothermia, Hemorrhagic shock and encephalopathy syndrome, Interleukin-6, Targeted temperature management.

Abbreviations

ANE: acute necrotizing encephalopathy; BHT: brain hypothermia therapy; CRP: C-reactive protein; CT: computed tomography; GCS: Glasgow Coma Scale; HSES: hemorrhagic shock and encephalopathy syndrome; IL: interleukin; MRI: magnetic resonance imaging; PCT: procalcitonin; TTM: targeted temperature management.

Introduction

Hemorrhagic shock and encephalopathy syndrome (HSES) is a severe type of encephalopathy that often leads to profound neurological sequelae or death. The diagnostic criteria of HSES, proposed by Levin et al[1] in 1983, include encephalopathy, shock, disseminated intravascular coagulation, diarrhea, decrease in hemoglobin or platelets, acidosis, elevated transaminase, renal dysfunction, and negative blood and cerebrospinal fluid cultures. HSES is a very rare encephalopathy with an incidence rate of 1%[2]. Hypercytokinemia and acute necrotizing encephalopathy (ANE)[3] have been indicated the pathogenesis of HSES.

Moreover, HSES is an encephalopathy with poor neurological prognosis and high mortality[4] that progresses fast, particularly during the first 24 h following onset. In some cases, patients suffer from brain edema at the time of admission, however, in other cases, significant brain edema may develop later[5]. A rapid diagnosis of HSES and immediate initiation of treatment in the early stage are the key factors for increasing the odds of a swift recovery. We herein report the successful outcome of a patient with HSES who underwent mild brain hypothermia therapy (BHT) followed by targeted temperature management (TTM). We also present the patient's cytokines profile.

Corresponding Author: Yuji Fujita, MD; e-mail: fujitay@dokkyomed.ac.jp

Case Presentation

A 4-year-old girl with fever and impaired consciousness was transported to our hospital. She had no medical history, and her vital signs and physical examination were as follows: Glasgow Coma Scale (GCS) score, 4 (eye [E] = 1, verbal [V] = 1, motor [M] = 2); body temperature, 40°C; heart rate, 220 beats/min; blood pressure, 70/40 mmHg; Babinski and Chaddock reflexes were positive. The patient's rapid antigen test for adenovirus was positive. Blood test results showed the following: white blood cell count, 8,700/μL; hemoglobin, 15.8 g/dL; platelet, 204,000/μL; aspartate transaminase, 56; lactate dehydrogenase, 365 IU/L; uric acid, 9.8 mg/dL; urea nitrogen, 31 mg/dL; creatinine, 1.44 mg/dL; glucose, 122 mg/dl; C-reactive protein (CRP), 15.02 mg/dL; procalcitonin (PCT), 824 pg/mL; pH, 7.259; pCO_2, 37.8 mmHg; HCO_3-, 16.4 mmol/L; prothrombin time and international normalized ratio, 1.70; activated partial thromboplastin time, 49.3 s. Although a brain computed tomography (CT) scan revealed general mild brain edema, no abnormalities were observed in the CT density of the brain. A cerebrospinal fluid examination was not performed due to the risk of brain herniation. Blood bacterial culture was negative. The electrocardiogram showed sinus tachycardia.

A presumptive diagnosis of shock was made, and the patient was admitted to the intensive care unit. As her blood pressure decreased rapidly, we began a continuous intravenous infusion of noradrenaline, vasopressin, and dobutamine to maintain the blood pressure. Simultaneously, she was treated for acute encephalopathy with 30 mg/kg of methylprednisolone and 1 g/kg of immunoglobulin therapy for 3 and 2 days, respectively, starting 4 h after symptom onset. Additionally, mild BHT was initiated concomitantly, and the circulatory condition was stabilized with inotropic support, including noradrenaline, dobutamine, and vasopressin. The target body temperature of 35°C was reached 6 h after symptom onset using mechanical ventilation (Figure 1). The following day, her circulatory condition improved, while a repeat brain CT scan revealed no progression of cerebral edema. Mild BHT was continued, with a target temperature of 35°C for 72 h, followed by a target of 36°C-37°C for the subsequent 96 h. Fresh frozen plasma was transfused on days 2, 8, and 10, and platelet concentrate was administered on day 3 (Figure 2). On day 8, brain magnetic resonance imaging (MRI) examination showed no abnormal findings. She was extubated on day 9. On day 11, she had blood in her stool and suffered from a low hemoglobin

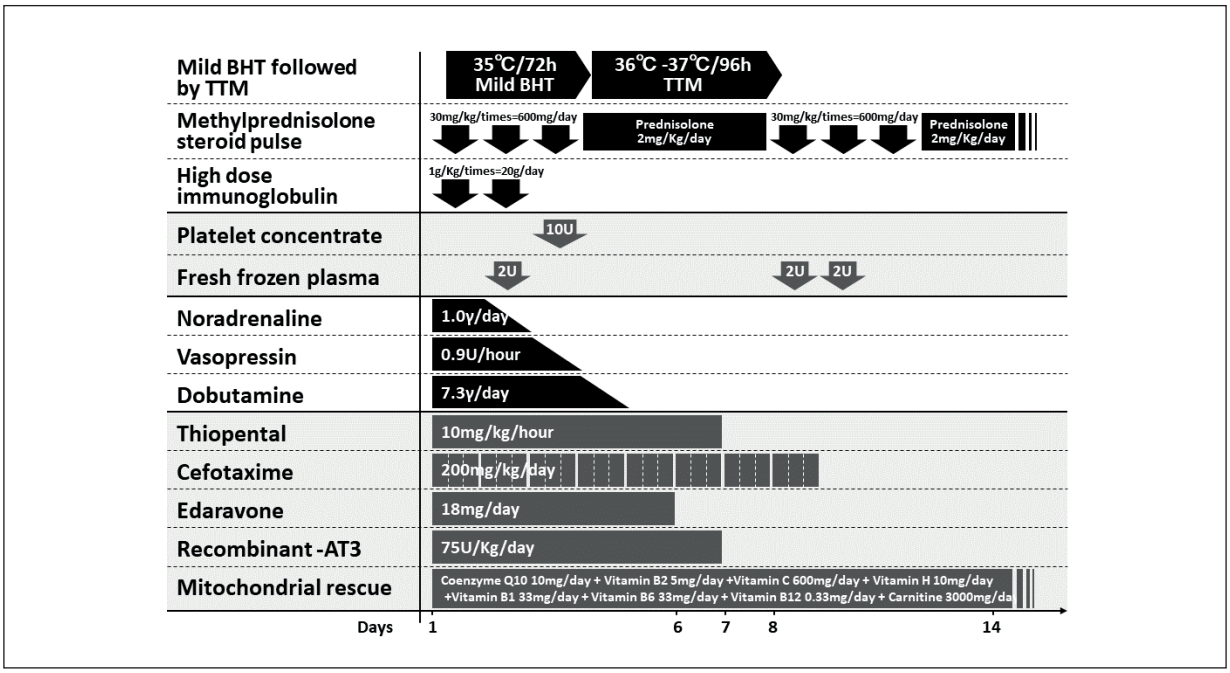

Figure 1. Mild BHT is performed for 72 h with a target temperature of 35°C, followed by TTM at 36°C-37°C for the subsequent 96 h. Circulatory condition is stabilized with noradrenaline in conjunction with corticosteroids, immunoglobulin therapy, and other treatments. *Abbreviations:* BHT, brain hypothermia therapy; TTM, targeted temperature management.

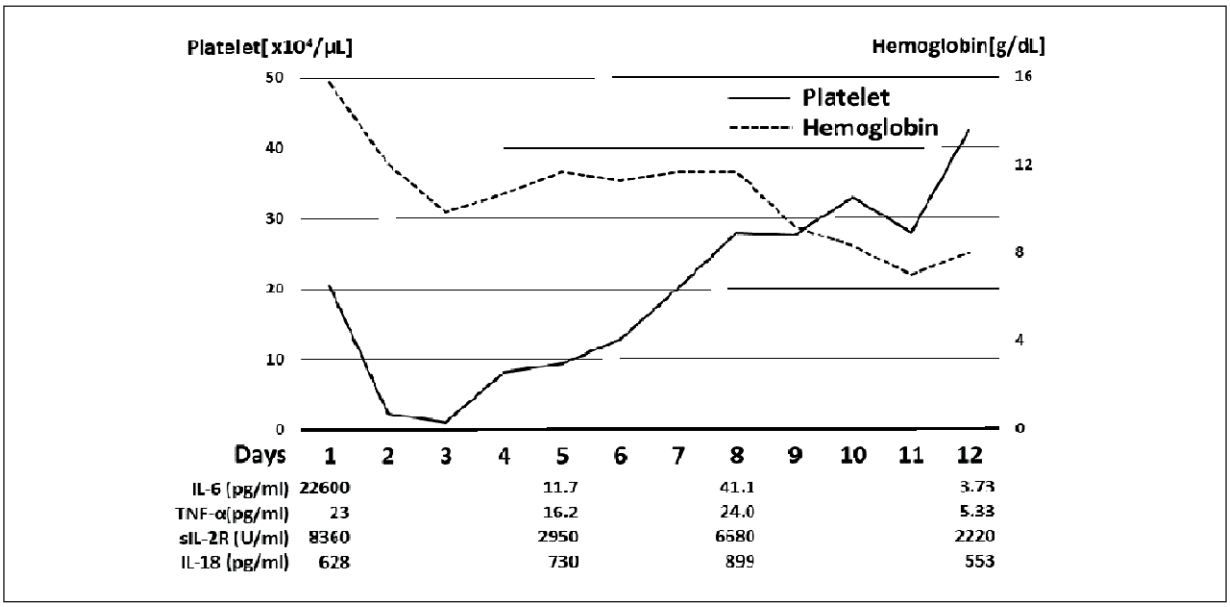

Figure 2. The platelet count declines to 10,400/μl, resulting in administration of platelet concentrate on day 3. Hemoglobin level declines to 7 g/dl due to gastrointestinal bleeding on day 11, whereas interleukin-6 levels are significantly elevated. *Abbreviations*: IL, interleukin; TFN, tumor necrosis factor; sIL-2R, soluble interleukin-2 receptor.

level, which was treated by the administration of proton pump inhibitor medications. She was diagnosed with HSES based on acute encephalopathy with shock, hypercytokinemia, decreased platelet count, coagulation disorder, renal injury, and intestinal bleeding, without specific acute encephalopathy. Her consciousness level and motor function gradually improved, she was discharged without neurological sequelae 28 days following symptom onset.

The patient's cytokines (interleukin [IL]-6, IL-18, tumor necrosis factor [TNF]-α, soluble IL-2 receptor [sIL-2R]) are shown in Figure 2.

Discussion

We presented a rare pediatric case of HSES with no neurological complications. To the best of our knowledge, most patients with HSES suffer severe neurological sequelae or death[6,7]. Few cases of HSES can recover without neurological sequelae[8]. The pathogenesis and effective treatment strategy remain unknown, therefore the factors that improve the prognosis of HSES are also unidentified.

HSES cases are observed more during the winter months[9], which is consistent with our patient's experience who was admitted to our hospital in January. Furthermore, HSES is usually associated with the thermal environment of infants[10]. These findings indicate that central body temperature is an important factor in the development of HSES, suggesting that temperature management is crucial factor during the treatment.

The pathogenesis of HSES remains unclear; although, hypercytokinemia is considered to play a dominant role. Interleukin (IL)-6 is a significant cytokine in acute encephalopathies, especially ANE and HSES, and possibly a marker for clinical severity. One study suggested that children with serum IL-6 levels > 15,000 pg/mL often have a low chance of survival[11]. In our case, the patient had an elevated level of IL-6 of 22,600 pg/mL when she was admitted to the hospital and despite the extremely high levels of IL-6, she recovered without any neurological sequelae. Another study reported that IL-6 and soluble IL-2 receptor levels are usually high in patients with HSES[12]. We also observed a high level of IL-2R (8,360 U/mL) in our patient. These findings indicate that hypercytokinemia is associated with the pathogenesis of HSES.

Rapid initiation of therapy in patients with HSES is important. Therapy should begin before the appearance of brain edema and the loss of contrast between the gray and white matter in CT imaging. Knowing this information, we

still do not have an effective treatment protocol for HSES. It is crucial that all pediatricians are aware of the possibility of HSES in febrile children with central nervous system symptoms and shock. Steroid and immunoglobulin therapy to suppress inflammatory cytokines may be considered, which is similarly used in ANE[13]. Nevertheless, the effectiveness of BHT and TTM in pediatric acute encephalopathy has not been established. It should be known and understood that the therapeutic window, prior to the onset of secondary brain damage, is very brief. BHT improves neurological prognosis if performed in the early stage of the disease [14-17]. In our case, BHT was initiated promptly, and a target temperature of 35°C was reached 6 h following symptom onset.

Conclusions

Our study demonstrated that acute encephalopathies with hypercytokinemia, including HSES and ANE, require prompt diagnosis and treatment to improve outcomes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research did not receive any specific grant funding from agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We would like to thank the Emergency and Critical Care Medicine staff for their care of this patient. We would also like to thank Editage (www.editage.com) for English language editing.

Authors' Contribution

Dr. Fujita collected and analyzed the data and drafted and revised the initial manuscript. Dr. Imataka, and Prof. Shigemi Yoshihara interpreted the data and revised the manuscript critically for important intellectual content. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

Informed Consent

Informed consent for publishing this case report was obtained from the patient's parents.

References

1) Levin M, Hjelm M, Kay JD, Pincott JR, Gould JD, Dinwiddie R, Matthew DJ. Haemorrhagic shock and encephalopathy: a new syndrome with a high mortality in young children. Lancet 1983; 2: 64-67.
2) Hoshino A, Saitoh M, Oka A, Okumura A, Kubota M, Saito Y, Takanashi JI, Hirose S, Yamagata T, Yamanouchi H, Mizuguchi M. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev 2012; 34: 337-343.
3) Mizuguchi M, Abe J, Mikkaichi K, Noma S, Yoshida K, Yamanaka T, Kamoshita S. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. J Neurol Neurosurg Psychiatry 1995; 58: 555-561.
4) Kuki I, Shiomi M, Okazaki S, Kawawaki H, Tomiwa K, Amo K, Togawa M, Ishikawa J, Rinka H. Characteristic neuroradiologic features in hemorrhagic shock and encephalopathy syndrome. J Child Neurol 2015; 30: 468-475.
5) Fukuda M, Yoshida T, Moroki M, Hirayu N, Nabeta M, Nakamura A, Uzu H, Takasu O. Influenza A with hemorrhagic shock and encephalopathy syndrome in an adult: a case report. Medicine (Baltimore) 2019; 98: e15012.
6) Gefen R, Eshel G, Abu-Kishk I, Lahat E, Youngster I, Rosenbloom E, Kozer E. Hemorrhagic shock and encephalopathy syndrome: clinical course and neurological outcome. J Child Neurol 2008; 23: 589-592.
7) Ince E, Kuloglu Z, Akinchi Z. Hemorrhagic shock and encephalopathy syndrome: neurologic features. Pediatr Emerg Care 2000; 16: 260-264.
8) Komori Y, Uchida N, Soejima N, Fujita Y, Matsumoto H. Successful outcome in an adult patient with influenza-associated hemorrhagic shock and encephalopathy syndrome. Intern Med 2020; 59: 2321-2326.
9) Sofer S, Yerushalmi B, Shahak E, Berenstein T, Schulman H. Possible aetiology of haemorrhagic shock and encephalopathy syndrome in the Negev area of Israel. Arch Dis Child 1996; 75: 332-334.
10) Bacon CJ, Bell SA, Gaventa JM, Greenwood DC. Case control study of thermal environment preceding haemorrhagic shock encephalopathy syndrome. Arch Dis Child 1999; 81: 155-158.
11) Aiba H, Mochizuki M, Kimura M, Hojo H. Predictive value of serum interleukin-6 level in influenza virus-associated encephalopathy. Neurology 2001; 57: 295-299.
12) Rinka H, Yoshida T, Kubota T, Tsuruwa M, Fuke A, Yoshimoto A, Kan M, Miyazaki D, Arimoto H, Miyaichi T, Kaji A, Miyamoto S, Kuki I, Shiomi M. Hemorrhagic shock and encephalopathy syndrome-the markers for an early HSES diagnosis. BMC Pediatr 2008; 8: 43.

13) Okumura A, Mizuguchi M, Kidokoro H, Tanaka M, Abe S, Hosoya M, Aiba H, Maegaki Y, Yamamoto H, Tanabe T, Noda E, Imataka G, Kurahashi H. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev 2009; 31: 211-217.

14) Kawano G, Iwata O, Iwata S, Kawano K, Obu K, Kuki I, Rinka H, Shiomi M, Yamanouchi H, Kakuma T, Takashima S, Matsuishi T. Determinants of outcomes following acute child encephalopathy and encephalitis: pivotal effect of early and delayed cooling. Arch Dis Child 2011; 96: 936-941.

15) Imataka G, Arisaka O. Brain hypothermia therapy for childhood acute encephalopathy based on clinical evidence. Exp Ther Med 2015; 10: 1624-1626.

16) Imataka G, Wake K, Yamanouchi H, Ono K, Arisaka O. Brain hypothermia therapy for status epilepticus in childhood. Eur Rev Med Pharmacol Sci 2014; 18: 1883-1888.

17) Tanaka T, Nagase H, Yamaguchi H, Ishida Y, Tomioka K, Nishiyama M, Toyoshima D, Maruyama A, Fujita K, Nozu K, Nishimura N, Kurosawa H, Tanaka R, Iijima K. Predicting the outcomes of targeted temperature management for children with seizures and/or impaired consciousness accompanied by fever without known etiology. Brain Dev 2019; 41: 604-613.