Brain hypothermia therapy for neonatal hypoxic-ischemic encephalopathy with a severely elevated serum creatine kinase level

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INTRODUCTION
There have been no reports on the clinical course and neurodevelopmental outcomes of patients with neonatal asphyxia and associated very high serum creatine kinase (CK) levels of above 20,000 IU/L. We experienced a rare case of a female infant with a severely elevated serum CK level (26,428 IU/L) associated with neonatal asphyxia at birth. The infant, suffering from moderate hypoxic–ischemic encephalopathy (HIE), was successfully treated with brain hypothermia therapy (BHT). This is the first report to present that the clinical course and short-term outcome for a patient with neonatal HIE and an associated very high serum CK level.

CASE REPORT
A 29-year-old Japanese woman was admitted to Takeda General Hospital complaining of diminished fetal movement at 39 weeks of gestation. She was a healthy woman (gravida 0, para 0) with no medical history, no family histories of neurodevelopmental disorder and no abnormal findings during pregnancy. Fetal heart rate monitoring had already shown late deceleration and no acceleration, and a baseline of 150 to 160 bpm with minimal variability. Doppler ultrasonography revealed oligohydramnios, ascites and an absence of fetal breathing movements. The umbilical artery pulsatility index was 0.62, and middle cerebral artery flow was undetectable. The patient was diagnosed with non-reassuring fetal status.
(NRFS) patterns, and an emergency cesarean section was performed. She delivered a 3,032 g surviving female infant without any definite anomalies. Umbilical artery blood gas analysis revealed a pH of 7.101, pO₂ of 11.6 mmHg, pCO₂ of 75.6 mmHg, with a base excess of -8.7 mmol/L. Her Apgar scores were 2 and 6 at 1 and 5 minutes after birth, respectively. She was intubated with an endotracheal tube soon after birth due to severe respiratory disorders, and admitted to the neonatal intensive care unit in our hospital. On admission, she was immediately started on mechanical ventilation, and laboratory tests were performed. The levels of deviation enzymes were significantly elevated (CK: 26,428 IU/L, CK myocardial band (MB): 1,690 IU/L, aspartate aminotransferase: 923 IU/L, alanine aminotransferase: 202 IU/L, lactate dehydrogenase: 4,307 IU/L, and alkaline phosphatase: 1,171 IU/L). Although, ultrasonography of the head revealed no abnormal findings, the patient experienced a number of seizures immediately after birth. She also showed lethargic consciousness, moderate hypotonia and absent Moro reflex. We diagnosed her as having moderate HIE based on Sarnat staging1). This case satisfied the criteria of the Japanese BHT guideline2). BHT was performed for this infant using head cooling (ArcticSun 2000, Medivance, USA) within 6 hours after birth to an esophageal temperature of 34.5°C. The esophageal probe was placed in the lower third of esophagus, and this temperature was evaluated as a brain temperature3). The esophageal temperature was maintained at 34.5°C for 72 hours, and rewarming was allowed to increase by 0.5°C per day to 35.5°C over 48 hours. The BHT could be completed without significant adverse events. At five days after birth, the infant could be removed from respiratory management. The severely high serum CK level spontaneously decreased, from 26,428 IU/L at birth, to 18,832 IU/L at one day after birth, 7,388 IU/L at two days after birth, 2,113 IU/L at three days after birth, 806 IU/L at four days after birth, and to 335 IU/L at five days after birth (Fig. 1), and her general condition was improved. She was discharged from our hospital at 25 days after birth. Her electroencephalogram results and automated auditory brain-stem response were normal at one month after birth. The first session of brain magnetic resonance imaging (MRI) was also performed, revealing the frontal cortex atrophy and low signals in a portion of the left lentiform nucleus (Fig. 2-A), left periventricular white matter and left cerebellum, those low signals were suggested as possible of hemorrhage. She has been regularly followed up, and without signs of epilepsy by a pediatrician. The second session of brain MRI at 10 months after birth revealed mild diffuse atrophy (Fig. 2-B). Her developmental score as evaluated using the Enjoji Scale of Infant Analytical Developmental Test (Enjoji and Aiya, 1980, printed by Keiotusin, Tokyo, Japan) was 84.7 and 64.0 at the age of 12 and 18 months, respectively.

**DISCUSSION**

BHT was successfully achieved in this infant

![Graph](attachment://Graph.png)

Fig. 1. The serum CK level was the highest (26,428 IU/L) at birth, and then decreased spontaneously during the brain hypothermia therapy without leading to multiple organ failure. That level was 335 IU/L at five days after birth.
suffering from moderate HIE with an associated very high serum CK level (26,428 IU/L) at birth by head cooling within 6 hours after birth to an esophageal temperature of 34.5°C. Neonatal asphyxia is a condition in which the brain is subjected to hypoxia, ischemia and hypercarbia, and can be caused by acute interruption of umbilical blood flow, premature placental separation, chronic uteroplacental insufficiency and failure to execute a proper resuscitation4). In this case, the delivered placenta and umbilical cord had no abnormal findings. Fetal ultrasonography revealed no abnormal findings until a few days prior to intervention. However, the final findings revealed oligohydramnios, fetal ascites and no rupture of membranes. Although the reason for NRFS in the present case is not clear, we speculate that the oligohydramnios and fetal ascites might be associated with NRFS, and which consequently might be resulted in the elevation observed in deviation enzyme levels at birth.

Although infants with mild HIE show no subsequent deficits, neurological sequelae (or death) have been reported to be 24% (5%) and 20% (80%) in moderate and severe HIE infants, respectively5). CK is an isoenzyme that is widely recognized in identifying damaged tissue, and is composed of varying combinations of subunits; including a dimer in the skeletal muscle and brain6). It has been reported that muscular dystrophies and rhabdomyolysis result in very high serum CK levels. The usual serum CK level is 15,000–35,000 IU/L in Duchene type of muscular dystrophy7). On the other hand, in healthy infants, the serum CK level is 70–380 IU/L at birth8). The CK-MB/-CK ratios are 0.3–3.1% and 1.4–5.4% at birth and at 72–100 hours after birth, respectively9), whereas the ratio was 6.3% at birth in our case. Further, in healthy infants, the CK brain band (BB)-/-CK ratios are 0.3–10.5% and 5.1–13.3% at birth and at 72–100 hours after birth, respectively10). Although we did not check the CK isoenzymes at birth in our case, applying the CK-BB level to the above ratio, the level can be estimated to be 1,000–3,500 IU/L. Nagdyman reported elevated serum CK-BB concentrations in infants with moderate or severe HIE within 24 hours after birth, with an average serum CK-BB level 46.5 IU/L (range, 21.4–83.0 IU/L), but it was not correlated with long-term neurodevelopmental delays10,11). As those studies included few cases with high serum CK levels such as that reported herein, the serum CK-BB level was of limited value in predicting severe brain damage after birth asphyxia. There are various biochemical indicators related to the severity of fetal distress or neonatal asphyxia; however, there are few reports focusing on the association between serum CK level and developmental outcome. In our short-term case, the developmental score at the age of 18 months is lower than the age of 12 months, and the brain MRI revealed mild atrophy at the age of 10 months. It may be possible to correlate high serum CK levels and long-term neurodevelopmental delays. Carefully observation and regular follow up is, therefore, considered to be necessary.

To the best of our knowledge, there have been no reports of CK levels as high as 26,428 IU/L in as-

Fig. 2-A. The first session of MRI at one month of age (Fluid-attenuated inversion recovery imaging sequences in the transverse plane) showed the frontal cortex atrophy and a low signal in a portion of the left lentiform nucleus.

2-B. The second session of imaging at ten months of age (Fluid-attenuated inversion recovery imaging sequences in the transverse plane) showed mild diffuse atrophy.
sociation with neonatal HIE and for which BHT was performed. Based on the China study group, which showed that mild hypothermia decreased the incidence of death or severe disability among infants with moderate or severe HIE, and there was no significant increase in adverse events (3), BHT was successfully applied in our case by head cooling to an esophageal temperature of 34.5°C. Consensus on Science with Treatment Recommendations showed that the temperature during rewarming should be increased by 0.5°C per hour over at least 4 hours (3). On the other hand, it was reported and recommended that rewarming for comatose adult survivors of cardiac arrest should be performed slowly and the body temperature kept within the normal range for up to 48 hours (13). Hayashi suggested that the rewarming time should be adjusted according to the severity of brain injury as short-term hypothermia in case of severe brain damage may worsen the outcome and brain injury mechanisms may progress with rewarming (14). As we were concerned that our patient might suffer multiple organ failure, we set the rewarming period at 48 hours. Although multiple organ failure can occur in association with severe asphyxia, there were safety and no significant adverse events during the BHT, and the CK level spontaneously decreased in this case.

Although we report only the short-term outcomes for this case, she presents neurodevelopmental delays at the age of 18 months. It may be correlated between high serum CK level and long-term neurodevelopmental delays. Clinical expectations regarding the development of effective management and treatment strategies for HIE infants with severely elevated serum CK levels during the neonatal period can only be formulated as more cases are encountered.

DECLARATION OF INTEREST

the authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES