Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.62, No.1(2022). p.72-8 DOI: 10.14238/pi62.1.2022.72-8

Case Report

Long-term follow-up of an infant with hypoxic-ischemic encephalopathy treated with hypothermia therapy

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Perinatal asphyxia is one of the most common causes of newborn mortality, with an incidence of two to five cases per 1,000 live births in developed countries and tenfold in developing countries.[1,2] Lack of oxygen at birth may cause hypoxic ischemic encephalopathy (HIE) with severe neurological consequences, such as cerebral palsy, global developmental delay, blindness or visual defects, hearing loss or deafness, and other comorbidities. Hypothermia therapy is currently the only management option for HIE included in neonatal intensive care unit (NICU) protocols.[3]

We report here a 24-month follow up of a full-term infant with moderate HIE who underwent hypothermia therapy for 72 hours. The patient had moderate sensorineural hearing loss (SNHL) at her first brainstem evoked response audiometry (BERA) examination at 5 months of age, but had normal hearing and neurodevelopment after 24 months of follow-up. **[Paediatr Indones. 2022;62:72-8 ; DOI: 10.14238/pi62.1.2022.72-8].**

Keywords: *hypoxic ischemic encephalopathy; asphyxia; hypothermia therapy; sensory neural hearing loss*

Hypoxic-ischemic encephalopathy (HIE) is one of the leading causes of disability and death in newborns throughout the world.[4] It is an important cause of brain injury in newborns, with long-term consequences on neurodevelopment. The incidence of HIE in developing countries is reported to be tenfold that in developed countries.[1] The underlying pathologic events of HIE are caused by systemic hypoxemia and/or reduced cerebral blood flow to the brain, resulting in primary and secondary energy failure.[4]

Various neurodevelopmental disorders that may arise as a long-term consequence of HIE include cerebral palsy, autistic spectrum disorders, cognitive disorders, language disorders, microcephaly, auditory and visual impairment, as well as seizure disorders.[5-7]

The management of HIE is often limited by a lack of available supportive therapy and inadequate facilities. In recent decades, hypothermia therapy has been a promising therapy for improving outcomes in infants with HIE.[8] We report here a 24-month follow-up of an infant with moderate HIE who received hypothermia therapy who had moderate SNHL during early follow-up.

The case

A 3,700-gram, appropriate-for-gestational-age (AGA), female infant underwent spontaneous vaginal delivery at 39 weeks of gestation in a peripheral hospital. Her mother, a 25-year-old primigravida, presented with premature rupture of the membranes

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Submitted May 19, 2020. Accepted January 5, 2022.

since 32 hours prior to delivery. The infant did not cry immediately upon delivery and received resuscitation which included chest compressions and intubation. Her Apgar scores were 2 at one minute and 3 at five minutes after birth. Two hours later, she was referred to our hospital with passive cooling. Physical examination revealed grunting, mild retraction, and tachypnea. As her Downes score was 3 and auto-extubation occurred during transport to the NICU, oxygenation was given using non-invasive mechanical ventilation. Upon arrival at the emergency room, her temperature was 36.1°C. She was cooled using an ice pack gel until her temperature reached 34.3°C, and hypothermia therapy was continued for 72 hours. An umbilical artery catheter (UAC) was also placed.

Laboratory examination showed a leukocyte count of 36,640/uL, a hemoglobin level of 12.6 g/dL, hematocrits of 35.6%, a platelet count of 245,000/uL, an immature-to-total neutrophil ratio (IT ratio) 0.33, and an immature-to-mature neutrophil ratio (IM ratio) of 0.51. Arterial blood gas analysis showed a pH of 7.29, PCO_2 of 30.4 mmHg, PO_2 of 55 mmHg, HCO_3 of 15.1 mmol/L, base excess of –12 mmol/L, an O_2 saturation of 90%, and a lactate level of 10.50 mmol/L, indicating metabolic acidosis, hypoxemia, and lactatemia.

Based on Sarnat staging (**Table 1**) and Thompson's score (**Table 2**), the patient was assessed as having moderate HIE.[6,7] She was treated for 19 days in the NICU and Perinatal Ward with moderate HIE, severe asphyxia, and caput succedaneum. During hospitalization, she was found to have clinical sepsis and given intravenous ampicillin and gentamycin. She also developed jaundice, for which she received phototherapy.

Cranial ultrasound performed on the third day of life supported the HIE diagnosis, with findings suggestive of an intracerebral hemorrhage. At 14 days of life, ultrasound revealed grade II (moderate) HIE and intraventricular hemorrhage.

On day 18 of life, a brain CT scan revealed a positive reversal sign of HIE and positive cerebellum sign (**Figure 1**). After 19 days of hospitalization, she was discharged with a weight of 3,958 grams with follow-up visits scheduled at the outpatient clinic.

We devised a 24-month follow-up plan for this patient. At 5 months of age, BERA showed moderate sensorineural hearing loss with a threshold of 30 dB in the left ear and 60 dB in the right ear. At 13 months of age a brain CT scan was done, which showed cerebral edema. However, as physical and neurological examination showed no remarkable abnormality, no specific treatment was given.

Table 1. Sarnat staging of hypoxic ischemic encephalopathy[6]

Level of consciousness	Stage I	Stage II	Stage III
	Hyper alert/ irritable	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Occulovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems decreased
Pupils	Normal	Miosis	Variable; often unequal; poor light refle
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Spars	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerabation)
Electroencephalogram findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake)	Early: periodic pattern with isopotential phases Later: totally isopotential
Duration	< 24 hours	2-14 days	Hours to weeks

Table 2. Thompson's score[7]

Sign	0	1	2	3
Tone	Normal	Hypertonia	Hypertonia	Flaccid
Consciousness	Normal	Hyperalert, stare	Lethargic	Comatose
Fits	Normal	Infrequent < 3 per day	Frequent > 3 per day	
Posture	Normal	Fisting/ cycling	Strong, distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent bites	
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)
Fontanelle	Normal	Full not tense	Tense	

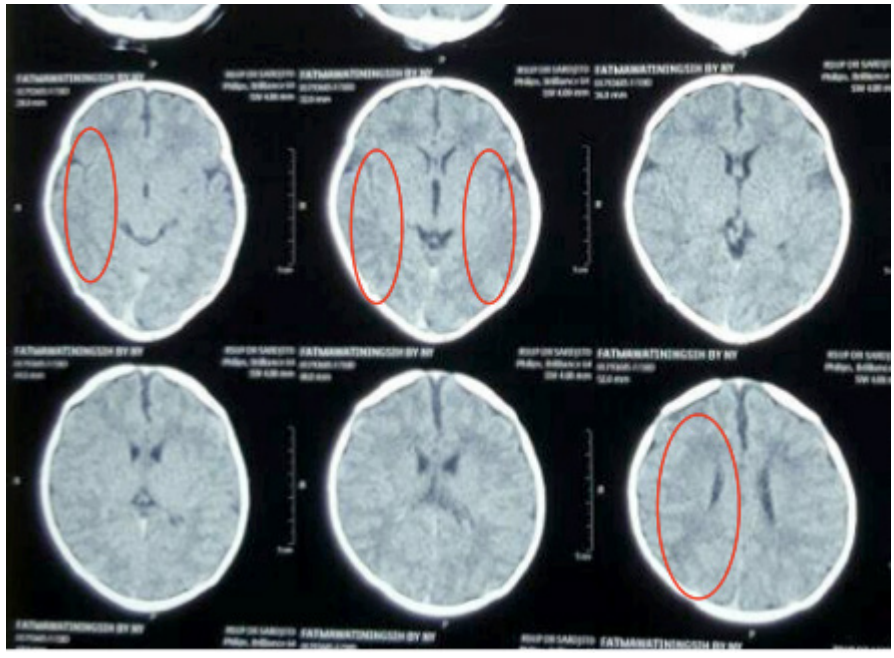

Figure 1. Brain CT scan on day 18 of life indicating a positive reversal sign of HIE and positive cerebellum sign (circles)

Follow-up visits were intended to identify and manage modifiable prognostic factors in order to improve the patient's outcome. The outcomes we aimed for were normal milestones for age, normal hearing and vision, as well as normal development, including language, communication skills, and behavior. The prognostic factors, evaluations and interventions, and observations of outcome are presented in **Table 3**.

Discussion

The incidence and mortality of HIE have declined in recent years, but complications in surviving infants have not changed much in the past 20 years. A meta-analysis revealed a reduced risk of mortality and neurologic disability in infants with moderate HIE (RR 0.67; 95%CI 0.56 to 0.81) and severe HIE (RR 0.83; 95% CI 0.74 to 0.92).[12]

The outcome of infants with HIE is associated with initial resuscitation rates. In a report of infants who underwent resuscitation that included chest compressions and intubation, such as our patient, neurodevelopmental outcomes at 18 months of age were normal in 80% and abnormal with morbidity in 6.7% of surviving cases, whereas 10% had died.[13]

HIE is known to cause damage to the cochlea; ventilator use has also been reported to increase

the incidence of hearing loss in infants. Before the hypothermia therapy era, the incidence of hearing loss in infants with a history of HIE was 17.1%; after the widespread implementation of hypothermia therapy, this incidence has decreased to 4.7 - 10.1%.[14,15]

Hypothermia therapy is an attempt to reduce the baby's body temperature to 33-34°C (cooling phase), maintain this temperature for 72 hours (maintenance phase), followed by a rewarming phase during which the body temperature is slowly returned to normal (36.5-37.5°C) within 12 hours.[16] This treatment modality can be performed on infants with moderate or severe HIE who meet a set of criteria, including a gestational age of >35 weeks, birth weight of ≥1,800 grams, absence of contraindications (uncontrolled pulmonary hypertension, critical bleeding, coagulopathy, or major congenital abnormalities). Evidence of HIE is characterized by APGAR scores, the need for mechanical ventilation or resuscitation for 10 minutes or more, an umbilical cord or blood gas pH of

Table 3. Prognostic factors, evaluations and interventions, and outcome observations in the patient at 24 months of age

Target outcomes	Prognostic factors	Interventions	Observations
Normal developmental milestones	Parental knowledge Stimulation/ physiotherapy Family support	Denver test CAT/CLAMS test* Brain CT scan evaluation	Neurological examination: no remarkable findings No signs of developmental delay during observation Brain CT scan: cerebral edema (**Figure 2**) Stimulation routinely given by parent
Normocephaly	Stimulation/ physiotherapy	Head circumference monitoring	Head circumference showed 0 < Z-score < - 2 SD, according to Nellhaus chart,[9] but tended to be close to -2 SD
Normal hearing	Parental knowledge Stimulation/ physiotherapy	BERA evaluation Hearing stimulation by parents Long-term auditory monitoring	BERA evaluation at 13 months of age showed normal hearing with a threshold of 30 dB in both ears
Normal vision	Parental knowledge Stimulation/ physiotherapy	Simple visual tests with pictures, colors, and objects around the house Ophthalmoscopy	Eye examination and ophthalmoscopy performed at 25 months of age was normal
Good nutritional status	Parental knowledge Psychosocial and economic status	Weight and height monitoring Nutritional intake and tolerance monitoring	During evaluation, the patient's nutritional status remained normal for correctional age according to WHO growth charts[10] (**Figure 3**)
Immunization completed	Parental knowledge Psychosocial and economic status	Timely vaccinations given according to the Indonesian Pediatric Society recommendations	The patient received BCG, hepatitis B, diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type B, poliovirus, pneumococcal conjugate, measles-rubella, and influenza vaccines
Healthy home and environment	Psychosocial and economic status Family support	Routine home visits Assessment using the scoring system of the Technical Guidelines for Assessing Healthy Homes of the Indonesian Ministry of Health before and after observation. A score of >1,068 indicates healthy living conditions[11]	During the observation period, the patient's Healthy Home Score improved from 950 at the time of the discharge to 1,112 at the 24-month follow-up, indicating improvement of the home condition

*Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale

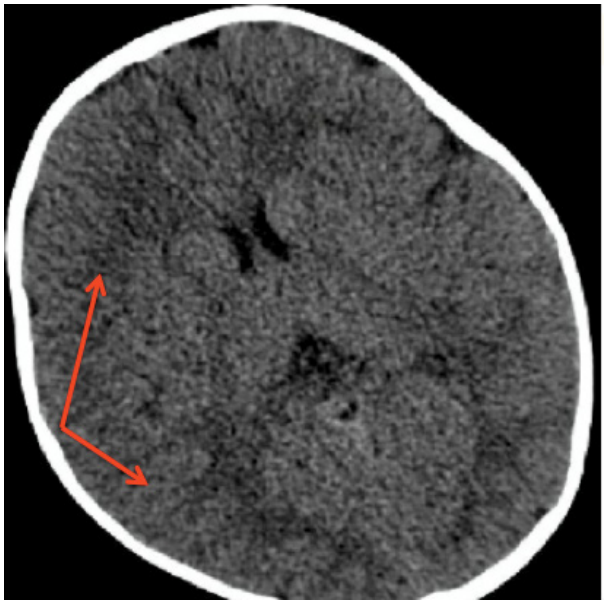

Figure 2. Brain CT scan at 13 months of age indicating cerebral edema (arrows) without remarkable findings in the neurological examination

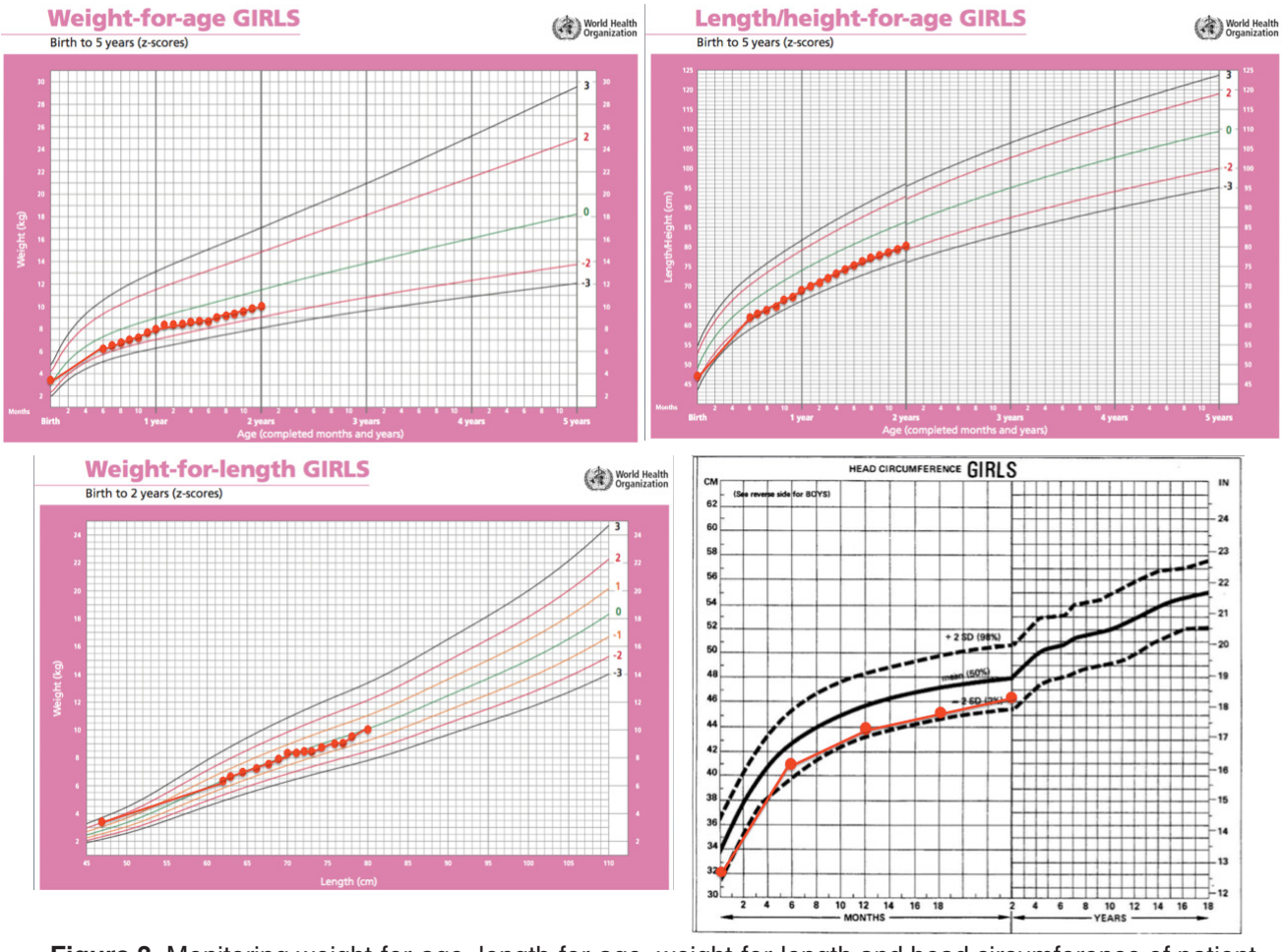

Figure 3. Monitoring weight-for-age, length-for-age, weight-for-length and head circumference of patient (results: - 2SD < Z score < 2 SD)

<7, or a base deficit of >12 within one hour of birth. Cooling therapy should be started within six hours of birth. Hypothermia therapy is the standard procedure for HIE management in developed countries and has been shown to reduce mortality and improve short- and long-term outcomes.[16]

The side effects of hypothermia therapy include decreased heart rate, increased need for inotropic therapy (our patient received dopamine), hypotension, anemia (Hb <10g/dL), leukopenia (<5,000/uL), thrombocytopenia (<150,000/uL), coagulopathy, hypoglycemia, hypokalemia, increased lactate, impaired renal function, and sepsis.[17] During the rewarming process, potential side effects include tachycardia, reduced blood pressure, electrolyte imbalance, hypoglycemia, increased risk of seizures, increased oxygen consumption, and increased CO_2 production.[17]

After 24 months of observation, our patient had no developmental delay and normal nutritional status. Her head circumference was just above -2SD; there is a known association between history of asphyxia and microcephaly. The child's hearing threshold normalized on the subsequent BERA examination, and she had no other comorbidities. Longer monitoring is needed, as several studies have reported behavioral and autistic disorders in such children at school age, diagnosed at a mean age of 11.2 years. Children with a history of HIE have also been reported to have lower full-scale IQ scores.[18-20]

In conclusion, it is important to start hypothermia therapy immediately, within 6 hours of birth, in infants with HIE meeting the criteria. Timely initiation of hypothermia therapy may prevent brain damage before a secondary energy failure phase occurs. This case report describes a neonate with HIE who was successfully treated with hypothermia therapy and had no detectable neurodevelopmental abnormality by 2 years of age. Regular monitoring and early intervention helps ensure good outcomes for HIE patients and should be continued beyond school age.

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