Journal of Pediatric Academy

Original Article

Year: 2022 Volume: 3 Issue: 3
Doi: 10.51271/jpea-2022-183

Evaluation and Neurodevelopmental Outcomes of Infants with Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia: A Single Center Experience

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Article Information

Article Type: Original Articles
Article Group: Neonatology

Received: 08.06.2022
Accepted: 11.10.2022
Available Online: 23.12.2022

Cite this article as: *Saygın Hekimoğlu B, Dilber B, Aktürk Acar F, Bezirganoğlu H, Eyüboğlu İ, Esenülkü G. Evaluation and Neurodevelopmental Outcomes of Infants with Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia: A Single Center Experience. J Pediatr Acad 2022; 3: 104-109.*

Abstract

Hypoxic ischemic encephalopathy (HIE) is an important cause of mortality and morbidity in newborns. The aim of this study is to evaluate the neurodevelopmental outcomes and rehabilition needs of infants followed up with a diagnosis of HIE who were treated with hypothermia in our unit. A total of 23 patients who met the criteria were retrospectively reviewed. Denver Developmental Screening Test II (Denver II DST) was used for the developmental screening. Patients were divided into groups as moderate and severe HIE based on Sarnat encephalopathy staging, as well as normal and abnormal groups based on Denver II DST results. Moderate HIE was detected in 17 (73.9%) patients, and severe HIE was detected in 6 (26.1%) patients. Patients with severe HIE were found to have lower apgar scores, more resistant metabolic acidosis, longer ventilation times, and more abnormal cranial magnetic resonance findings in the neonatal period ($p<0.05$). An abnormal Denver II DST was observed in 29.4% of individuals with moderate HIE and all patients with severe HIE (p:0.005). Speaking and fine motor impairments were more common in patients with severe HIE (p:0.018, p:0.014, respectively). Furthermore, cerebral palsy, epilepsy, and swallowing problems were also detected more frequently in patients with severe HIE (p: 0.035, p: 0.019, p: 0.011, respectively). Despite therapeutic hypothermia treatment, neurodevelopmental impairments were still seen in HIE neonates. Our findings showed that it is important to determine factors that may exacerbate the development of neurological sequelae in HIE patients for better follow-up and treatment approach.

Keywords: Hypoxic ischemic encephalopathy, therapeutic hypothermia, neurodevelopmental outcomes, newborn

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Introduction

Hypoxic-ischemic encephalopathy (HIE) is an acute progressive encephalopathy that manifests as convulsion, apnea, and abnormal muscle tone caused by perinatal hypoxia and ischemia.[1] Its frequency varies between 1-6 per 1000 live births in developed countries and 5-10 per 1000 live births in developing countries.[2] It has been reported to cause death in newborns, acute neurological damage in the early period, and permanent neurodevelopmental problems in motor, cognitive and behavioral areas after years.[3] Apgar score, blood gases, and encephalopathy findings are used for diagnosis. However, the relationship between the diagnostic criteria of asphyxia and the prognosis of patients is not fully known.[4]

Highlights

- Hypoxic ischemic encephalopathy (HIE) is an important cause of mortality and morbidity in newborns.
- In the neonatal period, male gender, low apgar score, severe acidosis, abnormal cranial MRI findings are risk factors that determine the neurodevelopmental prognosis of newborns with HIE.
- Epilepsy, cerebral palsy, and speech disorders are the most common chronic period problems in newborns with HIE.
- Monitoring and supporting the development of HIE cases with risk factors from the first months of life is very important for improving long-term outcomes.

Today, therapeutic hypothermia therapy is used to treat newborns with moderate and severe HIE. Studies have revealed that therapeutic hypothermia reduces mortality and positively affects neurodevelopmental prognoses.[5,6] However, it was reported that severe problems such as cerebral palsy, developmental delay, intellectual disability, epilepsy, blindness, and hearing loss could occur in children who survive despite therapeutic hypothermia.[5,7] HIE is a significant cause of developmental problems in our country, and the number of studies evaluating the developmental outcomes of infants treated with therapeutic hypothermia is a few.[8,9] As the number of data increases, our knowledge regarding the problems encountered in the follow-up of these patients and the frequency of these problems will increase, and timely intervention will be possible. Considering the benefits of early intervention, it is also crucial to know the risk factors to predict neurodevelopmental problems. The aim of this study is to evaluate the neurodevelopmental outcomes and rehabilitation needs of infants followed up with the diagnosis of HIE and treated with hypothermia in our unit.

Material and Method

Infants aged 9-43 months who were followed up with HIE diagnosis in the pediatric neurology outpatient clinic between January 1, 2018, and December 31, 2021, and treated with therapeutic hypothermia in the neonatal period in our unit were included in this study. The study excluded babies with a birth weight of <1800gr, gestational week of <35 weeks, congenital malformation, genetic disease, and congenital metabolic disease.

Whole-body cooling therapy is applied with the Tecotherm Neo (Inspiration Healthcare, UK) device to patients diagnosed with HIE and clinically evaluated as moderate and severe encephalopathy in our unit. Gestational week, birth weight, gender, mode of delivery, Apgar score, Sarnat stage at the first examination, blood gas and other biochemical test results taken in the first hour of life, perinatal risk factors, seizure history, hospitalization time, conventional and diffusion magnetic resonance imaging (MRI) results of patients who were treated with therapeutic hypothermia during the study period were retrospectively recorded from the hospital records. Patients were divided into 2 groups as moderate and severe HIE according to the Sarnat encephalopathy staging. MRI images in the neonatal period were re-evaluated by the same person who had ten years of pediatric radiology experience and was unaware of the patients' clinic.

In our study, the most recent neurological examinations, Denver II developmental screening test (DST) results, Electroencephalography (EEG) results, and hearing-vision evaluation results of the patients who were followed up in the pediatric neurology outpatient clinic were examined. The Denver II DST test was performed by the same person who has a Denver II DST certificate on the patients in our hospital's pediatric neurology outpatient clinic. Denver II DST is a test that evaluates the age-appropriate skills of children aged 0-6. Assessment is made in four sub-areas (personal-social, fine motor, gross motor, and speaking). Scores are determined according to their ability in these four areas.[10] According to Denver II DST results, the cases were classified into normal and abnormal groups.

The diagnosis of cerebral palsy was made considering hypotonia, spasticity, abnormal posture, increased tone, abnormal body movements, continuation of primitive reflexes, increased tendon reflexes, and delayed movement development according to the age of the patient. The patients were evaluated as spastic, dyskinetic, ataxic, hypotonic, and mixed types by cerebral palsy classification.

Ethics committee approval of the study was obtained from Trabzon Kanuni Training and Research Hospital Ethics Committee (Approval no: 2022/30).

Statistics

Statistical analyzes were performed using IBM SPSS (Statistical Package for Social Sciences) statistics software, version 24 (IBM Corp, Armonk, NY, USA). Descriptive statistics were expressed in numbers and percentages. The Chi-Square test and Fisher's Exact test examined relationships between categorical variables. Normally distributed groups were compared through Student's t-test, and non-normally distributed groups were compared through Mann Whitney U test. Results were evaluated at a 95% confidence interval, and a p-value of <0.05 was considered statistically significant.

Results

A total of 23 infants were included in the study. The most common antenatal risk factors were meconium aspiration syndrome (n:6,26%), cord entanglement (n:6,26.1%), placental abruption (n:4, 17.4%), uterine rupture (n:1, 4.3%), and prolonged rupture of membranes (n:1, 4.3%), respectively. The gestational week of the cases was 39.2±1.4 weeks, birth weight was 3194.4±462.0g, 14 (60.9%) were male, and 14 (60.9%) were delivered by cesarean section. Nine cases (39.1%) were born in our hospital, and 14 cases (60.9%) were referred from another hospital. The most common clinical findings were respiratory distress in 21 patients (91.3%), convulsions in 20 patients (87%), hypotension in 12 patients (52.2%), and hepatic dysfunction in 7 patients (30.4%). Inotropic support was administered to 52% of the cases due to hypotension. Resistant metabolic acidosis was detected only in the severe encephalopathy group (50%). According to the Sarnat stage, moderate HIE was found in 17 infants (73.9%) and severe HIE was found in 6 infants (26.1%). Patients with severe HIE were found to have lower apgar scores, more resistant metabolic acidosis, longer ventilation time, and abnormal cranial MRI findings in the neonatal period (p<0.05). A comparison of neonatal parameters of the patients according to the groups is presented in **Table 1**.

The mean age of the patients at the last evaluation was 18.3±9.2 months, and Denver II DST was applied to all patients at the last neurological examination. Denver II DST results were normal in 12 (52.2%) patients and abnormal in 11 (47.8%) patients. 90.9% of infants with abnormal Denver II DST results were male. Denver II DST results were abnormal in 29.4% of patients with moderate encephalopathy and in all patients with severe encephalopathy. Speaking (83.3%) and fine motor (100%) problems were found most frequently in infants with severe HIE.**Table 2** indicates the comparison of the sub-areas of Denver II DST according to the groups.

Table 2
Comparison of sub-scales of Denver II DST according to groups

Scale	Denver II DST		p
	Normal (n:12)	Abnormal (n:11)	
Speaking	14 (60.9)	9 (39.1)	0.003
Fine motor	11 (47.8)	12 (52.2)	<0.001
Gross motor	17 (73.9)	6 (26.1)	0.005
Personal social	18 (78.3)	5 (21.7)	0.640

Data are given as n (%), Abbreviation: Denver II developmental screening test, Denver II DST. Chi-Square test was used.

The chronic period results of infants with HIE are shown in **Table 3**. Epilepsy (100%), cerebral palsy (83.3%), and swallowing problems (50%) were found more frequently in infants with severe HIE compared to infants with moderate HIE (p:0.019, p:0.035, p:0.011). All of the infants with severe HIE needed physiotherapy, 66.7% needed speech therapy, 50% needed rehabilitation, and 33.3% needed vision and auditory therapies. Physiotherapy requirement was more frequent in infants with severe HIE compared to infants with moderate HIE (p: 0.014).

Table 1
Comparison of maternal and neonatal parameters of asphyxia infants with moderate and severe HIE

Parameter	Moderate HIE (n: 17)	Severe HIE (n:6)	p
Maternal age (years)	29.4±4.3	31.5±5.2	0.341***
Gravidity	1.7±1.2	3.2±1.7	0.044**
Gestational week (week)	39.4±1.4	38.8±1.3	0.431**
Birth weight (g)	3168.8±522.7	3266.7±238.0	0.666***
Gender (male)	9 (52.9%)	5 (%83.3)	0.340*
Mode of delivery (Cesarean)	9 (52.9%)	5 (%83.3)	0.340*
1st min Apgar scores	3 (0-6)	1 (0-1)	0.002**
5th min Apgar scores	6 (2-9)	2.5 (2-6)	0.002***
Birthplace			0.643*
Our hospital	6 (35.3%)	3 (%50.0)	
Another hospital	11 (64.7%)	3 (%50.0)	
1st hour blood gas			
ph	7.0±0.1	6.9±0.2	0.506***
HCO3	10.9±2.5	13.0±4.7	0.386***
Be	-17.6±3.3	-18.9±8.4	0.714***
Lactate	13.7±4.4	12.3±6.6	0.590***
MRI findings	4 (23.5%)	6 (100%)	0.002*
Diffusion MRI findings	4 (23.5%)	4 (66.7%)	0.131*
Sarnat			
Stage I	2 (11.8%)	0	
Stage II	15 (88.2%)	0	
Stage III	0	6 (100%)	
EEG findings	8 (47.1%)	2 (33.3%)	0.660*
Convulsion	14 (82.4%)	6 (100%)	0.539*
Hypotension	8 (47.1%)	4 (66.7%)	0.640*
Thrombocytopenia	8 (47.1%)	4 (66.7%)	0.640*
Kidney failure	2 (11.8%)	2 (33.3%)	0.270*
Liver dysfunction	5 (29.4%)	2 (33.3%)	1.000*
Pulmonary hypertension	1 (5.9%)	1 (16.7%)	0.462*
Inappropriate ADH	2 (11.8%)	1 (16.7%)	1.000*
Infection	4 (23.5%)	1 (16.7%)	1.000*
Mechanical ventilator duration (days)	3.5±5.2	8.3±6.8	0.016**
Total oxygen time (days)	9.8±8.9	17.5±12.5	0.101**
Neurological finding at discharge	1 (5.9%)	2 (33.3%)	0.155*
Length of stay (days)	22.6±13.8	24.5±11.3	0.392**

Data are given as mean±standard deviation or n (%). Abbreviations: HIE, Hypoxic-ischemic encephalopathy; EEG, Electroencephalography; ADH; Antidiuretic hormone. Chi-Square test*, Mann Whitney U test** and The Student's t-test*** were used.

Table 3
Chronic period outcomes of infants with HIE

Outcomes	n (%)
Epilepsy	13 (56.5)
Cerebral palsy	10 (43.5)
Language speaking	8 (34.8)
Swallowing problem	3 (13)
Deafness	2 (8.7)
Vision loss	2 (8.7)
Microcephaly	1 (4.3)
Hyperactivity/ anxiety disorder	1 (4.3)
Physiotherapy	12 (52.2)
Special education	6 (26.1)

Data are given as n (%). Abbreviation: HIE, Hypoxic-ischemic encephalopathy

The time of EEG for infants with HIE was 6.2±1.4 months, and the time of MRI scan was 12.4±9.5 days. 87% (n: 20) of the patients had convulsions in the neonatal period, but 50% (n: 10) of these patients had abnormal findings in MRI and EEG, and 55% (n:11) of them had abnormal Denver II DST results. There was no difference in pH, HCO3, and bE values between the infants with and without MRI findings (p>0.05). One of the patients with abnormal EEG had infantile spasm, while the others had focal epilepsy. It was determined that 65% (n:13) of the patients who had convulsions in the neonatal period were receiving drug treatment for epilepsy. All patients had monotherapy or adjunctive drug therapy. The most commonly used antiepileptic drugs were phenobarbital, levetiracetam, and clonazepam, respectively. EEG findings of all patients with abnormal EEG findings in the follow-up were improved as of the ninth month.

Discussion

In this study, neurodevelopmental delay was detected in approximately half of the cases that we followed up with the diagnosis of HIE for three years.

Detection of risk factors in neonatal asphyxia is of great importance in reducing the incidence and mortality rate of asphyxia.[11] The study of Majeed et al.[11] reported that lack of prenatal care, poor nutritional status, prenatal bleeding, and maternal toxemia increase the incidence of asphyxia. In our study, it was found that meconium aspiration syndrome and cord entanglement were more common in infants with HIE.

Our study detected a significant gender difference between asphyxia infants with normal and neurodevelopmental delay. 90% of infants with neurodevelopmental delay were male. Hussein et al.[12] investigated the levels of interleukin 8 and antioxidants in the cerebrospinal fluid of asphyxiated infants and reported that these were lower in male infants than in females. This result shows that male infants are more prone to brain damage and have a higher risk in terms of prognosis. The result of our study is compatible with the literature.

The relationship between mode of delivery and perinatal asphyxia is not clear. Utomo et al.[13] reported that cesarean delivery is a risk factor for asphyxia. Boskabadi et al.[4] reported that they could not find a relationship between the mode of delivery and birth asphyxia. In our study, 60% of asphyxia infants were delivered by cesarean section. However, considering the possible relationships between cesarean section indication and antepartum period, we think that it is not possible to establish a direct relationship between asphyxia and delivery method.

There are conflicting results in the literature regarding the effectiveness of the Apgar score in predicting mortality and neurodevelopmental outcomes.[4,14-18] Boskobadi et al.[4] reported that the 5th minute Apgar score helps predict neurodevelopmental problems in asphyxiated children. In the study of Nataraji et al.[15], in which 174 patients treated for hypothermia were investigated, it was reported that 75% of those with a 10-minute Apgar score of 0-3 died or became neurodevelopmentall disabled at the age of 6-7, and one-fifth of them lived unhindered at school age. Publications have reported that the neurodevelopment of infants with an Apgar score of zero at the 10th minute is not unfavorable.[17,18] In our study, 1st and 5th minute Apgar scores were lower in babies with severe HIE, and all of them had impaired neurological development. This result supports the idea that the Apgar score effectively predicts neurodevelopmental issues.

It has been previously reported that both pH and partial pressure of carbon dioxide in blood gas in newborns with HIE are potent modulators of cerebral blood flow and may contribute to brain damage.[1] Wayock et al.[19] reported a relationship between the initial low pH values and severe brain damage in MRI in newborns with HIE treated with therapeutic hypothermia. In our study, there was no difference in blood gas values between cases with moderate and severe encephalopathy and cases with and without MRI findings.

HIE is responsible for 60% of early-onset neonatal seizures.[20] The prognostic significance of seizures in infants with HIE is still controversial.[1] Despite hypothermia treatment, infants with HIE have been reported to have a higher risk of epilepsy in the first 2 years of life compared to the general population.[21] Seo et al.[22] reported that 82.4% of 83 infants diagnosed with asphyxia developed epilepsy during follow-up. In addition, it was reported in this study that epilepsy developed in only 41.2% of those who had convulsions in the neonatal period, and abnormal MRI scans were more common. In our study, it was found that 56.5% of infants with HIE were followed up with the diagnosis of epilepsy, and 65% of those who had convulsions in the neonatal period were diagnosed with epilepsy. MRI and EEG were abnormal in 50% of those who had convulsions in the neonatal period, and Denver II DST results were abnormal in 55%. These results show that convulsions alone are not sufficient to predict neurodevelopmental problems in asphyxia infants, and MRI and EEG findings are more determinative in evaluating the resulting brain damage and predicting prognosis.

The stage of clinical encephalopathy in infants with HIE treated therapeutic hypothermia may be helpful in predicting the neurodevelopmental prognosis of infants.[1] Wyatt et al.[23] reported that Sarnat's encephalopathy in the first 6 hours of life is strongly associated with neurodevelopmental outcomes in infants. However, Lally et al.[24] reported that the presence of moderate and severe encephalopathy in infants with HIE was insufficient to determine the poor prognosis. In our study, 26.1% of the cases had severe encephalopathy and all of these patients had neurological developmental delay. This result supports the idea that the Sarnat encephalopathy score can predict poor prognosis in patients.

Hemodynamic instability has been reported in 33-77% of newborns with HIE treated with therapeutic hypothermia.[1] In our study, inotropic support was administered to 52% of the cases due to hypotension. In a study evaluating 190 asphyxia newborns treated with hypothermia, it was reported that infants with hypotension had a higher

risk of developing brain damage on MRI.[25] More et al.[26] determined a relationship between the development of pulmonary hypertension and the development of brain damage. It was also reported that both hypoglycemia and hyperglycemia in early life are associated with poor neurodevelopmental outcomes.[1,26] However, in our study, no significant difference was found between patients with moderate and severe HIE in terms of clinical findings, except for resistant metabolic acidosis and prolonged ventilation. These results suggest that clinical findings alone are insufficient to determine neurodevelopmental outcomes in neonates with HIE.

Therapeutic hypothermia is the only known and effective treatment method in HIE today. A systematic review of a randomized controlled trial evaluating 1500 term and late preterm infants with moderate/severe encephalopathy reported that therapeutic hypothermia reduced mortality and improved neurodevelopmental outcomes in infants surviving 18 months of age.[6] In another systematic review of 1214 neonates with HIE who treated therapeutic hypothermia, death or severe neurodevelopmental disorders were observed in approximately half of them, whereas neurodevelopmental outcomes were normal in only 40%.[27] As far as we know, there are only two studies in the literature on the neurodevelopmental outcomes of patients treated with therapeutic hypothermia in our country.[8,9] It was reported that 92.4% of the patients in one of these studies and 44.6% of the patients in the other showed normal neurodevelopment.[8,9] In our study, similar to the study of Çelik et al.[9], normal neurodevelopment was found in 52% of the cases.

HIE is a critical cause of cerebral palsy. Studies have shown that the rate of cerebral palsy in newborns treated with therapeutic hypothermia is between 13-28% at 18 months.[5,7,27] In our study, the rate of cerebral palsy was 43.5%. The high rate of cerebral palsy in our study may be related to the fact that most of the cases were in the severe encephalopathy group and the number of cases was small. Sensory problems are common in children with HIE. In studies in the literature, the rate of vision loss was reported as %1.3-7 and the rate of hearing loss as 2.5-4% in children treated with therapeutic hypothermia.[5,7,29] In the study of Çelik et al.[9], in which 47 asphyxic infants were evaluated, it was indicated that 3 (%6.4) of the patients had hearing and 1 (%2.1) had vision disorders. In our study, vision loss was detected in 2 cases (%8.7), and hearing loss in 2 cases (%8.7). Similar to the study of Çelik et al.9, our study also showed that the need for physiotherapy is higher in patients with severe HIE. It was reported that social problems such as anxiety/depressive states, attention, memory, time perception, and orientation problems are more common in children with mild and moderate encephalopathy.[30,31] In our study, anxiety disorder and hyperactivity were found in a child with moderate encephalopathy findings in the neonatal period. In a study in which 239 children followed up with the diagnosis of moderate HIE were evaluated, it was reported that 12 of the cases were diagnosed with autism spectrum disorder at the age of 5 years.[32] No case diagnosed with autism was found in our study. However, studies evaluating the results of the longer-term follow-up of these patients are needed.

Our study has some limitations. The small number of cases, the experience of a single center, and the retrospective nature of our study are among the limitations of our study.

Conclusion

The incidence of neurodevelopmental problems in neonates with HIE is high and is associated with the severity of asphyxia. Our study is important in terms of revealing the effect of therapeutic hypothermia on morbidity in infants living in our country. The presence of severe encephalopathy findings, resistant metabolic acidosis, prolonged ventilation time and abnormal cranial Mrg findings in the neonatal period should be a warning for the risk of neurodevelopmental delay. In order to improve long-term outcomes of patients with HIE, it is essential to support their development by assessing the rates of neurological sequelae development throughout follow-up.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: Ethics committee approval of the study was obtained from Trabzon Kanuni Training and Research Hospital Ethics Committee (Approval no: 2022/30).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

References

1. Goswami I, Guillot M, Tam EWY. Predictors of Long-Term Neurodevelopmental Outcome of Hypoxic-Ischemic Encephalopathy Treated with Therapeutic Hypothermia. *Semin Neurol.* 2020;40:322-334. *[CrossRef]*
2. Shireen N, Nahar N, Mollah AH. Risk factors and short-term outcome of birth asphyxiated babies in Dhaka Medical College Hospital. *Bangladesh J Child Health.* 2009;33:83–89. *[CrossRef]*
3. Volpe JJ. Neonatal encephalopathy: an inadequate term for hypoxic-ischemic encephalopathy. *Ann Neurol.* 2012;72:156-166. *[CrossRef]*
4. Boskabadi H, Ashrafzadeh F, Doosti H, et al. Assessment of risk factors and prognosis in asphyxiated infants. *Iran J Pediatr.* 2015;25:2006. *[CrossRef]*
5. Jacobs SE, Morley CJ, Inder TE, et al. Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: a randomized controlled trial. *Arch Pediatr Adolesc Med.* 2011;165:692-700. *[CrossRef]*
6. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev.* 2013;2013:CD003311. *[CrossRef]*
7. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopath. *N Engl J Med.* 2009;361:1349-1358. *[CrossRef]*

8. Çelik K, Üstünyurt Z, Ergon EY, et al. Neurodevelopmental Outcomes in Therapeutic Hypothermia: A Single Center Experience. *Turkish J Pediatr Dis.* 2021;15:99-103. *[CrossRef]*
9. Çelik P. Neurodevelopmental outcomes of infants who underwent therapeutic hypothermia due to hypoxic ischemic encephalopathy. *Turkish J Pediatr Dis.*2021;15:359 – 364. *[CrossRef]*
10. Frankenburg WK, Doddr J, Archer P, et al. The Denver II: A major revision and restandardization of the Denver Development Screening Test. *Pediatrics.* 1992;89:91-97. *[CrossRef]*
11. Majeed R, Memon Y, Majeed F, Shaikh NP, Rajar UD. Risk factors of birth asphyxia. *J Ayub Med Coll Abbottabad.* 2007;19:67-71. *[CrossRef]*
12. Hussein MH, Daoud GA, Kakita H, et al. The sex differences of cerebrospinal fluid levels of interleukin 8 and antioxidants in asphyxiated newborns. *Shock.* 2007;28:154-159. *[CrossRef]*
13. Utomo MT. Risk factors for birth asphyxia. *Folia Medica Indonesiana.* 2011;47:211–214. *[CrossRef]*
14. Laptook AR, Shankaran S, Ambalavanan N, et al. Outcome of term infants using apgar scores at 10 minutes following hypoxic-ischemic encephalopathy. *Pediatrics.* 2009;124:1619-1626. *[CrossRef]*
15. Natarajan G, Shankaran S, Laptook AR, et al. Apgar scores at 10 min and outcomes at 6-7 years following hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed.* 2013;98:F473-F479. *[CrossRef]*
16. Sarkar S, Bhagat I, Dechert RE, Barks JD. Predicting death despite therapeutic hypothermia in infants with hypoxic-ischaemic encephalopathy. *Arch Dis Child Fetal Neonatal Ed.* 2010;95:F423-F428. *[CrossRef]*
17. Shah P, Anvekar A, McMichael J, Rao S. Outcomes of infants with Apgar score of zero at 10 min: the West Australian experience. *Arch Dis Child Fetal Neonatal Ed.* 2015;100:F492-F494. *[CrossRef]*
18. Kasdorf E, Laptook A, Azzopardi D, Jacobs S, Perlman JM. Improving infant outcome with a 10 min Apgar of 0. *Arch Dis Child Fetal Neonatal Ed.* 2015;100:F102-F105. *[CrossRef]*
19. Wayock CP, Meserole RL, Saria S, et al. Perinatal risk factors for severe injury in neonates treated with whole-body hypothermia for encephalopathy. *Am J Obstet Gynecol.* 2014;211:41.e1-41.e418. *[CrossRef]*
20. Limperopoulos C, Majnemer A, Rosenblatt B, et al. Association between electroencephalographic findings and neurologic status in infants with congenital heart defects. *J Child Neurol.* 2001;16:471-476. *[CrossRef]*
21. McDonough TL, Paolicchi JM, Heier LA, et al. Prediction of Future Epilepsy in Neonates With Hypoxic-Ischemic Encephalopathy Who Received Selective Head Cooling. *J Child Neurol.* 2017;32:630-637. *[CrossRef]*
22. Seo SY, Shim GH, Chey MJ, You SJ. Prognostic factors of neurological outcomes in late-preterm and term infants with perinatal asphyxia. *Korean J Pediatr.* 2016;59:440-445. *[CrossRef]*
23. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med.* 2009;37:S186-S202. *[CrossRef]*
24. Lally PJ, Montaldo P, Oliveira V, et al. Magnetic resonance spectroscopy assessment of brain injury after moderate hypothermia in neonatal encephalopathy: a prospective multicentre cohort study. *Lancet Neurol.* 2019;18:35-45. *[CrossRef]*
25. Al Balushi A, Barbosa Vargas S, Maluorni J, et al. Hypotension and Brain Injury in Asphyxiated Newborns Treated with Hypothermia. *Am J Perinatol.* 2018;35:31-38. *[CrossRef]*
26. More KS, Sakhuja P, Giesinger RE, et al. Cardiovascular Associations with Abnormal Brain Magnetic Resonance Imaging in Neonates with Hypoxic Ischemic Encephalopathy Undergoing Therapeutic Hypothermia and Rewarming. *Am J Perinatol.* 2018;35:979-989. *[CrossRef]*
27. Tagin MA, Woolcott CG, Vincer MJ, Whyte RK, Stinson DA. Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis. *Arch Pediatr Adolesc Med.* 2012;166:558-566. *[CrossRef]*
28. Martinello K, Hart AR, Yap S, Mitra S, Robertson NJ. Management and investigation of neonatal encephalopathy: 2017 update. *Arch Dis Child Fetal Neonatal Ed.* 2017;102:F346-F358. *[CrossRef]*
29. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med.* 2005;353:1574-1584. *[CrossRef]*
30. van Handel M, Swaab H, de Vries LS, Jongmans MJ. Behavioral outcome in children with a history of neonatal encephalopathy following perinatal asphyxia. *J Pediatr Psychol.* 2010;35:286-295. *[CrossRef]*
31. Lindström K, Lagerroos P, Gillberg C, Fernell E. Teenage outcome after being born at term with moderate neonatal encephalopathy. *Pediatr Neurol.* 2006;35:268-274. *[CrossRef]*
32. Badawi N, Dixon G, Felix JF, et al. Autism following a history of newborn encephalopathy: more than a coincidence?. *Dev Med Child Neurol.* 2006;48:85-89. *[CrossRef]*