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Editorial

# Recent studies are focus on the new treatments for hypoxic-ischemic encephalopathy (HIE) and long-term outcomes in later childhood and adolescence in children with a history on HIE

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**Key message**

Neonatal encephalopathy is the most important reason for morbidity and mortality. The early detection of neonate with high risk for hypoxic ischemic encephalopathy (HIE) and treatment are important for prevent long term complication. Hypothermia is currently standard treatment option for HIE. Several clinical studies have been performed due to improve the long term outcome. New therapeutic options including xenon, allopurinol, erythropoietin, topiramate will help to reduce neuropsychiatric disability.

Neonatal encephalopathy is the most important reason for morbidity and mortality. The early detection of neonate with high risk for hypoxic-ischemic encephalopathy (HIE) and treatment are important for preventing long-term complication. Hypothermia is currently standard treatment option for HIE. Several clinical studies have been performed due to improve the long-term outcome. New therapeutic options including xenon, allopurinol, erythropoietin (Epo), topiramate will help to reduce neuropsychiatric disability.

Neonatal encephalopathy, a clinically defined syndrome of abnormal neurologic function during infancy, manifests as a decreased level of consciousness or seizures and decreased motor tone in term-born and late preterm newborns.[1,2] The most common cause of neonatal encephalopathy is HIE, impaired cerebral function sustained as a result of perinatal asphyxia.[1,3] The incidence of HIE is about 8 per 1,000 live births worldwide.[4] Despite advances in neonatal care, HIE leads to serious neurologic problems, including cerebral palsy, epilepsy, and cognitive impairment. Although studies have investigated neurocognitive test results of patients before 3 years of age who were treated for HIE, few have examined data in late childhood and adolescence. Patients with normal neurodevelopmental outcomes at 36 months after HIE treatment are not immune to cognitive and behavioral problems in the school-age years because some neuropsychiatric development continues during the prepubertal period.[4,5] Therapeutic hypothermia for near-term infants with moderate to severe HIE reduces mortality or neuropsychiatric disability at 18–24 months of age.[6]

The review of Lee and Glass[4] described the results of previous studies of long-term cognitive outcomes from late childhood and school age, including neurodevelopmental outcomes before therapeutic hypothermia therapy and 2 randomized clinical trial outcomes after therapeutic hypothermia for HIE. They also reviewed clinical studies on neurodevelopmental outcomes after the administration of neuroprotective agents in combination with therapeutic hypothermia.

There is a strong relationship between HIE severity and neurodevelopmental outcomes prior to hypothermia therapy in late childhood and adolescence. Several studies have shown that children with moderate to severe HIE have significantly impaired neurodevelopmental outcomes, especially a lower intelligent quotient, visual-motor integration, receptive vocabulary scores, reading, and spelling.[7]

In 2005, the National Institute of Child Health and Human Development (NICHD) introduced the status of knowledge for safety and efficacy of therapeutic hypothermia therapy for HIE.[7] The current treatment protocol for full-term neonates with moderate to severe neonatal encephalopathy is to start therapeutic hypothermia within the first 6 hours of life for 72 hours to a depth of 33°C–34°C.[4] Many randomized clinical trials and a systematic review showed that therapeutic hypothermia for neonates with moderate to severe HIE positively affects mortality or neurodevelopmental disability at the age of 24 months, but few studies have examined the long-term outcomes until school age.[8] In the NICHD trial, whole-body hypothermia treatment reduced mortality or severe disability rates in late childhood. However, the NICHD Neonatal Research Network revealed that therapeutic hypothermia did not completely prevent a cognitive outcome.[6] In the Total Body Hypothermia for Neonatal Encephalopathy trial, therapeutic hypothermia

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reduced risk of cerebral palsy, improved cognitive function and psychomotor outcomes.

However, several studies have indicated that therapeutic hypothermia alone is not sufficient to reduce mortality and long-term disability at 18 months. In addition, cognitive problems remain a concern for patients with HIE at school age.[9] Therefore, several neuroprotective drugs that could be used with hypothermia treatment include Epo, xenon, melatonin, stem cells, and antiepileptic agents. Epo has remarkable neuroprotective and neuroregenerative effects on neurons and oligodendrocytes.[10] Several clinical trials are currently ongoing, aiming to determine the primary outcome and neurodevelopmental disability at 6–18 months.[3,4,9] After the studies are completed and their results are promising, a long-term study in school-age children will be necessary.

Xenon is an odorless, dense, monoatomic gas that has been approved as an inhalational anesthetic in adults. Xenon rapidly crosses the blood-brain barrier and depresses amplitude – integrated electroencephalographic background voltage activity and suppressant effects in neonates with HIE.[11] The current evidence is insufficient for combination therapy with hypothermia.[4,11] Melatonin combined with hypothermia reduced seizure frequency and improved outcomes without neurologic disability compared to hypothermia alone. However, there have been no long-term studies of its effectiveness.[4]

See the article "Cognitive outcomes in late childhood and adolescence of neonatal hypoxic-ischemic encephalopathy" via https://doi.org/10.3345/cep.2021.00164.

## Footnotes

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