

Methods for assessing the severity of perinatal asphyxia and early prognostic tools in neonates with hypoxic–ischemic encephalopathy treated with therapeutic hypothermia

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Abstract

Despite the progress in perinatal care, perinatal asphyxia (PA) remains a significant problem in neonatology. The development of therapeutic hypothermia (TH) has improved the prognosis, but it still remains uncertain in hypoxic neonates. The evaluation of the severity of ischemia/hypoxia after birth is crucial to the choice of treatment, and with accurate long-term prognosis, appropriate further patient care can be planned. This article presents various methods for the preliminary assessment of brain damage and prognosis in newborns with PA treated with TH. The importance of assessing the neurological condition and the usefulness of laboratory and electrophysiological testing and imaging are discussed. New methods are also noted, which are at the stage of clinical trials. A combination of the prognostic tests presented in this article can provide greater prognostic accuracy for predicting long-term neurological outcomes in infants with hypoxic–ischemic encephalopathy (HIE) undergoing TH than either of these tests independently. Acknowledging the limitations of individual tools in certain clinical situations and the integration of the information available from multiple biomarkers may help improve the accuracy of prognostication.

Key words: perinatal asphyxia, neonate, prediction factors, therapeutic hypothermia, hypoxic–ischemic encephalopathy

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Introduction

Despite recent advances in perinatal care, neonatal hypoxic–ischemic encephalopathy (HIE) is one of the most common causes of severe neurological deficit in children, present in approx. 15 out of 10,000 live births.¹ According to the World Health Organization (WHO), perinatal asphyxia (PA) represents the 3rd most common cause of neonatal death (23%). This means that all over the world, almost 600,000 newborns die every year, and at least as many develop severe complications such as epilepsy, cerebral palsy and developmental delay due to acute perinatal sentinel events.² Therapeutic hypothermia (TH) is a method of treatment that has proven effective in protecting the brain against the effects of ischemia/hypoxia in neonates after PA; it is recommended in both term and near-term newborns.^{3,4} The qualification criteria and contraindications for TH are adjusted as knowledge progresses and they are included in recommendations and standards for the treatment of newborns. In this age group, 2 methods of cooling are available: selective head hypothermia and whole body hypothermia. Although the incidence rate of HIE is known and TH is increasingly available, no accurate data on the frequency of this treatment are available.

The mechanism for such neurological protection is thought to be multifactorial, including limitation of post-arrest endothelial dysfunction, decreased free radical release and blunting of the post-reperfusion inflammatory cascade. Early evaluation of the degree of brain damage in newborns after PA is of great importance in determining the appropriate management and prognosis. This assessment is based on a complex analysis of different factors.

The aim of this article is to present the methods used to estimate the severity of PA and the prognostic tools for neonates with HIE treated with TH.

Clinical assessment of neurological status

The neurological status at birth and during treatment is routinely assessed in neonatal wards. Assessing a newborn's neurological status after PA is usually difficult due to the serious overall condition and the need to use drugs which affect the brain. The use of scales makes it possible to objectify the evaluation and compare results between different patients.

The Apgar scale is primarily used to assess the condition of a newborn at birth and is one of the basic criteria for pre-qualification for TH treatment. It is also useful as a prognostic tool, though the results of studies are ambiguous. Laptok et al. showed that the Apgar score at 10 min provides useful prognostic data for infants with HIE. They noticed that death or moderate/severe disability is common, but not uniform, with Apgar scores <3.⁵ Shah et al. found that 1/3 of infants with a 10-min Apgar score

of 0 who survived to reach the neonatal intensive care unit had normal scores on formal developmental assessments.⁶

The Sarnat scale estimates the severity of neurological disorders in newborns after PA. It distinguishes 3 stages of HIE: stage 1 – mild encephalopathy associated with hyperalertness, sympathetic overdrive and a normal electroencephalogram (EEG); stage 2 – moderate encephalopathy marked by obtundation, hypotonia, multifocal seizures, and an EEG showing periodic or continuous delta activity; and stage 3 – severe encephalopathy in which infants are stuporous and flaccid with an isoelectric or periodic EEG. This scale is one of the factors which is widely used in qualifying a newborn for TH treatment, but it is also a prognostic tool. The creators of the scale noted that infants who did not enter stage 3 and who had signs of stage 2 for fewer than 5 days had developed normally on follow-up, but persistence of stage 2 for a week or failure of the EEG to normalize predicted later neurological impairment or death.⁷ Short-term neurological improvement expressed by the Sarnat scale predicts a neurodevelopmental outcome at 18–24 months.⁸

The Thompson scale is also suitable for assessing the neurological status of neonates after PA. It takes into account 9 parameters; the score ranges from 0–22 points and is directly proportional to the severity of the neurological condition. This scale is also helpful in determining the prognosis for neurological development. Thompson et al. noted that children with a maximum of 10 points developed properly in the 1st year of life, while 65% of those with more than 10 points and 92% with more than 15 points developed incorrectly.⁹ Mendler et al. demonstrated the usefulness of this scale as a prognostic tool.¹⁰

Laboratory tests

Among the laboratory tests, acid-base balance holds a special place because metabolic acidosis is the 2nd pre-qualification criterion for TH treatment, next to the Apgar assessment. The consensus is that the severity of lactacidemia reflects the degree of fetal hypoxia–ischemia, but a single lactate measurement gives no definitive information regarding the duration of asphyxia. Metabolic acidosis also has a prognostic value. Worsening metabolic acidosis at birth correlated with severe brain injury in neonates who were treated with TH.¹¹ Moreover, higher serum level of lactate following TH and abnormal results of brain magnetic resonance imaging (MRI) are associated with a poor neurodevelopmental outcome.¹² Results obtained by other authors are similar. Also, the meta-analysis carried out by Malin et al. showed that low arterial cord pH was significantly associated with neonatal mortality, HIE, intraventricular hemorrhage, or periventricular leukomalacia.¹³

Because PA affects the whole body, it is understandable that it causes an increase in the activity of enzymes which are markers of damage to various organs. Liver enzymes,

myocardial injury biomarkers and other enzymes are often measured in newborns with HIE, being widely available and relatively cheap. Muniraman et al. demonstrated a relationship between the degree of hypoxia and transaminases (aspartate transaminase (AST) and alanine transaminase (ALT)), alkaline phosphatase and ammonia levels.¹⁴ Research conducted by Montaldo et al. showed that early cardiac troponin I (CT-1) concentration correlates with the severity of HIE and with development at 18 months.¹⁵ It is suggested to use CT-1, myoglobin and creatine kinase-Mb as new biomarkers for diagnosis of neonatal HIE.¹⁶ Changes in lactate dehydrogenase are associated with central gray matter lesions and may be a useful biomarker for predicting future neurodevelopmental prognosis in infants with HIE.¹⁷ Although the hypoxia markers mentioned above have been studied many times and are quite widely used in clinical practice, there are currently no consistent data to establish thresholds corresponding to HIE severity.

A consistent finding across a number of studies is the up-regulation of the innate immune system, as evidenced by the increased levels of cytokines in newborns with HIE. Levels of inflammatory interleukins (ILs; IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, and IL-10), monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor α (TNF- α) increase significantly in newborns with HIE and correlate with both the severity of HIE and outcomes.¹⁸ Attention was also paid to the usefulness of determining the levels of specific biomarkers targeting the so-called “neurovascular unit”, which may be helpful in assessing the severity of HIE and prognosis, but which are currently at the stage of clinical trials, are usually expensive and are difficult to obtain. Calcium-binding proteins and other brain biomarkers have been taken into account. Roka et al. and Giuseppe et al. noted that serum S100B protein and neuron-specific enolase (NSE) levels are elevated in newborns with HIE.^{19,20} Moreover, it was also shown that serum S100B and NSE levels in babies with HIE are associated with neurodevelopmental disorders at 15 months.²¹ Ennen et al. noted that serum glial fibrillary acidic protein levels during the 1st week of life were elevated in neonates with HIE and were predictive of brain injury on MRI.²² Florio et al. have shown that newborns with HIE have elevated serum levels of activin A and concluded that this parameter is also taken into account as a prognostic tool.²³ Douglas-Escobar et al. showed that ubiquitin C-terminal hydrolase L1 levels have the potential to predict long-term neurological disorder in these patients.²⁴ Lv et al. noted the predictive value of serum tau protein level for neurodevelopmental outcome in neonates with HIE.²⁵

There have been a few publications on the basis of which it can be assumed that other markers may prove useful in assessing HIE severity and predicting prognosis. The following markers have been considered: plasma neurofilament light protein, interferon, sercetoneurin, osteopontin, monocyte chemotactic protein-1, macrophage inflammatory protein 1a, vascular endothelial growth factor (VEGF),

leptin, adiponectin, and erythropoietin.^{26–31} The metabolic products of HIE reveal early biomarkers of injury which deprive the neonatal brain of oxygen and glucose, and which trigger a biochemical cascade of many adverse reactions. The details and range of metabolic change occurring in response to HIE remains unclear, but research on the relationship between the severity of HIE and metabolomic profile analysis in umbilical cord blood, serum and urine (mainly amino acid, acylcarnitine and organic acid profiles) is promising and suggest they might be used as a new prognostic tool and treatment targets, but these studies are at the experimental stage. Moreover, the laboratory equipment for metabolome assays is not very accessible.^{32,33}

Electrophysiological tests

Among electrophysiological tests, amplitude-integrated EEG (aEEG) plays a special role, because it is one of the qualification factors for TH treatment and it is routinely monitored during such treatment. It requires 3 electrodes to be placed on the head of the newborn; it is quite easy to perform and the recording is interpreted in comparison to several patterns. Continuous monitoring of aEEG allows the bioelectrical function of the brain and its trend to be estimated. It is also very useful in detecting subclinical seizures. Its usefulness in the prognosis of newborns after PA has also been demonstrated. Liu et al. noted that aEEG reflects the degree of the lesion as well as the long-term prognosis of newborns with HIE.³⁴ The usefulness of aEEG in the prognosis of newborns after PA has been confirmed in research conducted by other authors.^{35–37} Also, from the systematic literature review carried out by Del Río, it follows that aEEG background activity, recorded during the first 72 h of life, has a strong predictive value in infants with HIE treated with TH or not. In another meta-analysis, the authors concluded that a persistently abnormal aEEG at 48 h or later is associated with an adverse neurodevelopmental outcome.^{38,39} The implementation and especially the interpretation of the classic, multi-channel EEG is more difficult, but provides additional information on the degree of brain damage and prognosis. It has been noted that electrographic seizure burden is associated with severity of brain injury on MRI in newborns with HIE undergoing TH.⁴⁰ Other authors have demonstrated that burst suppression, low voltage and flat traces in the EEG of term neonates with HIE most accurately predict the long-term neurodevelopmental outcome and that excessive EEG discontinuity is associated with increased cerebral tissue injury on MRI and is predictive of abnormal neurodevelopmental outcome in infants treated with TH.^{41,42} Weeke et al. noted that severely abnormal EEG background activity at 36 h and 48 h of life was associated with severe injury on MRI and abnormal neurodevelopmental outcomes.⁴³ A meta-analysis performed by Han et al. found that EEG

background activity is predictive of long-term neurological outcome in TH-treated neonates with HIE, and that burst suppression, low voltage and flat trace are potential predictors of death or neurodevelopmental impairment.⁴⁴ Another systematic review and meta-analysis confirms the immense usefulness of EEG as a prognostic tool.⁴⁵

The brain injury after PA affects various areas of the brain and may also include the brainstem. Brainstem evoked potentials (BEPs) are used to diagnose various types of brain damage. Some authors note the usefulness of the BEPs in predicting prognosis in newborns with HIE, while others have reported that a bilateral absence of cortical somatosensory evoked potentials (SSEPs) predicts moderate/severe MRI pattern of injury in newborns treated with TH.⁴⁶ Cainelli et al. considered that among BEPs, visual evoked potentials (VEP) constitute the single best neurophysiological prognostic marker, but the combination of neurophysiological tests is more valuable.⁴⁷

Neuroimaging

Neuroimaging plays a special role in determining the prognosis of newborns with HIE. Cranial ultrasound (CUS) is a readily available, inexpensive bedside examination that is routinely performed on children with HIE, but its prognostic value is limited. It has several limitations, such as low sensitivity for detecting cortical, cerebellar and brainstem lesions, marked inter-observer variability, and operator dependency. Edema dominates in early brain ultrasound imaging in newborns after PA, and assessment of its echostructure is difficult and subjective. Cranial Doppler ultrasonography is a method that objectively assesses cerebral arterial blood flow and resistance. Measurements using the Doppler technique are usually taken in the middle cerebral artery. It was noted that TH reduced the importance of measuring resistance in cerebral vessels; nevertheless, Gerner et al. found that pre- and post-cooling transfontanellar duplex brain sonography resistive index (RI) values may be a useful prognostic tool, in conjunction with other clinical information for neonates with HIE.⁴⁸ Likewise, Annink et al. developed and validated a CUS scoring system that takes into account the RI and the sum of deep grey matter and white matter involvement, and noted that it is associated with neurodevelopmental outcome in these patients.⁴⁹

The importance of computed tomography (CT) in diagnosing HIE and predicting prognosis has diminished considerably with the popularization of MRI. The CT is less sensitive and less specific than MRI in diagnosing neonatal HIE with much lower tissue resolution; another major disadvantage is radiation exposure. For these reasons, CT is usually omitted in the diagnostic chain. However, CT is more sensitive in detecting intracranial hemorrhage than ultrasonography and requires much less time than MRI; therefore, it may be useful in some situations.⁵⁰

The MRI is nowadays a standard tool for determining the pattern and severity of brain injury as well as the prognosis in infants with HIE. This method yields equal insight into all brain structures. Conventional MRI techniques have proven useful in assessing the severity of brain damage and predicting the development of newborns with HIE.⁵¹ Newer MRI techniques have also been developed that are useful in assessing the brains of newborns with HIE. Gradient-echo T2*-weighted images and susceptibility-weighted imaging (SWI) allow for the detection of both hemorrhage and calcifications, which is important because as many as 38% of TH-treated patients have intracranial hemorrhage (ICH). Although preliminary results suggest that HIE remains an independent risk factor for delayed neurodevelopment in these neonates – while ICH seems to have no significant effect – further studies are needed to elucidate this.⁵² Diffusion-weighted imaging (DWI) has also been studied.⁵³ Rana et al. noted that apparent diffusion coefficient value can be used as a marker to detect chronic hypoxic–ischemic brain injury.⁵⁴

Magnetic resonance spectroscopy (MRS) is increasingly being performed. Mitra et al. showed that lactate/N-acetylaspartate levels in proton MRS within 2 weeks of birth accurately predict two-year motor, cognitive and language outcomes in neonatal encephalopathy after TH.⁵⁵ Lemmon et al. noted that diffusion tensor imaging (DTI) may be useful in predicting the development of newborns with HIE.⁵⁶ Some authors have proposed study models and MRI estimation scales to objectify the results. Trivedi et al. proposed a validated clinical MRI injury scoring system in neonates with HIE, wherein signal abnormality was scored on T1-weighted, T2-weighted and DWI sequences, and was assessed in 5 regions; MRI injury was graded as none, mild, moderate, or severe. They showed that this scoring system is a significant predictor of neurodevelopmental outcome at 18–24 months in neonates with HIE.⁵⁷ Also, Weeke et al. suggested a novel MRI score, which includes DWI and proton MRS (HMRS), assesses all important brain areas and has predictive value for outcomes at 2 years of age and at school age in infants with HIE.⁵⁸

Other methods

There are several articles whose authors point out the importance of near infra-red spectroscopy in prognosis in newborns with HIE. Jain et al. found that increasing regional oxygen saturation is associated with moderate/severe brain injury as assessed using MRI and correlates with poor neurodevelopmental outcomes in infants with HIE undergoing TH.⁵⁹ Heart rate variability analysis is also drawing attention. Kayton et al. found a correlation between heart rate characteristic index score and severity of brain injury in neonates with HIE.⁶⁰ Because brain damage causes a dysfunction of the thermoregulation center, the method of assessing the degree of brain damage and




prognosis based on non-invasive estimation of endogenous heat production has also garnered interest recently.⁶¹ Preliminary results are encouraging. Mietzsch et al. examined the correlation between servo-controlled mattress temperature and the degree of brain damage in newborns treated with TH, and concluded that the output temperature of cooling devices is a potential and easily obtainable early physiological biomarker of outcome.⁶²

Summary

A reliable, evidence-based prognosis is essential for parental counseling regarding possible long-term sequelae. Despite the significant development of various diagnostic methods, assessing the degree of brain damage and prognosis in newborns with HIE treated with TH still remains a challenge, because all diagnostic tools have limitations: none are fully sensitive and specific, some cannot be performed in the intensive care unit, others are expensive, and some are only at the stage of assessing clinical suitability. The predictive value of an individual test for subsequent outcomes leaves a great deal to be desired. It seems that a combination of the prognostic tests presented in this article would provide greater prognostic accuracy for predicting long-term neurological outcomes in infants with HIE undergoing HT than any of these tests independently.^{38,45}

Acknowledging the limitations of individual tools in certain clinical situations and integrating the information available from multiple biomarkers may help improve the accuracy of prognostication.

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