A review of the conundrum of mild hypoxic-ischemic encephalopathy: Current challenges and moving forward

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ABSTRACT

A review of the conundrum called mild hypoxic-ischemic encephalopathy (HIE) is provided. During the past decades, the definition of HIE has evolved to accommodate the short window of time required for the initiation of therapeutic hypothermia. Also, neurological evaluations have changed with the use of simpler staging systems that can be applied within the first 6 h of life. In this review, we discuss the challenges in the identification of newborns with "mild HIE" within 6 h after birth, the limitations in the existing early biomarkers of brain injury, and the current knowledge gaps in the long term neurodevelopmental outcomes of infants diagnosed with mild HIE. Progress in the understanding of mild HIE and its sequelae continues to be hindered by the lack of a standardized definition for mild HIE that will reliably identify at-risk infants who may benefit from neuroprotective strategies.

1. Introduction

There is an urgent need to better understand and elucidate the conundrum called "mild hypoxic-ischemic encephalopathy (HIE)." As neuroprotective therapies are utilized and studied for moderate and severe HIE, similar neuroprotective strategies may benefit the outcome of infants with milder forms of encephalopathy. Yet, the field has been hindered by some inherent properties of this condition. Chief and foremost is the lack of a precise and uniform definition for what constitutes 'mild HIE' in neonates with perinatal acidosis. There is no question that the neurological examination is subjective in nature and abnormalities may be subtle and difficult to discern. In addition, the timing of the insult affects not only the clinical presentation but also the progression of the encephalopathy. In the early hours after a significant hypoxic-ischemic event, the majority of newborns do not demonstrate clear signs of moderate or severe brain compromise yet these abnormalities may develop in the ensuing hours to days after birth.

Since hypothermia does not protect all affected neonates from neurocognitive impairment, adjuvant therapies are being sought and studied for the moderate and severe HIE. Development of a standardized consensus definition for what constitutes mild HIE which can be ascertained within 6 h of birth is needed, as well as development of biomarkers that will identify precisely the subgroup of mild HIE infants who are likely to develop brain injury. These are essential for the planning of future trials of neuroprotection in this patient population.

1.1. Defining and staging hypoxic-ischemic encephalopathy: A historical perspective

Neonatal brain injury is recognized clinically on the basis of a distinctive encephalopathy that evolves from hyper-excitability to lethargy and stupor during the first week of life [2,3]. According to Amiel-Tison [4] in the original description of neonatal encephalopathy associated with an obstetrical event, no single specific sign could characterize it. Instead, a group of signs and symptoms indicated varying degrees of brain dysfunction. Following this principle, Sarnat and Sarnat [2] in 1976 developed a grading system based on serial and comprehensive neurological examinations and electroencephalographic (EEG) recordings performed on 21 asphyxiated newborns (Table 1). Stage 1 or mild HIE was defined as a state of hyperalertness with normal tone, mild
Table 1
Neonatal neurological scores applied to infants with perinatal asphyxia and mild HIE.

<table>
<thead>
<tr>
<th>Author, year (journal)</th>
<th>N</th>
<th>Definition of perinatal asphyxia</th>
<th>Age at exam</th>
<th>Mild HIE definition</th>
<th>Outcomes of infants with mild HIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarnat and Sarnat, 1976 (Arch Neurol) [2]</td>
<td>21</td>
<td>Well defined episode of fetal distress or Apgar score ≤ 5 at 1 or 5 min after delivery (MAS, RDS, maternal drug use were excluded)</td>
<td>Serial exams performed at 12 to 24 h intervals for the first 6 days</td>
<td>Hyperalert, normal tone, mild distal flexion, overactive stretch reflexes, segmental myoclonus, weak suck, strong (low threshold) Moro, normal oculovestibular reflex and slight tonic neck reflex. Mydriasis, tachycardia, sparse bronchial salivary secretions, and normal or decreased GI motility. No seizures and normal EEG (awake)</td>
<td>All 7 infants that exhibited features of stage 1 evolved to stage 2 in the following 18 h but stayed at this stage for no longer than 5 days. All these infants had normal outcomes at 1 year of age</td>
</tr>
<tr>
<td>Amiel-Tison, 1979 (Advances in perinatal neurology) [8]</td>
<td>34</td>
<td>NA</td>
<td>NA</td>
<td>Hyperexcitability and mild abnormalities of tone. Responsiveness is normal; primary reflexes are present. No seizures. These signs persist for varying periods.</td>
<td>NA</td>
</tr>
<tr>
<td>Amiel-Tison and Elisson, 1986 (Dev Med Child Neuro) [3]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Hyperexcitability sleeping or fussy and abnormal tone. Hypotonic scarf sign, poor head control or hypereextendend neck. Stretch reflexes exaggerated. Uses a cut-off point of 7 days to score as 1a or 1b</td>
<td>Neonates with perinatal asphyxia who have no or only transient neurological signs and who became normal by day 7 (stage 1a) were normal</td>
</tr>
<tr>
<td>Lipper et al., 1986 (Dev Med Child Neuro) [4]</td>
<td>34</td>
<td>Apgar score at 1 or 5 min ≤ 6 + fetal distress (fetal bradycardia, variable or late decelerations, loss of beat-to-beat variability, and/or fetal scalp pH &lt; 7.2) or cord pH &lt; 7.2, need for resuscitation at birth, and meconium aspiration.</td>
<td>First 24 h of life</td>
<td>Post Asphyxia Score (PAS): 17 items for neurological assessment. Total score ranging from 0 (worse) to 39 (optimal). No definition of mild.</td>
<td>Assessed at 1 year of age. PAS had good accuracy to predict abnormal MDI, PDI and neurological examinations. No specific outcome of mild HIE provided.</td>
</tr>
<tr>
<td>Thompson et al., 1997 (Acta Paediatrica) [7]</td>
<td>45</td>
<td>NA</td>
<td>Exams done daily</td>
<td>Based on the Sarnat score but simpler. Mild HIE was defined as normal LOC or hyperalert and staring with normal or decreased SA and exaggerated response to minimal stimuli. Posture showing fisting or cycling. Normal suck, grasp and Moro reflexes. Normal breathing or hyperventilation and no clinical seizures. Fontanel full but not tense.</td>
<td>All 10 patients with maximum score ≤ 10 during the whole hospitalization were classified as mild. The score correlate well with mild HIE by using the Sarnat score and none of these patients had CP.</td>
</tr>
<tr>
<td>Perez et al. (SIBEN score), 2017 (Rev. Assoc. Med. Bras.) [5]</td>
<td>26</td>
<td>Apgar score ≤ 5 at 1, 5, or 10 min of life</td>
<td>10 min of life, repeated every 2–3 h as needed</td>
<td>Siben Score: diagnosis according to highest number of items (above 3) found in the corresponding HIE grade of 10 categories (LOC, SA, posture, tone, suction, Moro reflex, heart rate, breathing, and convulsion). Mild HIE categorized by hyperalert, normal spontaneous activity, mild distal flexion, normal tone, weak suction, strong Moro reflex, mydriasis, tachycardia, spontaneous breathing, and no convulsions.</td>
<td>NA</td>
</tr>
<tr>
<td>Prempunpong et al. (PRIME study), 2017 (J. Perinatal) [6]</td>
<td>54</td>
<td>pH ≤ 7.0 or BD ≥ 16 mmol/L in arterial or venous umbilical cord blood or any blood specimen during the 1st hour after birth. If pH 7.01–7.15, or BD 10–15.9 mmol/L, or blood gas not available, additional criteria required: acute obstetric event and either a 10 min Apgar score ≤ 5 or assisted ventilation initiated at birth and continued ≥ 10 min</td>
<td>≤ 6 h of life</td>
<td>Modified Sarnat score: ≥ 1 abnormal category but no evidence of moderate or severe HIE (defined as moderate and/or severe abnormality in three categories).</td>
<td>Abnormal aEEG, brain MRI or neurological exam at discharge found in 52% of the infants with mild HIE</td>
</tr>
</tbody>
</table>

Legend: NA = not available; EEG = electroencephalography; GI = gastrointestinal; MAS = meconium aspiration syndrome; RDS = respiratory distress syndrome; MDI = motor developmental index; PDI = psychological developmental index; SA = spontaneous activity; EEG = electroencephalogram; aEEG = amplitude integrated electroencephalogram; MRI = magnetic resonance image.
distal flexion, overactive stretch reflexes, segmental myoclonus, weak suck, strong or low threshold for eliciting the Moro reflex, normal oculocephalistic reflex, and slight tonic neck reflex. Mydriasis, tachycardia, sparse secretions, and normal or decreased gastrointestinal motility also were present. No seizures were noted and the awake EEG was normal. This mild stage was usually brief in duration (<24 h), although the 7 with initial stage 1 encephalopathy subsequently all evolved to stage 2 in the next day. All of the infants with mild HIE had a normal outcome defined by the absence of cerebral palsy, visual impairment (vision < 20/60), deafness, or cognitive delay (>3SD) at 12 months of age. In later years, several other neonatal neurological scoring systems for mild HIE have been developed but as shown in Table 1, without any uniform criteria or consensus to its definition [2,5–10].

The Sarnat staging system has become the most widely used classification of HIE for prediction of neurodevelopment. The school performance of children classified as mild HIE based on the Sarnat system was observed to be similar to that of normal children [11]. This correlation between Sarnat stages and outcomes at 3, 5, and 8 years of age was further explored in larger cohorts by using the worst stage assigned during the first week of life [11–14]. In those studies, none of the infants with mild HIE died or had major handicap. Since neurological assessment becomes more precise as the child grows older, longer follow-up evaluations of mild HIE cohorts were done. In the Netherlands, survivors of perinatal asphyxia were tested at 9–10 years of age using the Child Behavior Checklist (CBCL), Teacher’s Report Form (TRF), Diagnostic Interview Schedule for Children (DSM IV), and Social Behavior Questionnaire [15]. Subtle differences were noted, with children who had mild HIE having Intelligence Quotient (IQ) score of 98.1 ± 12.3 (mean ± SD) versus 109.0 ± 12.0 in normal control children. In addition, social behavior and memory problems also were significantly higher among children with mild HIE. In a population based study in the United Kingdom, Odd et al. [16] also reported at 8 years of age an increased risk of low IQ score (<80) among children who had been resuscitated at birth, a finding that was independent of the presence of neonatal encephalopathy. Data from the pre-hypothermia era suggest that while no death or major disability occurred among children who had mild HIE, subtle developmental, language, attention, and behavioral problems were noted later in life [11,13,15,16,19,20]. It is important to note that an important contributor to the ongoing conundrum of mild HIE is the fact that the published studies (Tables 1, 2) have different entry criteria, wide range of length of follow-up, and different outcome variables.

1.2. Challenges of the early neurological evaluation for identification of at-risk infants

In the pre-hypothermia era, the neurological staging systems were used to define the degrees of abnormality and assess the likelihood of poor neurodevelopmental outcome. During the therapeutic hypothermia era, the use of the staging systems shifted to identification of infants who may or may not benefit from the treatment. Therefore, physicians performing a neurological evaluation had to reckon with the limited therapeutic window of 6 h for initiation of hypothermia, a time period where the neurological findings may not be easy to define and can change significantly over time. As a result, the definition of HIE was extrapolated to the use of a modified Sarnat staging system (no EEG, exam simplified to six categories [21]).

The reliability of an early neurological evaluation was first investigated in a study performed at Parkland Hospital, Dallas, TX. Substantial difficulties in assigning the level of HIE at 6 to 12 h of age were reported using the modified Sarnat staging [22]. The neurological examinations were performed by neonatologists who were certified in the neurological examination using the standardized NICHD Neonatal Research Network evaluation [21]. The investigators found that the specific stage of encephalopathy in 25% of newborns with fetal acidosis (umbilical cord pH < 7.00) could not be determined as their level of consciousness and neurological examination fluctuated between mild and moderate, and so they were classified as having an intermediate stage of HIE (Stages 1–2). In addition, a third of the infants progressed to have more severe encephalopathy in the first week of life.

The time of the insult affects the clinical presentation as well as the progression of neonatal encephalopathy. Although the timing of the insult is predominantly perinatal, it is not always clearly identified and could encompass antenatal as well as acute on chronic insults. Infants who had a severe antenatal event may recover by the time of birth at which time the stage of encephalopathy is perceived as mild. In contrast, an infant with a more acute insult can have only mild abnormalities on neurological examination in the first 6 h of age which can then evolve to moderate or severe abnormalities after the first day of life. In addition, possible confounding variables such as maternal sedation, anesthesia, or tocolytics (e.g. magnesium sulfate) may play a role in the accurate determination of the stage of HIE when the neurological examination is performed immediately after birth.

The hospital outcomes of infants with perinatal acidosis who do not did not meet NICHD examination criteria for hypothermia therapy were selectively studied at Parkland hospital [23]. Abnormal short-term outcomes were noted in 12 (20%) of 60 infants who had only 1–2 abnormal categories on the modified Sarnat examination performed by NICHD NRN certified examiners in the first 6 h of age. Specifically, at the time of discharge from the neonatal intensive care unit (NICU), 12 (20%) infants experienced an abnormal short-term outcome such as feeding difficulties (n = 8), abnormal neurologic examination at discharge (n = 7), abnormal brain magnetic resonance imaging (n = 6), seizures (n = 5), gastrostomy (n = 1), or death (n = 1), as well as prolonged NICU hospitalization.

Two multicenter randomized trials of hypothermia included several infants with mild HIE due to the inherent difficulties with the early neurological examination, despite the intent to enroll only infants with moderate to severe HIE. The ICE trial [24], a pragmatic study that used ice packs for cooling, included 42 infants with mild HIE. At follow up, death or major disability was noted in 38% and 25% of children in the control and cooled groups, respectively, with an odds ratio (95% CI) of 0.53 (0.17–1.66). In the selective head cooling trial, 39 infants with mild HIE were enrolled and 21 of them received the cooling therapy [25]. Different from the ICE trial, death or major disability was not observed in any infant with mild HIE. However, at 2 years of age, a low Developmental Quotient (DQ) < 85 was noted in 32% (6/19) of cooled

Table 2

Pre-hypothermia era studies including mild NE infants and developmental outcomes.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Mild NE (n)</th>
<th>Age at assessment (years)</th>
<th>Neurodevelopmental outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson, 1985 [15]</td>
<td>64</td>
<td>3.5</td>
<td>No disability, visual, hearing, language or motor skills</td>
</tr>
<tr>
<td>Robertson, 1988 [13]</td>
<td>55</td>
<td>5.5</td>
<td>No differences in psychoeducational school-readiness</td>
</tr>
<tr>
<td>Odd, 2011 [14]</td>
<td>Resuscitation Population</td>
<td>8</td>
<td>Attention problems, memory and language skills and need for educational support at school</td>
</tr>
</tbody>
</table>
and 47% (7/15) of non-cooled infants with mild HIE.

2. Contemporary definitions of mild HIE based on examination within 6 h of birth

Following the acceptance of hypothermia as a standard of care for infants with moderate or severe asphyxia, a practice drift of cooling infants with mild HIE has been uniformly reported in international registries and databases [26–28]. All of these registries defined mild HIE based on the modified Sarnat staging criteria assigned in the first 6 h of life but no details were provided on the number of abnormal categories needed or if some categories carried a higher weight for cooling. In the largest registry of mild HIE in the US (The Children's Hospital National Database), 76% of infants with mild HIE received therapeutic hypothermia [29] but the definition of mild HIE in the first 6 h and outcomes beyond discharge were not provided.

The recent Prospective Research in Infants with Mild Encephalopathy (PRIME) study [8] used a broad definition of mild HIE on infants who did not meet the NICHD criteria for cooling (moderate or severe in ≥3 categories). Infants were classified as having mild HIE based on the presence of significant perinatal acidosis and ≥1 abnormalities in any of the six categories of the modified Sarnat score (Table 3). This definition although empirical was standardized, and specified a priori then applied internationally by certified examiners across academic centers. Short-term abnormalities including abnormalities on aEEG at < 6 h of life, brain MRI at < 30 days, or abnormal neurological exam at discharge were noted in 52% of the 54 patients studied.

Encephalopathy is better represented as a spectrum rather than a categorical mild vs moderate-severe classification. There is currently no accepted consensus definition of mild HIE within the first 6 h after birth. The following section will review biomarkers to help identify and define the mild HIE infants at highest risk.

2.1. Early electroencephalogram (EEG) and/or amplitude EEG (aEEG)

When EEG is not available in the first day of life, the aEEG is a simple, non-invasive bedside tool that permits continuous evaluation of cortical cerebral electrical activity and has been used widely in the neonatal literature for detection, staging, and prognosis of seizures.

In 2001, a retrospective single center study investigated the usefulness of aEEG within the first 72 h of life and brain MRI in 25 infants with HIE [30]. Of the 7 infants classified with mild HIE, 6 had normal background activity and 1 had dysmature activity. All of these infants had normal neurodevelopmental outcomes at 2 years of age.

In two case-control studies, Murray et al. [31,32] reported the cognitive outcome of mild HIE infants born from 2003 to 2005 when assessed at 2 and 5 years of age. In both studies, mild HIE was determined at 6, 12, and 24 h of life by using an EEG grading system. A grade 1 or mild was defined as a continuous background pattern with slightly abnormal activity (e.g. mild asymmetry, mild voltage depression, or poorly defined sleep-wake cycle). In the first cohort (n = 44), all cases with a normal or mildly abnormal EEG within the first 6 h after birth had normal outcomes at 2 years of age [31]. The subsequent study used a similar methodology but a slightly different cohort of mild? HIE infants (n = 47) and included normal patients as controls (n = 30) [32]. Study participants were evaluated at 5 years of age and key findings included significantly lower cognitive outcomes when compared to historical control infants. Infants with mild HIE (based on EEG at 6 h of life) had a full-scale IQ of 99 (94–112), a verbal IQ of 105 (99–111), and a performance IQ of 103 (98–112) compared to a full scale IQ of 117 (110–124), verbal IQ of 116 (112–125), and performance IQ of 115 (107–124) in the control group [32].

A number of studies have investigated the correlation between early aEEG findings and both short- and long-term outcomes with an overall good predictive ability in infants with moderate or severe HIE [33–38]. These findings, in combination with the simplicity of a bedside aEEG, have increased the use of this test as an additional assessment to help clarify uncertainties on the neurological exam. In infants with mild HIE, the aEEG may be normal or show a slightly increase in discontinuity of the background activity (slightly broader band) and cyclicity [39], which might be challenging to determine within 6 h.

In asphyxiated infants, aEEG has been assessed as early as 3–6 h after birth in a few small, single center studies. In 1995, Eken and colleagues [40] investigated the predictive value of early aEEG measurements (< 6 h of life) in HIE patients where severity was graded by Sarnat scoring. Of the 34 infants studied, 11 had mild HIE, with 10 of them having aEEG recordings that exhibited normal continuous background activity. For the total population of all stages of HIE, the aEEG had a 94.1% sensitivity and 78.6% specificity for the prediction of neurodevelopmental outcomes at 6–24 months of age. A similar study investigated early aEEG patterns (< 6 h of life) in 47 asphyxiated infants, 9 of whom were normal, 5 had mild HIE, and 24 had moderate-severe HIE by Sarnat scoring [41]. Unfortunately, the study only focused on prediction of outcomes, thus limiting any interpretations regarding its ability to differentiate HIE severity. Of the 26 infants with normal aEEG patterns, 25 infants had normal outcomes at follow-up (1 to 6 years of age). One infant with psychomotor delay at 4 years of age had no signs of HIE in the NICU and the delay was attributed to other causes. Nevertheless, a normal, continuous background activity on the aEEG, as typically seen in mild HIE patients, was associated with a good outcome, with an overall accuracy of aEEG patterns of 91.5%. Recently, in a retrospective analysis of 122 cooled infants from 2008 to 2014, Weeke et al. [42] compared the Thompson Encephalopathy score with aEEG, both performed early in life (before cooling). Twenty (16%) infants were classified as having mild HIE on the neurological score but were cooled based on aEEG findings of discontinuous normal voltage (DNV), burst suppression (BS), or a more abnormal pattern. Only two (10%) of these 20 mild HIE infants had adverse outcomes and in both, a rapid deterioration in neurological examination was noted over subsequent hours. Although a good correlation between early aEEG and the Thompson score was observed, the study was not able to differentiate which of the assessments was better in selecting neonates for therapeutic hypothermia.

When focusing on the studies done prospectively, the positive predictive value of the aEEG was around 60% early on, and optimally
increases after 48 h of age during therapy. This, along with technical artifacts, drift in baseline related to lead placements all contribute to limit the usefulness and enthusiasm in use of aEEG abnormalities as necessary criteria in order to receive neuroprotective therapies. In the PRIME study [8], aEEG was performed at a median age of 5.5 h of life (IQR = 4.8, 6.4) and classified later by blinded examiners. A total of 54 infants were enrolled, with 50 having a normal aEEG and 4 had DNV tracings. Twenty-four (48%) of the 50 infants with normal aEEG and 2 (50%) of 4 infants with DNV had abnormal neurological examination at discharge and/or abnormal brain MRI.

Early measures of EEG/aEEG could be useful to support the diagnosis of mild HIE, but only as an adjunct measure given that the positive predictive value improves after 48 h and that most of these infants have normal background activity in the first 6 h of age.

2.2. Heart rate variability (HRV) in infants with mild HIE

HRV has been investigated extensively in asphyxiated infants, but most studies focused on infants with moderate and severe HIE either for predictive accuracy of the outcome of death/disability [43–46], or evaluation of HRV changes during therapeutic hypothermia [47,48]. To date, there are no studies that have investigated the ability of HRV to differentiate between the level of encephalopathy (mild, moderate, or severe), either alone or in combination with neurological exam or other assessment tools. Two studies from the same group of investigators at Cork University, Ireland included infants with mild HIE [49,50]. In the first study [49] performed in the pre-hypothermia era, HRV was measured between 12 and 48 h of life in 61 infants, 17 of whom were normal, healthy infants, while 22 had mild, 9 moderate, and 13 severe HIE (severity was defined by EEG grading). A statistically significant negative correlation was observed, with HRV reduced as severity of encephalopathy increased. Although statistical comparisons were not provided, a considerable reduction in HRV was observed between normal and mild HIE infants. These results indicate the potential for HRV to differentiate between the level of encephalopathy in HIE patients within 48 h of life. Furthermore, multiple HRV features had significant correlations with neurodevelopmental outcomes at 2 years of age, with moderately strong area under the receiver operating curves ranging from 0.73 to 0.80. In another study [50], similar reductions in HRV were noted between mild to moderate and severe groups, although differences between the mild and moderate infants appeared attenuated by hypothermia.

HRV analysis has the potential to help in the identification of infants at higher risk of abnormal neurodevelopmental outcomes not actual brain injury. Further research is necessary to better determine the accuracy of HRV as a diagnostic tool for mild HIE. Such studies should include a larger number of infants and establish normative reference values.

2.3. Serum inflammatory and neuronal biomarkers

Cytokines are mediators in the common pathways associated with perinatal brain injury induced by a variety of insults. A prospective cohort study of a panel of biomarkers in term newborns admitted to the Parkland Hospital NICU, Dallas showed that serum interleukin (IL)-6 concentration by 6 h of age was the only cytokine that significantly correlated with the neurological Dubowitz score that quantifies hypotonia [51–53]. Elevated concentrations of IL-6 and IL-8 have also been consistently reported in the CSF and serum of asphyxiated full-term infants. [54] Higher concentrations of IL-1β, IL-6, TNF-α, and IL-8 in the blood of neonates with HIE also have been associated with abnormal neurodevelopmental outcome [55,56]. Before the hypothermia era, meta-analysis studies highlighted both serum IL-1β and serum IL-6 concentrations measured before 96 h of age in infants with encephalopathy [57] as biomarkers predictive of abnormal neurodevelopmental outcomes. In a more recent contemporary cohort of 30 cooled newborns with HIE, Chalak et al. reported IL-1, IL-6, IL-8, tumor necrosis factor and interferon to be elevated at 6–24 h after birth and associated with later abnormal neurological outcomes at 18–24 months [58].

The microglia and astrocytes can produce glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase (UCH-L1), S100B, neuron specific enolase (NSE) as well as other factors in response to hypoxic-ischemic injury. [59,60] Multiple small pilot studies [58,61–64], although novel, have not been powered or validated for prediction of long term outcomes. GFAP is an intermediate filament protein that is released from astrocytes into the blood upon astrocyte death. Serum GFAP has been reported to be significantly elevated in newborns undergoing hypothermia therapy when compared with controls where a GFAP threshold level > 0.15 ng/mL following hypothermia was associated with an abnormal brain MRI. [65] UCH-L1 serum cut off values > 100 ng/mL have been reported in neonates with HIE who subsequently died [61]. Another recent study showed that UCH-L1 was elevated in the umbilical arterial cord plasma while GFAP was significantly higher at 72 h of cooling in infants with NE who developed adverse outcomes. [63].

Chalak et al. recently conducted a prospective pilot cohort study and measured neuronal glial fibrillary acidic protein (GFAP) along with ubiquitin carboxyl-terminal hydrolase L1, and cytokines in the serum obtained from umbilical cord arterial blood, as well as serially from an indwelling umbilical artery catheter. Serum GFAP and ubiquitin concentrations correlated with severity of NE, with higher levels in moderate to severe HIE as compared to those with mild HIE who were not cooled. [58].

An ideal serum biomarker would be measured in real time and directly reflect the neurovascular unit function and be predictive of outcomes [67–69]. Such a biomarker would enhance the ability to stratify the insult severity by identifying neonates with mild NE who might benefit from a neuroprotective strategy, and those with moderate–severe NE who need added interventions to improve outcomes. The quest of such a single serum biomarker has been elusive and it is more likely that a panel of biomarkers is needed.

Chalak et al. recent studies were aimed to measure in real time physiological biomarkers indicating brain health with a novel analytical “wavelet neurovascular bundle”. This wavelet analysis may allow noninvasive quantification at the bedside of neurovascular coupling NVC (by combining metrics obtained from NIRS and EEG) [70]. The pilot findings using this new bundle support early improved stratification of NE severity and also provide early physiological markers of outcome predictions [71].

Despite the promising research listed above, there are no currently available serum and or physiological biomarkers available in real time to be recommended for clinical use.

3. Conclusions

The short time period determined by the therapeutic window (<6 h of life) has created a real challenge for the definition of mild HIE. Following the positive effect of hypothermia for infants with moderate and severe HIE, many centers have shifted from published protocols and started to apply this therapy in infants with mild HIE. Unfortunately, a standardized definition is lacking and significant gaps in knowledge remain. Thus, the immediate goal should be to find early biomarkers to reliably identify the subset of newborns with mild HIE who will go on to develop significant brain injury. There is an urgent need for studies to select a panel from the biomarkers discussed in this review, to allow discrimination between truly mild HIE and evolving HIE within the narrow therapeutic window.

Efforts should be made to develop an international consortium of expertise and follow-up the long-term neurodevelopmental outcomes of this population. Importantly, investigations of early biomarkers able to improve the ability to identify which infants with mild HIE are at the
highest risks of abnormal outcomes are needed. Possibly, a comprehensive approach using a combination of standardized neurological assessment, aEEG or EEG and HRV measurements, may be needed to simultaneously provide accurate predictions as well as an objective early definition of mild HIE. This would help to target a subgroup of mild HIE infants when testing neuroprotective interventions.

Summary key guidelines

- The Conundrum of mild HIE is complicated by the significant gaps in knowledge related to the short time frame (6 h after birth) allocated to define mild HIE and lack of agreement on a standardized definition.
- A few small retrospective or observational studies reported short- and long-term abnormalities in a small proportion of mild HIE infants which does not justify the widespread use of therapeutic hypothermia in all of these infants. In the current era, long-term outcomes of mild HIE infants are needed.

Research directions

- An international consortium of experts is needed to standardize definitions of mild HIE within the first 6 h of age as well as registries for reporting long-term neurodevelopmental outcomes of this population.
- Panel(s) of early biomarkers that can improve the current ability to identify infants with mild HIE who are at highest risk of abnormal outcomes is needed. This would help target selected newborns with mild HIE who could benefit from neuroprotective interventions.
- Randomized controlled trials are needed to evaluate the safety and efficacy of neuroprotective strategies in mild HIE.

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Conflict of interest statement

None of the authors has any conflict of interest to declare.

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