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EDITORIAL

# Neonatal encephalopathy and hypoxic–ischemic encephalopathy: moving from controversy to consensus definitions and subclassification

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Neonatal encephalopathy (NE) is a "clinical syndrome of disturbed neurologic function in the first week after birth in an infant born at or beyond 35 weeks of gestation, manifest by a subnormal level of consciousness or seizures, often accompanied by difficulty with initiating and maintaining respiration, and depression of tone and reflexes."[1,2] This broad clinical definition does not specify subgroups, etiology, or guide management.[3–5] This editorial aims to describe variations in the definition of neonatal encephalopathy and etiological subgroups of NE used in research and clinical practice. Our group aims to develop consensus definitions to improve understanding of diagnosis and treatment and to help improve how families are informed about these conditions.

NE and hypoxic–ischemic encephalopathy (HIE) are often used interchangeably to describe a full-term baby with an abnormal neurological exam at birth and evidence of perinatal hypoxia–ischemia. In reality, HIE is a subgroup of NE. This ambiguity hinders case definition, collaborative research, and data synthesis and confuses families and caregivers. Therefore, consensus on diagnosis, terminology, and illness classification in these babies is desirable.[6,7]

There is a wide variation in the term "HIE" in the published literature, although hypoxia–ischemia is the most common discrete etiology of NE in term and near-term infants. The American Colleges of Obstetrics, Gynecology, and Pediatrics (ACOG-AAP) task force defined HIE as a retrospectively designated diagnosis.[1] The ACOG-AAP task force proposed starting with the definition of NE and subsequently, depending on the historical factors around the time of birth, magnetic resonance imaging (MRI) findings, evidence of multiorgan dysfunction, and the absence of other diagnoses that could account for the clinical picture, before sub-classifying a case as HIE. The ACOG-AAP classification of NE suggests neonatal signs and associated factors that increase the likelihood that acute peripartum/intrapartum HI contributed to the development of an acute encephalopathy. These neonatal signs include an Apgar score <5 at 5 and 10 min; fetal umbilical acidemia (pH < 7.0 or base deficit ≥12 mmol/L); neuroimaging evidence of acute brain injury on MRI or magnetic resonance spectroscopy consistent with hypoxic ischemia; the presence of multi-organ dysfunction. The associated factors include a sentinel hypoxic or ischemic event occurring immediately before or during labor and/or birth, fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event, timing and type of brain injury patterns observed on imaging consistent with an etiology of an acute peripartum or intrapartum event, and developmental outcome of spastic quadriplegia or dyskinetic cerebral palsy.[1] They suggest the evidence for the diagnosis of HIE is strengthened using neuroimaging when the timing and type of brain injury pattern is consistent with an etiology of acute peripartum or intrapartum event, with no evidence of other proximal or distal factors that could be contributors, and that are associated with spastic quadriplegia or dyskinetic cerebral palsy as potential developmental outcomes.[1]

The key limitation of the ACOG-AAP guidelines is that they were designed to identify cases that are very likely to be due to a hypoxic–ischemic event alone and to focus on the most severely affected infants. This may not be appropriate for recruitment to a clinical trial. Up to about 15% of cases of cerebral palsy are related to acute hypoxia–ischemia in term and near-term infants. At the same time, there is considerable debate about whether or not the AAP-ACOG definition may exclude some cases of HIE, because of factors such as milder acidosis or higher Apgar scores;[8,9] nonclassical patterns of injury on MRI; progressive, subacute evolution of HIE;[10] incomplete data, such as outcomes that do not include severe motor deficit; or incomplete data collection.

By contrast with HIE, NE is etiologically heterogeneous and linked to a wide range of risk factors.[3] In the only prospective population-based study, NE was associated with abnormal placenta, family history of seizures, infertility treatment, maternal thyroid disease, low socioeconomic status, and congenital malformations.[11–13] Several potential risk factors have been confirmed in other studies, including fetal growth aberration, abnormal head size and other evidence of maldevelopment, major placental infarction, marked infection, and other major abnormalities.[4,5] Broadly, we can divide these risk factors into findings consistent with greater risk for HI, or for combinations of other etiologies with hypoxia–ischemia, which could influence prognosis and may require consideration in the design of treatment trials, and for non-HI-related etiology.

Abnormalities of the placenta are present in many infants with NE, greatly exceeding their frequency in infants without encephalopathy.[14] A placental examination may reveal evidence of infectious, inflammatory, or thrombotic lesions and other important diagnostic information. Critically, reduced placental volume on modern imaging is highly associated with reduced feto-placental blood oxygen saturation and fetal growth restriction, likely increasing the risk of acute HI around the time of birth.[15] Further, there is some preliminary animal and human evidence suggesting that some, but not all, forms of infection/inflammation may be associated with an attenuated response to therapeutic hypothermia in infants with NE and might require alternative targeted immunotherapies.[16,17]

Conversely, in the High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) trial, in infants with moderate-to-severe encephalopathy, 4% of infants had an additional clinical diagnoses

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that could contribute to neurological disability, not including potential placental, whole genome, or metabolic diagnoses.[18] This shows that at least occasionally other forms of NE can be mistaken for HIE at birth. In some cases, congenital neuromuscular disorders may involve abnormal tone, movements, and respiratory insufficiency and so may be mistaken for NE, especially in the absence of neuromonitoring. Interestingly, in this study, 85% of 321 cases with available placentae showed acute (20%) or chronic (21%) or combined (43) abnormalities; chronic abnormalities were associated with a significantly greater base deficit supporting a role for chronic placental changes in HIE.[19] The reader should note that genomics and other risk factors have not yet been reported, and so potentially there could be additional contributing factors. Metabolic and/or genetic disorders may present in the neonatal period with neurologic and respiratory depression and seizures and may mimic perinatal insults, though early electroencephalogram (EEG) monitoring can help to identify these causes.[3] The initial background pattern is very different to encephalopathy caused by HI and the evolution of the background and seizures (if present) can be characteristic, e.g., in channelopathies.[20] Moreover, with advances in genetic diagnosis, defects previously undiagnosed or untreatable except with supportive care may be novel targets for gene-directed therapies in the future.[21]

Thus, understanding the etiology of NE is an important step to develop targeted neuroprotective strategies. We suggest that subclassification of NE, commonly used in other disorders such as stroke and cerebral palsy,[22] is possible and that in future targeted clinical trials NE could be stratified by etiology. Subclassification and consensus definition will allow better collaboration and development of appropriate therapies for each subgroup, as a single "magic bullet" therapy is unlikely to treat all potential causes of NE.

While the clinical features of NE are readily recognized, identifying the precise causal pathway is often challenging. Precision in defining etiology may facilitate targeted neuroprotection and treatment. Careful clinical phenotyping may help differentiation of NE by cause. This requires examination of the obstetric course and fetal monitoring records; careful and repeated neurological examination; early multichannel EEG or aEEG recordings of background brain activity; MRI and ultrasound brain imaging; and microbiological, biochemical and genetic analysis to rule out sepsis, inborn errors of metabolism, or epileptic encephalopathies, where indicated.[23] In comparison, in animal models where the mechanism of injury is known to be hypoxia–ischemia, the term HIE should be used.

In human infants, hypoxia–ischemia is difficult to quantify in dose, duration, and severity, unlike in experimental paradigms. Further understanding of pathogenesis in humans as well as in animal paradigms is required to improve and develop new therapies and individualize care as new diagnostic approaches and therapeutic possibilities emerge.[24–26] This may ultimately broaden the types of NE that are amenable to therapy. In the newborn period, before workup and course are known, we believe that descriptive terminology such as NE is preferable to an etiology-based designation such as HIE, which implies a single known etiology. In the immediate newborn period, this diagnosis is usually presumptive only, and must await confirmation. Clinical categorization, such as NE caused by sepsis, genetic causes, stroke, or those with a multifocal origin is required to ensure targeted management where possible for non-HIE causes. In addition, clear diagnosis is crucial for parents to help them to access accurate prognostic information and support.

There is also a requirement for a broader definition, including milder cases that may benefit from therapeutic hypothermia or other future therapies. Mild NE due to hypoxia–ischemia remains variably defined. Most infants considered to have mild NE in the first 6 h of age recover uneventfully. However, a systematic review has demonstrated abnormal outcomes in one quarter of this population[27] and one prospective study reported developmental disability in up to 16%, including two children who later had autism.[28] While of potential benefit, the risk/benefit of providing therapeutic hypothermia to mild NE is not yet well characterized especially as it relates to cost and family disruption. Should infants considered to have mild NE due to HIE be treated with hypothermia? The tendency toward therapeutic creep creates a need for well-considered definitions and trials specifically targeted on this mildly affected and probably highly heterogeneous subgroup. As clinical trials of neonatal treatment are under consideration for this group, a consensus definition of mild NE due to hypoxia–ischemia is urgently needed.[29] In the future, drug treatments with a better safety profile and less adverse effects may be deemed to be more effective for infants with mild NE.

The requirement for a broader definition of NE also extends to low–middle-income countries. While the greatest burden of NE occurs in these areas, there is also no therapy available to decrease the mortality and morbidity of NE or HIE, after the recent HELIX (hypothermia for moderate or severe neonatal encephalopathy in low-income and middle-income countries) study[30] showed that not only did TH not decrease the combined outcome of death or disability in India, Sri Lanka, and Bangladesh, it significantly increased mortality alone. A broader definition incorporating the features noted in infants with NE in these regions is required. The requirements for novel treatment strategies in these regions will be aided by the performance of high-quality trials, which will be aided by a clear case definition and accurate biomarkers to aid subclassification.

Parent involvement in these definitions is essential to ensure that the definition and terminology are clear.[31,32] Families have defined priorities such as clear content, clarity of language, and to be explicitly told the medical diagnosis of NE. An international evidence-based consensus is required to define NE, classify the subgroups, and their diagnostic criteria so that parents can understand the possible outcomes and advocate for resources for their children.

This group has developed a protocol for a consensus definition of NE. The evidence synthesis has started with a systematic review of definitions of NE used in randomized controlled trials involving patients with NE. This has revealed a huge disparity between, and little consensus on, definitions of NE. The next stage is to complete a protocol for a study to develop an international and multidisciplinary consensus definition using a modified Delphi consensus approach. The Delphi approach is an iterative process with repeated rounds of evaluation and voting to help determine consensus among a group of experts and parents with different levels of knowledge and expertise. We will use an online real-time Delphi approach to arrive at a consensus definition.

In conclusion, controversy remains about the terms NE and HIE.[33,34] Collaboration with journals and relevant societies, such as the Newborn Brain Society (www.newbornbrainsociety.org), may be a key mechanism to ensure consistency and dissemination of consensus definitions in the future. An international consensus on definitions of NE and subgroups is one step that may help support the progress of future therapies and international collaborations.

"A rose by any other name would smell as sweet …"
Shakespeare's *Romeo and Juliet*

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The authors declare no competing interests.

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Ethical approval was not required for this review of the literature.

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