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

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A B S T R A C T

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.

Given the difficulty of establishing a precise diagnosis and the complex pathophysiology related to the uncertain timing, severity, and patterns of the fetal insult [1], neonates with neonatal encephalopathy (NE) are currently viewed dichotomously: those who do or do not qualify for therapy based on an early neurologic examination performed within 6 h of 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

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Table 1
Neonatal neurological scores applied to infants with perinatal asphyxia and mild HIE.

Author, year (journal)	N	Definition of perinatal asphyxia	Age at exam	Mild HIE definition	Outcomes of infants with mild HIE
Sarnat and Sarnat, 1976 (Arch Neurol) [2]	21	Well defined episode of fetal distress or Apgar score ≤ 5 at 1 or 5 min after delivery (MAS, RDS, maternal drug use were excluded)	Serial exams performed at 12 to 24 h intervals for the first 6 days	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)	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
Amiel-Tison, 1979 (Advances in perinatal neurology) [8]	34	NA	NA	Hyperexcitability and mild abnormalities of tone. Responsiveness is normal; primary reflexes are present. No seizures. These signs persist for varying periods.	NA
Amiel-Tison and Elisson, 1986 (Dev Med Child Neurol) [3]	NA	NA	NA	Hyperexcitability sleeping or fussy and abnormal tone. Hypotonic scarf sign, poor head control or hyperextended neck. Stretch reflexes exaggerated. Uses a cut-off point of 7 days to score as 1a or 1b	Neonates with perinatal asphyxia who have *no* or *only transient* neurological signs and who became normal by day 7 (stage 1a) were normal
Lipper et al., 1986 (Dev Med Child Neurol) [4]	34	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 < 7.2) or cord pH < 7.2, need for resuscitation at birth, and meconium aspiration.	First 24 h of life	Post Asphyxia Score (PAS): 17 items for neurological assessment. Total score ranging from 0 (worse) to 39 (optimal). No definition of mild.	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.
Thompson et al., 1997 (Acta Paediatrica) [7]	45	NA	Exams done daily	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.	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.
Perez et al. (SIBEN score), 2017 (Rev. Assoc. Med. Bras.) [5]	26	Apgar score ≤ 5 at 1, 5, or 10 min of life	10 min of life, repeated every 2–3 h as needed	Siben Score: diagnosis according to highest number of items (above 3) found in the corresponding HIE grade of 10 categories (LOC, SA, posture, tonus, 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.	NA
Prempunpong et al. (PRIME study), 2017 (J.Perinatol) [6]	54	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	≤ 6 h of life	Modified Sarnat score: ≥1 abnormal category but no evidence of moderate or severe HIE (defined as moderate and/or severe abnormality in three categories).	Abnormal aEEG, brain MRI or neurological exam at discharge found in 52% of the infants with mild HIE

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.