Pediatric RESEARCH

EDITORIAL

Neonatal encephalopathy versus Hypoxic-Ischemic Encephalopathy

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Neonatal encephalopathy (NE) is a complex syndrome characterized by seizures, an altered level of consciousness, and/or an inability to initiate or maintain respiration.[1] Although the incidence show variation, it is estimated as many as 3 per 1000 live births are affected.[2] Infants may display multiorgan as well as neurological dysfunction.[3] NE is an "umbrella" term that does not describe a specific etiology. Therapeutic hypothermia is the only validated treatment other than supportive intensive care.[4] Although here are multiple causes of NE including hypoxia-ischemia (leading to hypoxic-ischemic encephalopathy (HIE)), perinatal infections, placental abnormalities, metabolic disorders, coagulopathies, and neonatal vascular stroke the cause is unidentified in more than half of the cases.[5]

The terms HIE and NE are used interchangeably in the literature when describing human and animal newborns. Previously the former editors of Pediatric Research, Olaf Dammann and Pierre Gressens, called for the definition to be clarified with the term NE to be used. However, this clarification has not been reflected in the literature. The term HIE is very appropriately used in an animal model where there is a well-delineated exposure to hypoxia, ischemia or both. In human infants sentinel events such as cord prolapse, uterine rupture, or abruptio placentae may be clearly associated with HIE but often HIE is a secondary event. Therefore although hypoxia-ischemia may be involved, it is known to be the sole instigator of encephalopathy in an estimated 7% of infants with NE.[6] The Vermont Oxford Network Neonatal Encephalopathy Registry found that an asphyxia event accounted for 15% and inflammation 24 % of cases of NE with other maternal etiologies also implicated ($n = 4165$).[5]

Therefore all other etiologies of encephalopathy are encompassed by the term NE including metabolic, septic, thromboembolic, and genetic. There are no definitive biomarkers of HIE in humans. Although surrogates such as nucleated red blood cells, umbilical arterial blood pH, troponin have been suggested, no correlation has been made in animal models with defined measured hypoxic exposure. Treatment of conditions such as sepsis and investigations regrading genetic and metabolic causes may be hindered by the assumption that the diagnosis is HIE. The use of the umbrella term NE allows the clinician to explore the etiology more definitively.

It has been proposed that in term and late preterm infants with no identifiable sentinel events, the term NE should be used.[7,8] It is difficult to prove the presence of cerebral hypoxic ischemia with the exception of well characterized animal models and particular cases of neonatal stroke. All current parameters including cord blood pH and seizures are non-specific.[7] Some of the patterns of brain injury seen in NE patients can be produced in animal models by hypoxia-ischemia but this does not prove that all NE is due to HIE.[7] The few published population-based studies have shown that antepartum and non-asphyxial risk factors are associated with NE.[8] On the contrary some authors state that HIE is the cause of NE in 50%–80% of cases based on clinical, EEG, and MRI criteria.[1] A different pattern of injury can be seen on MRI for HIE compared to other causes of NE, but this finding does not rule out HIE or other causes of NE as the cause of injury. The pattern of injury in HIE depends on the severity, duration, and repetitiveness of the hypoxia-ischemia and can lead to involvement of basal ganglia, thalami, brain stem, and/or cerebral white matter in different combinations.[1]

The lack of a consensus term to describe infants with NE and with other causes of encephalopathy has an impact on improving their outcomes as it impedes the larger collaborative networks and the future development of mega-trials. We suggest that in order to study NE in wide international collaborations, consensus on the name of the condition is essential. This will then allow subclassification into different groups by etiology who may benefit from more individualized treatment regimens.

ADDITIONAL INFORMATION

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