Cause for optimism in mild hypoxic ischaemic hypoxic encephalopathy

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The objective of the study by Törn et al. was to determine if mild hypoxic ischaemic encephalopathy (HIE) was associated with severe neurological outcomes utilizing a population-based approach facilitated by five linked Swedish national databases. The rationale given was that while moderate to severe HIE is known to be associated with significant neurological morbidity, long-term disability, and mortality in children, less is known about mild HIE. The authors note that half of the cases of HIE are mild and they cite a systematic review of 250 infants (Conway JM, et al. *Early human development* . 2018; 120:80-7) showing a 22% prevalence of abnormal neurological outcomes in this disorder. There is therefore potential for significant

burden of disease in mild HIE. Törn et al. chose a primary composite outcome that included cerebral palsy, epilepsy, mental retardation and death in children with mild HIE and non HIE cohorts followed up to 6 years of age. With a median follow-up of 3.3 years of age, 17 of 414 (4.1%) and 4786 of 504,661 (0.95%), in the mild HIE and non HIE cohorts respectively, had the composite outcome with an adjusted hazard ratio of 3.85 (95% CI: 2.27-6.50)

In 1976 Sarnat and Sarnat reported clinical and EEG features of 21 neonates at term who experienced ischaemic-anoxic encephalopathy (Sarnat HB et al. *Arch Neurol.* 1976; 33:696–705). This temporal classification divided the infants into three progressively deteriorating stages. Fast forward to the current millennium and Sarnat's original classification is used to differentiate between infants with mild and moderate/severe HIE, the latter two categories benefiting from therapeutic hypothermia (Jacobs SE et al. *Cochrane Database Syst Rev.* 2013, Issue 1. Art. No.: CD003311). Seven infants with moderate or severe HIE is the number needed to treat (NNT) to prevent one adverse neurological outcome.

Therapeutic hypothermia is not standard of care in mild HIE; however, in a survey of neonatal clinicians from 35 countries the vast majority would support a large randomized controlled trial to examine neurodevelopmental outcomes (Singla M, et al. *Neonatology.* 2022; 119:712-718). The results from this methodical Swedish cohort study provide data that can be used to direct further research. The composite outcomes in HIE are lower than expected, and one could infer similar outcomes in high resource settings. The data are reassuring and will be useful for clinicians in counseling and reassuring parents with infants affected by mild HIE. Regarding a randomized controlled trial of therapeutic hypothermia in mild HIE: it would appear, based on the data provided by Törn et al., if we hypothesize this therapy would result in a 50% reduction in the composite outcome, the NNT would be approximately 50. This compares unfavorably to the NNT of 7 in moderate/severe HIE. Perhaps, further insight could be gained by review of individual patient data, particularly with respect to antenatal and neonatal course, imaging, EEG, and biochemical data in order to identify a subset that might benefit from therapeutic hypothermia or other novel therapy.

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