maternal obesity, and maternal diabetes, were not assessed. In addition to considering these potential confounders, more research is needed to identify mechanisms linking respiratory disease, ROP, and intraventricular hemorrhage to subsequent ADHD, towards the goal of interrupting these mechanisms.

Given the high frequency of ADHD among infants born preterm, prevention of preterm birth is a potential strategy for decreasing the prevalence of ADHD in children. Although the success of efforts to prevent preterm birth has been limited in high-income countries, the risk of recurrent preterm birth (among mothers with a history of prior preterm birth) can be decreased by treatment with 17-alpha-hydroxyprogesterone beginning in the 16th week of pregnancy.[4] Each of the risk factors for ADHD that were identified by Tso et al. is potentially modifiable. Certain specific respiratory infections, including pertussis, diphtheria, and group B streptococcal pneumonia are preventable. The risk of ROP in infants born extremely preterm and very preterm can be reduced by targeting oxygen saturations,[5] and the impact of ROP on visual function can be improved with surgical interventions. Evidence-based interventions to prevent intraventricular hemorrhage include antenatal treatment of mothers with corticosteroids and prophylactic indomethacin, although the latter has potential side effects that has limited its use. Equally important are rehabilitative therapies and educational support for children with early symptoms, and/or at high risk of ADHD. Future research is needed to determine if such interventions will modify the risk of ADHD, or if there are other modifiable prenatal risk factors that can moderate this increased risk.

DATA AVAILABILITY STATEMENT

No original data were used to develop this commentary

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Hippocampus and hypothermia: A missing link

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While therapeutic hypothermia improves outcome after moderate and severe neonatal hypoxic-ischaemic encephalopathy (HIE) in high-income countries, many cooled infants without cerebral palsy (CP) have cognitive impairment and memory deficits during childhood.[1] They are less school-ready than typically developing peers and often have behavioural difficulties and special educational needs. These children may easily slip through the net if careful, long-term follow-up assessments are not performed. Despite the substantial health impact of these issues, significant knowledge gaps about the underlying mechanisms and therapeutic options remain.

Spencer et al.[2] report additional childhood outcome and neuroimaging data from the Bristol cohort of 31 infants who had therapeutic hypothermia between 2007 and 2012, but did not have CP. On comparison with 32 typically developing age-matched peers, the cooled infants had substantial cognitive and memory impairment at early

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school-age. They also had lower whole-brain grey and white matter volumes, hippocampal and thalamic volumes than typically developing peers. Cortical injury on neonatal magnetic resonance imaging (MRI) was associated with reduced volumes of hippocampi, thalami, grey matter, and white matter. While some of the analysis is exploratory, it is nevertheless important. These neuroimaging data add to the earlier reports of suboptimal cognition, working memory, and lower volume of mammillary bodies from this cohort while raising some important new questions.[1,3]

Why does hippocampal injury persist in children without CP despite rescue hypothermic neuroprotection? Excluding children with CP suggests that this cohort of cooled infants were probably at the milder end of neonatal brain injury, where hypothermia is expected to be more neuroprotective. Hippocampus is one of the first regions to be injured in preclinical models of hypoxic–ischemic injury, well before deep brain nuclei injury.[4] And yet no clear correlation of clinical condition at birth and injury to hippocampus or mammillary bodies is apparent. These issues are further complicated by the fact that hippocampus is not fully developed in humans before the age of 4 years; hence these injuries may be overlooked on neonatal MRI, especially when thicker slices are used.

Although preclinical models of single acute hypoxia-ischemia have had a major role in the discovery of hypothermic neuroprotection, clinical scenario is far more heterogenous than current preclinical models. More complex preclinical models, representative of clinical scenario, are required to further advance the field of neuroprotection. Another major implication of these observations relates to the therapeutic drift of cooling in mild encephalopathy. Although CP is unlikely after mild encephalopathy, many of these infants have cognitive and memory deficits during childhood. Does it mean that hypothermia may not benefit these infants? Clearly, further research is required to explore these issues.

DATA AVAILABILITY STATEMENT

Not required

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Does hand function continue to develop in older children and adolescents with cerebral palsy?

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It is difficult to conduct a longitudinal development study in a single cohort due its long-term nature and associated by-products such as participant attrition, research continuity, funding, and changing sample size. Eliasson et al.[1] overcome these challenges in a new study, conducted over an average of 13 years, that uses the Assisting Hand Assessment (AHA) in a repeated measures design to describe the development of affected hand use in children with unilateral cerebral palsy between the ages of 18 months and 18 years. Their findings support previous research that AHA scores together with Manual Ability Classification System (MACS) level at 18 months of age are predictive of future developmental patterns and that performance develops rapidly through infancy and early childhood, and stabilizes (regardless of MACS level) by age 7 years with relatively little further development.[2] A key takeaway is that most of hand use development occurs during early childhood, which underscores the importance of early intervention. While this conclusion is important and indisputable, care must be taken not to conclude the opposite – that subtle aspects of hand function important for more controlled tasks do not continue to develop beyond this point.

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