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COMMENT

Neonatal hypoglycemia: pre-emptive monitoring and treatment may result in normal neurodevelopmental outcome

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In this issue, Kennedy et al.[1] report on caudate volumes and neurodevelopmental outcomes at 9–10 years of age in the "Children with hypoglycemia and their later development" (CHYLD) study in children with and without a history of neonatal hypoglycemia. Smaller caudate volume in this cohort is reported to be associated with greater parent-reported emotional and behavioral difficulties, and poorer prosocial behavior. However, neonatal hypoglycemia was not found to be a mediator in this relationship, except in the case of visual memory, where only those children without neonatal hypoglycemia showed significant associations with caudate volume. Children with neonatal hypoglycemia did not show significant associations between caudate volume and visual memory outcomes.

Neonatal hypoglycemia has previously been demonstrated by numerous reports to be associated with posterior-predominant brain injury, resulting in a triad of neurodevelopmental impairment, cortical visual loss, and epilepsy. Brain MRI in the neonatal period has been reported to demonstrate a specific posterior-predominant brain injury pattern, particularly in the parieto-occipital white matter and pulvinar nucleus of the thalamus.[2,3] Follow-up imaging later in life demonstrates gliosis and volume loss in these same regions.[4] Children with a history of neonatal hypoglycemia have been reported to have lower developmental scores at 8 years of life compared to children without.[5] Early diffusion restriction in the calcarine cortex on brain MRI is associated with abnormal visual evoked potentials in the first week of life and increased risk for long-term cortical visual impairment, including blindness or homonymous hemianopsia.[6] Long-term consequences also include increased risk for epilepsy, including infantile spasms or focal epilepsy from occipital gliosis, and can be intractable in infancy or early childhood.[4,7]

A common feature of these aforementioned studies are that all are based on retrospective case reports and cohorts, where infants were identified after the adverse outcomes were already documented. Glucose values recorded were limited by pre-existing clinical practice, and thus the true severity and duration of hypoglycemia was difficult to quantify. As well, risk factors for brain injury could not be clearly delineated. However, as a result of studies such as these, awareness of the neurological risks of neonatal hypoglycemia has become more recognized, and the clinical management of neonatal hypoglycemia has improved in the last few decades.

The CHYLD study presents a number of critical improvements to previous research into neonatal hypoglycemia, involving a prospective cohort study of infants at risk for hypoglycemia, incorporating continuous glucose monitoring in a majority of enrolled subjects, and targeting treatment to maintain glucose levels above 2.6 mmol/L (47 mg/dL). Employing a prospective study design enables a better assessment of the overall risk for brain injury in this population. Meanwhile continuous glucose monitoring enables better documentation of the true incidence of hypoglycemia.[8]

However, targeting treatment prospectively to maintain levels about 2.6 mmol/L (47 mg/dL) is a significant shift from the prior retrospective reports, potentially avoiding more severe injury resulting from prolonged and severe hypoglycemia. This bears out in the study results. The CHYLD study group recently reported that, in their large cohort of 480 children, neonatal hypoglycemia was not found to be associated with lower educational achievement at age 9–10 years.[9]

The CHYLD study did not include brain imaging in the neonatal period. However, this current report includes magnetic resonance imaging (MRI) studies at age 9–10 years in a subset of 101 subjects, of which 70 experienced neonatal hypoglycemia. Out of these 70 children, only one (1.4%) had imaging changes consistent with the previously reported pattern of parieto-occipital white matter injury. While this later neuroimaging potentially underestimates the total number of children who would have demonstrated acute brain injury in the newborn period, it does provide an important window as to the frequency of lasting measurable brain injury. Thus, either the true incidence of brain injury after neonatal hypoglycemia is actually very low, or prospective treatment of hypoglycemia in this cohort was effective in minimizing the severity and duration of hypoglycemia to prevent resultant brain injury and adverse outcomes.

The results of the CHYLD study provide a lot of hope, in that they suggest that close glucose monitoring in at-risk newborns and defined treatment thresholds may result in good outcomes after neonatal hypoglycemia. It is important to note that, while continuous glucose monitoring was performed for the majority of the infants in this study, management of hypoglycemia was solely based on bedside intermittent testing.[10] Especially considering that continuous glucose monitoring remains not widely available for clinical use, it is helpful to know that intermittent bedside testing seems to be adequate for good clinical outcomes. Indeed, only 17 out of the 70 children in this study were reported to have severe hypoglycemia, defined as any hypoglycemia event <2 mmol/L (36 mg/dL) or ≥3 hypoglycemic events.

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Despite improved clinical awareness, infants not prospectively monitored continue to be at risk. There has been a dramatic increase in the awareness of clinicians to the importance of monitoring for and treating neonatal hypoglycemia over the last few decades. Despite these efforts, neonates continue to present with neonatal hypoglycemia with symptoms of encephalopathy and seizures. These children do demonstrate the corresponding findings of parieto-occipital brain injury on early neuroimaging. Long-term consequences of severe neurodevelopmental impairment, cortical visual impairment, infantile spasms, and refractory childhood epilepsy continue to regularly occur. These patients often present to medical care too late for inclusion in prospective research studies, and are thus not well represented in the literature. More efforts are needed to pre-emptively identify newborns at risk for monitoring and intervention.

The CHYLD study, with its prospective and continuous glucose monitoring, has provided us with much needed information regarding the positive long-term outcomes of newborns adequately monitored and treated for neonatal hypoglycemia. Further studies are needed to better understand risk factors for neonatal hypoglycemia. More clarity is also needed to understand the severity and duration of hypoglycemia that result in brain injury, as well as risk factors that predispose particular newborn infants to brain injury in the context of hypoglycemia. This information would help to target monitoring and treatment in an efficient way to prevent neurodevelopmental impairment, cortical visual impairment, and refractory epilepsy seen in severe cases of neonatal hypoglycemic brain injury.

DATA AVAILABILITY

Data sharing not applicable to this article as no datasets were generated or analyzed.

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ADDITIONAL INFORMATION

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