Pediatric RESEARCH

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COMMENT

The cerebellum's role in neonatal brain injury

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Pediatric Research (2021) 89:1055–1056; https://doi.org/10.1038/s41390-020-01326-0

In the article titled, "Cerebellar injury in term neonates with hypoxic–ischemic encephalopathy is underestimated," the Utrecht team highlights important knowledge gaps regarding the current limitations in neuroimaging of the cerebellum in neonatal asphyxia and the importance of histopathological cerebellar findings.[1]

Despite the small numbers of autopsy samples available, and the selection biases that are inherent to the nature of autopsy reports that are only obtained in severe cases who succumb from the insult severity, this important study compares the histological autopsy findings to the brain magnetic resonance imaging (MRI) diffusion-weighted imaging results obtained in the first week of life preceding death in severe hypoxic–ischemic encephalopathy (HIE) cases. All infants in this study underwent hypothermia therapy and their MRI findings were also compared to normal controls. Although histopathological injury was detected in all cerebellar structures, there was no correlation between antemortem apparent diffusion coefficient (ADC) and postmortem histopathology implying that a normal MRI ADC does not guarantee a lack of injury to the cerebellum.

These observations of the importance of the cerebellum are not specific to HIE and appear to encompass the neonatal developing brain in general. The developing brain physiology is of paramount importance as the volume of the cerebellum increases 5-fold from 24 weeks to term gestation while its surface area increases by 30-fold. Autopsy studies identify the incidence of cerebellar hemorrhage to be the highest under 25 gestational weeks, a time at which the cerebellum has acquired only 25% of its expected term volume. The underlying mechanism of injury is that cerebellar insults during the critical periods of neonatal development result in interruption of the cerebello-cerebral pathways and the contralateral cerebral cortex.

As pointed in a prior editorial, the importance of identifying cerebellar lesions is that it carries strong correlations with poor intelligence quotient and motor outcomes.[2] Studies of premature cerebella using MRI show an unexpectedly high incidence of cerebellar hemorrhage, which are associated with localized cerebellar hypoplasia not detected by ultrasound.[3] A recent population-based Swedish cohort showed that the volumes of the cerebellum and the brainstem correlated positively with fine motor skills in preterm children at 6.5 years of age.[4] Therefore, injury to the cerebellum causes not only immediate damage but also affects growth and connectivity in the developing brain.

The bottle neck occurs in the neuroimaging ability to identify the cerebellar injury. Cerebellar injury in preterm infants is currently poorly identified by sonography, even after the necessary dedicated posterior fossa/mastoid views are obtained. As identified in a recent neuroimaging algorithm review, a brain MRI obtained at term equivalent age is needed to detect the cerebellar and white matter punctate injury in the developing neonate.[5] The current published study findings in HIE are further concerning that even MRI ADC measurements can detect only evidence of severe cytotoxic cerebellar edema. This suggests that even an MRI can only allow diagnosis of extreme abnormalities. It is therefore critically important to improve our standard neuroimaging algorithm with dedicated standardized scoring, volumetric tools, and machine learning strategies to include the black box that is the cerebellum.[6]

In summary, when it comes to neuroimaging the neonatal cerebellum, we are not able to see some histopathological injury. This article's findings highlight the importance of seeking histopathological reports and correlations. Unfortunately, it seems that autopsy and histopathology of the neonatal brain is a dying art that is rarely sought anymore in our current neonatal intensive care units. Future steps to address knowledge gaps regarding the role of the cerebellum will depend on machine learning and quantitative features[7] that need to be made available at the bedside in order to facilitate decision-making, early referral, and follow-up for a detailed trajectory of outcomes. As such, the future will heavily depend on a full battery of serial examinations and standardized neuroimaging biomarkers, assessed as a trajectory of neurodevelopmental evaluations.[8] Research targeted to pre-specified and mechanistically derived hypotheses regarding cerebellar injury are needed. Future neuroprotective trials should target a trajectory of developmental assessments and biomarkers for detection of outcomes.

ACKNOWLEDGEMENTS

I thank Dr. Donna Ferriero for providing her thoughtful review. The study was funded by NIH Grant 5R01NS102617-03 National Institute of Neurological Disorders and Stroke awarded to L.C.

ADDITIONAL INFORMATION

Competing interests: The author declares no competing interests.

Consent: No patients discussed, so no consent was needed.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Received: 13 October 2020 Revised: 28 October 2020 Accepted: 3 November 2020
Published online: 19 January 2021

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