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COMMENT

Brain creatine alteration and executive function deficits in children born very preterm

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A paper by Schnider and co-workers[1] published recently in *Pediatric Research* has investigated a possible association between impaired brain metabolism and executive function deficits in 54 children born very preterm (VPT). The authors found lower glutamate–glutamine-to-creatine ratio (Glx/Cr) and higher myo-inositol-to-creatine ratio (mI/Cr) in the frontal white matter of VPT children aged 8–15 years, with lower executive functions associated with lower frontal Glx/Cr ratio in both VPT- and term-born peers and higher mI/Cr ratios in the VPT group only. It appears that VPT birth is associated with long-lasting location-specific metabolic disturbances in the brain of affected children, with such metabolic turmoil partly responsible for deficits reported in executive function at school age. However, these results should be interpreted with caution since the authors failed to account for possible changes in creatine metabolism in VPT while obtaining brain metabolites using proton magnetic resonance spectroscopy (MRS).

The authors used creatine as the reference metabolite and a denominator in ratios of various resonance amplitudes, under the premise that concentrations of creatine remain relatively stable in the brain. However, it appears that creatine levels are rather sensitive to numerous conditions of the developing brain,[2] including prematurity-related clinical complications. For instance, the presence of cerebellar injury in infants born prematurely was consistently associated with reduced concentrations of creatine (along with *N*-acetyl aspartate and choline), while cerebral cortical brain injury severity was inversely associated with both creatine and choline.[3] Assuming stable creatine levels by Schnider and co-workers[1] could avert any correction for possible variability of creatine alteration across brain regions and minimize the clinical significance of relative quantification and each of the ratios evaluated. More accurate methods of metabolic quantification involving absolute quantification of relevant spectra in combination with a structural analysis of the MRS volume of interest[4] might be needed to elucidate metabolic disturbances in VPT.

On top of that, location-specific changes in creatine levels could be considered by itself as a biomarker of impaired brain biochemistry and executive function deficit in VPT. Altered brain creatine levels in both the gray and white matter were reported in several studies with preterm newborns, including a sub-sample of premature infants with cerebellar and cerebral cortical brain injury,[3] premature-born infants without evidence of brain injury,[5] and premature neonates with normal conventional magnetic resonance imaging,[6] all suggesting altered energy homeostasis that may instigate a delay in brain maturation. It appears that developing brain deficient in creatine causes impoverished axonal networks and reduced synaptic density,[7] both recognized as pathophysiological substrates of executive function deficits. Schnider and co-workers[1] did not provide any information about absolute quantification of creatine concentrations across various brain compartments in the study population or the relationship between brain creatine levels and global executive function abilities. This information would be of considerable added value.

ADDITIONAL INFORMATION

Competing interests: The author declares no competing interests.

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REFERENCES

1. Schnider, B. et al. Altered brain metabolism contributes to executive function deficits in school-aged children born very preterm. *Pediatr. Res.* https://doi.org/10.1038/s41390-020-1024-1 (2020).
2. Dezortova, M. & Hajek, M. (1)H MR spectroscopy in pediatrics. *Eur. J. Radiol.* **67**, 240–249 (2008).
3. Brossard-Racine, M. et al. Altered cerebellar biochemical profiles in infants born prematurely. *Sci. Rep.* **7**, 8143 (2017).
4. Turner, C. E., & Gant, N. in *Magnetic Resonance Spectroscopy* (eds Stagg, C. & Rothman, D.) 91–103 (Academic, Cambridge, MA, 2014).
5. Blüml, S., Wisnowski, J. L., Nelson, M. D. Jr, Paquette, L. & Panigrahy, A. Metabolic maturation of white matter is altered in preterm infants. *PLoS ONE* **9**, e85829 (2014).
6. Koob, M. et al. Creatine, glutamine plus glutamate, and macromolecules are decreased in the central white matter of premature neonates around term. *PLoS ONE* **11**, e0160990 (2016).
7. Stockler, S., Schutz, P. W. & Salomons, G. S. Cerebral creatine deficiency syndromes: clinical aspects, treatment and pathophysiology. *Subcell. Biochem.* **46**, 149–166 (2007).

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