Manganese Neurotoxicity may Underlie the Association between Early Life Iron Deficiency and Impaired Spatial Cognition in Neonatal Piglets

Dear Editor,

~2 billion people worldwide suffer from iron deficiency (FeD) (1). Rytych et al. (2) have highlighted the consequences of FeD during a vulnerable, early postnatal period for neurocognitive development. However, the authors overlook a potentially important interaction between Fe and manganese (Mn). Rodents suffering from FeD have elevated brain Mn concentrations (3). Children with FeD anemia have increased whole blood Mn concentrations (4) and dietary FeD upregulates the Mn transporters, divalent metal transporter-1 and the transferrin receptor, in the developing brain (5).

In humans, Mn excess and FeD are associated with remarkably similar deficits in cognitive and neuropsychological performance during childhood (6). Both Fe and Mn preferentially affect full scale IQ-measurements, school-age mathematical performance and domains of executive function, such as visual recognition and memory (7). Animal models of dietary Mn exposure demonstrate altered behaviors and learning patterns in maze experiments (8).

Additionally, a potential effect of FeD on olfactory development, rather than a direct effect on cognitive development, may explain the maze task results because even neonatal piglets can orient to the presence of milk (9) used as a reward. Fe-deficient rats demonstrate a reduction in serotonin transporter binding in the olfactory tubercle (10), and in non-human primates this decreases expression of olfactory receptors (11). Similarly, the influence of excessive Mn exposure on the olfactory system has been well established.

Thus, despite the interest generated by the paper by Rytych et al. (2), additional work is needed before the authors can conclude that their findings are due to a direct effect of FeD on neurocognitive development and not due to concomitant Mn overload and Mn-induced neurotoxicity.

Nathalie L. Maitre
Judy L. Aschner
Michael Aschner*
Department of Pediatrics,
Vanderbilt University Medical Center,
Nashville, TN

Literature Cited


*Author disclosures: N. L. Maitre, J. L. Aschner, and M. Aschner, no conflicts of interest.

*To whom correspondence should be addressed. E-mail: michael.aschner@vanderbilt.edu.