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Commentary

Metabolomics, stunting and neurodevelopment

Meta van den Heuvel [a,b,c,*]

[a] Divsision of Pediatrics, Hospital for Sick children, Toronto, Canada
[b] Department of Pediatrics, University of Toronto, Toronto, Canada
[c] Centre for Global Health, Hospital for Sick Children, Toronto, Canada

Globally an estimated 250 million children (43%) younger than 5 years of age are at risk of not reaching their full developmental potential [1]. The Sustainable Development Goals have prioritized early child development outcomes - seeing it as essential to the transformation the world needs to achieve by 2030 [2]. Early childhood neurodevelopmental outcomes have a key impact on long-term individual and population health outcomes. Childhood stunting (height-for-age; HAZ < -2) is identified as an important risk factor for poor child development. Significant associations have been identified between stunting and motor and cognitive development in children two years of age or younger [3,4]. However *how specifically* stunting influences child neurodevelopment remains unknown. Growing evidence demonstrates the independent and interrelated roles of both malnutrition and inflammation on neurodevelopment [5]. Importantly, current interventions aimed at preventing stunting (e.g. maternal diet supplementation, prevention of infection during pregnancy and the promotion of breastfeeding) and treating stunting (e.g. diet diversification and diet supplementation of children) have only be marginally effective and for most of these interventions the impact on child development outcomes remain unclear [4,6]. New targeted interventions are urgently needed to address both stunting and child neurodevelopmental outcomes in order to meet the Sustainable Development Goals.

The article of Moreau et al. in EBioMedicine is an excellent example of innovative research that explored the association between metabolic pathways and both linear growth and cognitive outcomes [7]. The authors performed targeted metabolomics on a sub-cohort (n = 130) of the PROVIDE study which was designed to examine oral vaccine efficacy in a longitudinal cohort of undernourished children in Bangladesh [8]. The prevalence of stunting was 10.8% at enrollment and 29.6% at 2 years of age in this sub-cohort and remained fairly stable – with a high percentage children at risk for stunting (HAZ between −1 and >−2). Neurocognitive outcomes were assessed with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) at 4 years of age. Plasma samples were collected at 9- and 36-month time points for each child. The authors identified an association between distinct metabolites and growth and neurocognitive outcomes; interestingly growth outcomes were mainly predicted by 9-month metabolic profiles and neurocognitive outcomes mainly by 36-month metabolic profiles. Improved growth outcomes were seen with increased hydroxysphingomyelin and phosphatidylcholine levels and total essential amino acids. Higher neurocognitive scores were seen in children who had higher levels of phosphatidylcholines. Poor growth outcomes were associated with high levels of medium to long chain acylcarnitines and bile acid conjugation. Acylcarnitines and aminoacids were generally not associated with neurocognitive outcomes, with one exception; the amino acid Threonine measured at both 9 and 36 months was positively associated with neurocognitive outcomes.

The study of Moreau et al. is one of the first studies that demonstrated that separate metabolic pathways might relate to stunting and neurocognition [7]. The wide range of metabolites associated with growth outcomes could be related to factors such as insufficient diet and environmental enteric dysfunction and have been identified in other studies [9]. Although growth parameters were measured longitudinally – only some children had neurocognition outcomes measured at two time points. Development is a nonlinear process and it is unclear if the identified metabolites influenced individual developmental trajectories. In addition, important predictors for child development e.g. maternal mental health were not accounted for. Unexpectedly, not the 9-month but only the 36-month phosphatidylcholines were predominantly associated with neurocognitive outcomes. Phosphatidylcholines are the main component of plasma membranes and low circulating phosphatidylcholines have been linked to increased gut permeability [9]. Additionally, the synthesis of sphingomyelins, which are essential for myelination, depends on phosphatidylcholines. In a study by Di Giovanni et al. children with severe acute malnutrition demonstrated delayed phosphatidylcholine recovery even after nutritional rehabilitation [9]. This could suggest that the 36-month phosphatidylcholines are biomarkers of a chronic process occurring later in childhood. Further research should explore the role of phosphatidylcholines in younger children and their relation to gut health and neurodevelopmental trajectories. Interestingly, both the 9- and 36-month plasma levels of Threonine, an essential amino acid that supports the central nervous and immune system and is also a major component of the intestinal mucosa, were associated with neurocognitive scores. In the study of Moreau et al. it would have been interesting to combine the results of metabolomics with levels of systemic inflammatory markers (e.g. C-reactive protein, pro-inflammatory cytokines), biomarkers of intestinal inflammation and barrier dysfunction (e.g. fecal biomarkers like

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* Corresponding author at: Division of Paediatric Medicine, 555 University Ave, M5G 1X8 ON, Toronto, Canada.
E-mail address: mathilda.vandenheuvel@sickkids.ca.

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calprotectin) and microbiome analysis in order to provide further insight in possible mechanistic pathways.

The research by Moreau et al. made an important contribution to our understanding of the association between growth, metabolism and neurocognitive outcomes. However, in order to develop targeted interventions longitudinal research is needed that focuses on the complex relationship between nutrition, inflammation and neurodevelopment outcomes [5]. This research should also include more functional and structural outcomes of brain development in order to allow for a better understanding *how* specific aspects of nutrition, metabolomics and inflammation impact neurodevelopment [10].

Disclosure

The author declared no conflicts of interest.

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