EBioMedicine 17 (2017) 9–10

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Secondary Carnitine Deficiency in Environmental Enteric Dysfunction

Girija Ramakrishnan *, William A. Petri Jr.

Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia, USA

ARTICLE INFO

Article history:
Received 14 February 2017
Accepted 14 February 2017
Available online 16 February 2017

An interesting paper by Semba et al. (2017) in this issue of *EBioMedicine* describes the use of a metabolomics-based approach to identify deficiencies of carnitine and fatty acid metabolism in children with environmental enteric dysfunction (EED) in rural Malawi.

As stated in the paper, EED (also termed environmental enteropathy in the literature) is generally associated with poor nutrition, pathogen exposure and inadequate hygiene, typical of many low-income settings throughout the world. Having no overt symptoms, EED is characterized by histo-pathological abnormalities of the small intestine with associated features of intestinal barrier disruption, nutrient mal-absorption and gut inflammation. The prevalence of EED in children has significant negative consequences including growth faltering, vaccine failure and developmental neurocognitive deficits (Watanabe and Petri, 2016). Unfortunately, EED in children is not easily diagnosed and is most clearly evident only upon outcome. Getting a handle on biomarkers for early diagnosis is a highly desirable, but challenging goal since multiple factors including nutrition, infection, inflammation and loss of gut integrity contribute to the syndrome (Naylor et al., 2015).

In their cross-sectional study, Semba and colleagues deployed the urinary lactulose and mannitol (L:M ratio) test to identify children with EED in the cohort of 400 ranging in age from 1 to 5 years. This differential sugar absorption test provides a read-out of gut integrity. It is however known to be difficult to administer correctly and reliably, particularly with regard to very young children, and region and population-specific factors could influence the representative "normal" ratio (Denno et al., 2014). It is also recommended that the dose of the administered sugars be normalized to body weight (Denno et al., 2014). With these caveats, a more cogent approach would be to include additional readouts for gut dysfunction such as stool neopterin or myeloperoxidase that signal gut inflammation or Reg1B, a marker of intestinal cell damage, as well as an index of growth such as HAZ score so as to have a composite index for EED (Kosek et al., 2013).

In this study, the plasma from the children was analyzed by LC-MS using a discovery platform and 677 metabolites were definitively identified with relative quantitation. Using a false discovery rate approach, 77 of these metabolites were statistically correlated with EED as diagnosed by gut permeability. The authors note the positive correlation with L:M ratio of 16 metabolites, which include acylcarnitines as well as fatty acid oxidation intermediates. These metabolites are indicators of secondary carnitine deficiency and defective fatty acid oxidation, which the authors suggest may be a feature of EED, or at least of gut permeability. Carnitine, important for fatty acid shuttling into mitochondria for β-oxidation, may be obtained from animal sources in the diet or may be synthesized *de novo* from amino acids lysine and methionine. Given the corn-based diet of the cohort, one may anticipate that not just carnitine, but lysine and methionine levels may also be significantly depressed in these children. The question of whether the changed metabolites also correlate with HAZ of the children is not addressed in the paper. Additionally it may be informative to look at these metabolites in urine as a different, and more accessible, substrate.

In previous publications, the authors have reported on targeted analyses of plasma from this same cohort using a different platform, identifying correlation of specific bile acids, phosphatidylcholines and several essential amino acids with gut permeability or HAZ index (Semba et al., 2016a,b,c). Tryptophan, citrulline and ornithine, identified previously and also in other studies (Kosek et al., 2016; Guerrant et al., 2016) are shown in the current report as negatively correlating with L:M ratio, engendering confidence that these amino acids may truly represent biomarkers of EED in children. However, other metabolites identified in the previous publications on this cohort are not replicated in the current study, as acknowledged by the authors. This study highlights nicely the current limitations of using metabolomics as a tool: procedural differences between the different platforms and the choice of statistical methods influence the set of specific metabolites that is identified every time. Regardless, the study warrants further exploration of metabolites identified herein in future studies.

Poor nutrition centered on a grain-based diet is common in parts of the world where EED among children is prevalent. The deficiency of protein, and particularly animal protein, in these situations has been long recognized, but a potential role for carnitine deficiency has been proposed for the first time by this study. There is great interest in seeing if the observed association of secondary carnitine deficiency with EED receives independent confirmation using other geographically distinct populations, and ideally, with a longitudinal study that also evaluates

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2017.01.026.
* Corresponding author.
E-mail address: gr6q@virginia.edu (G. Ramakrishnan).

http://dx.doi.org/10.1016/j.ebiom.2017.02.014

the outcome. Verification using alternate methods is also essential in the quest to identify a suite of reliable biomarkers for diagnosis of EED.

Disclosure

The authors declared no conflicts of interest.

References

Denno, D.M., et al., 2014. Use of the lactulose to mannitol ratio to evaluate childhood environmental enteric dysfunction: a systematic review. Clin. Infect. Dis. 59, S213–S219.
Guerrant, R.L., et al., 2016. Biomarkers of environmental enteropathy, inflammation, stunting, and impaired growth in children in Northeast Brazil. PLoS One 11, 1–20.
Kosek, M., et al., 2013. Fecal markers of intestinal inflammation and permeability associated with the subsequent acquisition of linear growth deficits in infants. Am.J.Trop. Med. Hyg. 88, 390–396.
Kosek, M.N., et al., 2016. Plasma tryptophan and the kynurenine-tryptophan ratio are associated with the acquisition of statural growth deficits and oral vaccine underperformance in populations with environmental enteropathy. Am. J. Trop. Med. Hyg. 95, 928–937.
Naylor, C., et al., 2015. Environmental enteropathy, oral vaccine failure and growth faltering in infants in Bangladesh. EBioMedicine 2, 1759–1766.
Semba, R.D., et al., 2016a. Child stunting is associated with low circulating essential amino acids. EBioMedicine 6, 246–252.
Semba, R.D., et al., 2016b. Metabolic alterations in children with environmental enteric dysfunction. Nat. Publ. Gr.:1–9 http://dx.doi.org/10.1038/srep28009.
Semba, R.D., et al., 2016c. Environmental enteric dysfunction is associated with altered bile acid metabolism. J. Pediatr. Gastroenterol. Nutr. http://dx.doi.org/10.1097/MPG.0000000000001313.
Semba, R.D., et al., 2017. Environmental enteric dysfunction is associated with carnitine deficiency and altered fatty acid oxidation. EBioMedicine 17, 57–66.
Watanabe, K., Petri, W.A., 2016. Environmental enteropathy: elusive but significant subclinical abnormalities in developing countries. EBioMedicine 10, 25–32.