Stunting: The Need for Application of Advances in Technology to Understand a Complex Health Problem

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A R T I C L E   I N F O

Article history:
Received 8 March 2016
Accepted 8 March 2016
Available online 12 March 2016

Stunting is a complex health challenge, the causative mechanisms for which are still poorly understood. Despite concerted efforts at improving childhood nutritional and health status during the Millennium Development Goal era, the reduction in stunting in Africa particularly was a modest 10–15% with a wide variation across different countries. As such, stunting remains an intractable problem that continues to affect one-quarter of the world’s young children. Stunted children have a higher risk of mortality — stunting is responsible for 14% of childhood deaths, decreased motor and cognitive function as well as behavioral abnormalities, and impaired immunity (Weise, 2012). Long-term health consequences include shorter adult height (Victora et al., 2008), less schooling (Weise, 2012), reduced physical work capacity and low wages in adulthood (de Onis et al., 2012), increased risk of high body fat/obesity and cardiovascular disease (Victora et al., 2008), and poor perinatal outcomes in offspring born to stunted mothers (Victora et al., 2008).

It is currently understood that the main causes of stunting begin in utero and manifest by age 2–3 years, and include intrauterine growth retardation and undernutrition, often in combination with frequent infections such as diarrhea (Weise, 2012). Other predictors of stunting include suboptimal breastfeeding and complementary feeding practices, low birth weight, child neglect or negative parent/child interactions, and lower maternal education (Weise, 2012). Nutritional supplementation interventions to reduce stunting have had mixed results. Iron with folic acid during pregnancy (Nisar et al., 2016) and iron alone among children (Chwang et al., 1988), were beneficial for improving stunting; however, iron alone or with zinc during infancy had no effect on growth (Dijkhuizen et al., 2001). Even if ten evidence-based nutritional interventions are applied at 90% coverage, only a 20% reduction in stunting would be achieved (Bhutta et al., 2013).

To realize the United Nations’ Sustainable Development Goal #2 and the World Health Assembly’s target of 40% reduction in the number of stunted children under five years of age by 2025 (Weise, 2012), it is crucial to understand the pathogenesis of stunting. Human growth is regulated by the mechanistic target of rapamycin complex 1 (mTORC1), a pathway that is mediated by the availability of amino acids (Semba et al., 2016). As the amino acid requirements of young children—particularly those at high risk of stunting—are not established, and advances in metabolomics and mass spectrometry facilitate the rapid quantification of serum metabolites including amino acids, it is timely to investigate their role in the pathogenesis of stunting.

The prevalence of stunting is highest in Africa at 40% overall, with few signs of improvement among these 64 million children since 2010 (de Onis et al., 2012). Malawi has one of the highest rates of stunting, with a prevalence of 48% and 41% in rural and urban areas, respectively (USAID, 2014). In the cross-sectional study by Semba et al., published in this issue of EBioMedicine, 62% (N = 313 children aged 12–59 months) were stunted in six rural villages of southern Malawi (Semba et al., 2016). Using a targeted metabolomics approach to measure amino acids, glycerophospholipids, sphingolipids, and other metabolites, the authors found that amino acid concentrations were associated with stunting. All nine essential amino acids were significantly lower in the serum of stunted children compared to controls (HAZ > –2). Additionally, stunted children had significantly lower serum concentrations of conditionally essential amino acids (arginine, glycine, and glutamine), non-essential amino acids (asparagine, glutamate, and serine) and six sphingolipids, as well as altered serum glycerophospholipid concentrations.

Author-identified strengths of the current study include the use of LC–MS/MS methodology for quantification of serum metabolites, the community-based sample in rural Africa where stunting is prevalent, and a validated platform for quantification of serum metabolites. Additional strengths include the large sample size, and exclusion of children with diarrhea to lessen infection-related confounding factors. The major limitation is that it is a cross-sectional study and the possibility of reverse causation warrants some caution in interpretation of the results as another metabolic abnormality may cause stunting that in turn can...
lead to some form of protein loss leading to the observations. For example, a recent report indicated that undernutrition can increase the proteolytic activity of the gut microbiome (Mayneris-Perxachs et al., 2016). Semba et al.’s study provides support for larger longitudinal prospective studies to better understand the correlation between amino acids and stunting before initiating randomized controlled trials to further explore the potential causality of this association (Semba et al., 2016). Additionally, future studies regarding other potential mediators of stunting, such as vitamin D and the taxonomic and functional gene expression of the gut microbiome, must be undertaken to completely capture the causes of stunting. It is well established that vitamin D modulates immunity in addition to its role in bone homeostasis, which is also regulated by mTORC1. Several essential amino acids, including tryptophan and threonine, are involved in gastrointestinal function by acting as precursors for critical neurotransmitters such as serotonin or components of the mucus layer in the gut (respectively) (Semba et al., 2016). Low amino acid levels and their subsequent effect on linear growth metabolism including mTORC1 depression may have repercussions on the current recommendations for micronutrient and lipid supplementation that are found to be less effective than predicted. Additionally, as Semba et al. note, this study gives support to the negative impact of protein malnutrition on growth, which has been de-emphasized since the 1970s in favor of addressing micronutrient deficiencies. Elucidating the mechanistic pathways that lead to stunting through application of advances in modern technology — and this study is an important step in that direction — are critical for its prevention to improve immediate and long-term health for millions of children around the world.

Disclosure

SM is a co-inventor of the Cornell NutriPhone, a smartphone-based method of determining nutritional status at the point of care. SM is also founder of a new research institute at Cornell University - Institute for Nutritional Sciences, Global Health, and Technology (INSIGHT) - focused on application of modern technology to global health problems. SLH reports no conflicts of interest.

Acknowledgments

The authors are grateful to Professor Anura Kurpad, St. John’s Research Institute, for his review of a draft of this commentary and feedback.

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