Commentary: Mechanisms of kwashiorkor-associated immune suppression: Insights from human, mouse, and pig studies

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Introduction

Derangement in functional immunity is a characteristic of children with severe malnutrition (SM). Deaths among children with SM are principally from infections, and understanding their pathophysiology to develop effective treatment strategies is essential to improving outcomes. Several reviews have discussed the state of knowledge of SM immunology (1–3). However, differences in immune function between kwashiorkor and wasting have not been adequately documented.
We were delighted to see a review of kwashiorkor-associated immune suppression, as there are very few reports that have studied kwashiorkor-specific immunological changes, especially in clinical settings. However, we believe that the review of Michael et al. (4) on kwashiorkor-associated immune function contains several oversimplifications and extrapolations of results given the recognized heterogeneity and power limitations of existing immunological assessments in SM (5). We believe that clarity in reporting results from clinical studies (also highlighted by literature reviews cited by Michael et al.) and in how they compare to experimental models is essential to add value to the wider field of malnutrition-related immunology. Therefore, while we applaud the authors for their work, we are concerned about several aspects of their recent review for reasons we discussed in this commentary.

Discussion

Firstly, the idea that reduced protein intake leads to hypoalbuminemia, which decreases oncotic pressure leading to edema in kwashiorkor, is widely believed, but this is an oversimplification which is not supported by strong evidence. In a recent study, we found that hypoalbuminemia is associated but alone was insufficient to explain edema in kwashiorkor (6). Other factors apart from hypoalbuminemia and low protein intake must develop kwashiorkor (7), such as extracellular matrix (ECM) degradation and lymphatic damage (6). Moreover, it was previously shown that edema in children with kwashiorkor resolved even when they were treated with a protein-deficient diet (8), and despite a small increase in serum albumin concentration among children whose edema resolved or improved, serum albumin concentrations remained far below clinically recognized norms in children (6, 9). It is important to emphasize that oversimplification of kwashiorkor etiology (presented in the review text and Figure 2 but unsupported by empirical evidence) can result in ineffective treatment strategies.

Secondly, some of the immune function effects stated in the review are not borne out by the cited references. It is tempting to suggest that kwashiorkor is characterized by a “profound impaired immune function,” as the authors claim. For instance, diseases with heightened inflammation are associated with ECM degradation, and the degradation of the ECM is linked to immune function (10). However, the papers cited did not study kwashiorkor specifically. For instance, the paper by Hughes et al. (11) involved both wasting and kwashiorkor. Half of these children also had HIV, and most likely had other infections, which resulted in their hospital admission. The analysis by Hughes et al. was controlled for edema; thus, no kwashiorkor-specific estimates were presented in the paper. The table given below lists statements about kwashiorkor-associated immunological characteristics in the review by Michael et al. that are not supported by the cited references.

### Evaluation of claims regarding kwashiorkor-associated immunological changes.

| Claim                                                                 | Reference cited | What the referenced study did or observed |
|----------------------------------------------------------------------|-----------------|------------------------------------------|
| “Zambian children with kwashiorkor had normal numbers of white blood cells (WBCs), however, although the numbers of monocyte-derived DCs were reduced in their peripheral blood. The kwashiorkor-induced impairments were rescued following intervention using a protein-sufficient diet” | (11)            | Study involved children with severe malnutrition, but no kwashiorkor-specific estimates were presented in the paper. N = 57 kwashiorkor; 24 marasmus; and 39 had HIV |
| “Fas (CD95/apoptosis antigen 1), a gene that signals to initiate apoptosis, is highly expressed in neutrophils, monocytes, and lymphocytes in kwashiorkor children indicative of impaired regulation of immunity and lymphoid homeostasis” | (12)            | CD95 expression of neutrophil and lymphocyte was found higher in kwashiorkor than healthy controls without differences in monocyte CD95 gene expression. Neither apoptosis nor life-span of the cell types were assessed to support claims for differential life cycle of WBC by SM nor kwashiorkor specifically. There were no differences in CD95 expression in neutrophils, lymphocytes and monocytes between kwashiorkor and marasmus. This indicates that CD95 gene expression is generally affected by malnutrition, not specifically to kwashiorkor. |
| “Children with kwashiorkor and/or respiratory/gastrointestinal infections had increased apoptotic T cells, increased Fas (CD95) expression, and reduced levels of IL-7/IL-7 Rea and expressed inhibitory receptor-programmed death (PD-1) expression on T cells” | (13)            | The study included children with severe malnutrition, but no kwashiorkor-specific estimates were presented in the paper. N = 10 kwashiorkor; 19 marasmus |
| “Decreased numbers of B lymphocytes in kwashiorkor children with gastrointestinal or respiratory infections compared with well-nourished children having similar infections” | (14)            | The study involved children with severe malnutrition, but no kwashiorkor-specific estimates were presented in the paper. N = 3 kwashiorkor; 7 marasmus |
| “increased risk of Gram-negative bacteremia in hospitalized kwashiorkor children” | (15)            | Our study involved all children under the age of 13 years who were admitted to a hospital. No kwashiorkor-specific |

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“Studies from Bangladeshi children revealed that the kwashiorkor-associated faecal microbiota was significantly less diverse (immature) compared with that of age-matched healthy children. However, this condition was reversible, and the microbiome composition has been restored to the diverse (mature) phenotype when these kwashiorkor children were given RUTF and treated with antibiotics” (16)

The cited studies involved patients with inflammatory bowel disease. No kwashiorkor-specific estimates were presented in the paper.

“Kwashiorkor children (6 to 59 months old) were treated for 7 days with cefdinir, amoxicillin, or placebo in combination with RUTF, showed that children that received RUTF and antibiotics had accelerated weight gain, decreased mortality rates, and increased recovery rates than those who received placebo” (17)

Study involved children with severe malnutrition, but no kwashiorkor-specific estimates were presented in the paper.

“Clinical studies in children have revealed a relationship between lower seroconversion rates associated with oral vaccines and kwashiorkor” (18, 19)

The review highlighted interesting immune features in children with severe malnutrition but did not specifically describe the immune function in kwashiorkor. Hence, the reported similarities between the immune function of children with kwashiorkor and gnotobiotic pig models cannot be used to establish the face validity of the porcine model.

Kwashiorkor-specific studies on immune function are still lacking, providing an opportunity for further translational research. Rather than viewing experimental models as the “only alternative to clinical studies,” we regard insights from clinical and translational immunology studies as essential to achieve the goal of the authors of carefully selecting appropriate, evidence-based mechanistic and pre-clinical models that can support therapeutic interventions for SM.

Author Contributions

GBG wrote the initial draft. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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