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Applied nutritional investigation

Systemic inflammation, growth factors, and linear growth in the setting of infection and malnutrition

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ABSTRACT

Objectives: Deficits in weight gain and linear growth are seen frequently among children in areas where malnutrition and recurrent infections are common. Although both inflammation and malnutrition can result in growth hormone (GH) resistance, the interrelationships of infection, inflammation, and growth deficits in developing areas remain unclear. The aim of this study was to evaluate relationships between low levels of systemic inflammation, growth factors, and anthropometry in a case–control cohort of underweight and normal weight children in northern Brazil. Methods: We evaluated data from 147 children ages 6 to 24 mo evaluated in the MAL-ED (Interactions of Malnutrition and Enteric Disease) case–control study following recruitment from a nutrition clinic for impoverished families in Fortaleza, Brazil. We used nonparametric tests and linear regression to evaluate relationships between current symptoms of infections (assessed by questionnaire), systemic inflammation (assessed by high-sensitivity C-reactive protein [hsCRP]), the GH insulin-like growth factor-1 (IGF-1) axis, and measures of anthropometry. All models were adjusted for age and sex.

Results: Children with recent symptoms of diarrhea, cough, and fever (compared with those without symptoms) had higher hsCRP levels; those with recent diarrhea and fever also had lower IGF-1 and higher GH levels. Stool myeloperoxidase was positively associated with serum hsCRP. hsCRP was in turn positively associated with GH and negatively associated with IGF-1 and IGF-binding protein-3 (IGFBP-3), suggesting a state of GH resistance. After adjustment for hsCRP, IGF-1 and IGFBP-3 were positively and GH was negatively associated with Z scores for height and weight.

Conclusions: Infection and inflammation were linked to evidence of GH resistance, whereas levels of GH, IGF-1, and IGFBP-3 were associated with growth indices independent of hsCRP. These data implicate complex interrelationships between infection, nutritional status, GH axis, and linear growth in children from a developing area.

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AML participated in the study design and acquisition of the data. AF participated in the study design and acquisition of the data. AH participated in the study design and acquisition of the data. RP participated in the study design and analysis. AAL participated in the study design and acquisition of the data. RLG participated in the study design, analysis and write-up of the data. The authors have no conflicts of interest to declare.

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Introduction

Recurrent infections are associated with lower growth velocity and stunting in children in developing areas of the world [1]. This is supported by previous findings that demonstrated temporal links between slowed growth and repeated infections [2], as well as by more recent cohorts evaluated for growth related to clinically relevant diarrheal [3–5] and respiratory [6,7] infections. Enteric infections involving poor growth have been linked to subclinical infections and may exhibit both systemic inflammation and elevations in stool inflammatory markers such as myeloperoxidase, α1 antitrypsin, and neopterin without overt diarrheal symptoms [8]. The presence of systemic inflammation during infection may play a role in growth suppression, as similar linear growth deficits have been noted in other conditions with high levels of systemic inflammation, such as Crohn's disease and juvenile idiopathic arthritis, in which poor growth is associated with high levels of inflammatory markers, low levels of important growth factors such as insulin-like growth factor (IGF)-1, and poor responsiveness of the growth plate [9–12].

Preclinical models of inflammatory disease have demonstrated direct relationships between systemic inflammation, growth hormone (GH) signaling, and linear growth [13]. Higher systemic inflammation is related to GH resistance at the level of the liver as evidenced by the following:

- higher systemic levels of growth hormone [14],
- lower hepatic production of IGF-1 and IGF binding-protein-3 (IGFBP-3),
- lower systemic levels of IGF-1 and IGFBP-3, and
- slowed linear growth (gray lines in Fig. 1) [15].

Blocking systemic inflammation with antibodies against tumor necrosis factor-α reversed each of these GH signaling outcomes, suggesting direct relationships [15]. Links between infections, inflammatory markers such as C-reactive protein (CRP), and levels of IGF-1 recently have been demonstrated in a cohort of young children followed in Zimbabwe [10]. Similarly, a group of researchers in Uganda studied children presenting with severe acute malnutrition (mean weight-for-height Z scores of -4.2), reporting high levels of systemic inflammation and GH and low levels of IGF-1 [16]. However, the degree of inflammation required for suppression of GH signaling is unclear. Although major infections can involve elevations of CRP to >300 mg/L [17], more common infections have been associated with minor elevations in CRP, as tested in the more sensitive assay "high-sensitivity" CRP (hsCRP), producing levels of 15 to 30 mg/L [18,19].

Thus, the relationship between lower levels of the systemic inflammation and GH signaling in humans requires further investigation. The aim of this study was to evaluate relationships between low levels of systemic inflammation, growth factors, and anthropometry in a case–control cohort of underweight and normal weight children in northern Brazil. Our hypothesis was that even low levels of inflammation would be associated with GH resistance, including lower levels of IGF-1 and IGFBP-3 and higher levels of GH through lack of feedback. A link between inflammation and the GH–IGF-1 axis may have implications for growth faltering among children in developing areas of the world.

Methods

The present study was performed as an extension of the MAL-ED (Interactions of Malnutrition and Enteric Disease) study with an extended biomarker study, both funded by the Bill and Melinda Gates Foundation. As part

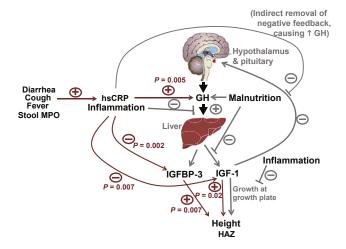


Fig. 1. Conceptual model of the effect of inflammation on regulation of the GH-IGF-1 axis. Lines in gray portray associations from preclinical studies and lines in red portray findings from this study. Stimulatory effects or positive associations are indicted (+); inhibition or inverse associations are indicated by (-) signs. Preclinical studies (gray lines) demonstrate effects of inflammation to induce GH resistance at the level of the liver, resulting in decreased expression of IGF-1 and IGFBP-3; this results in an increase in circulating GH by loss of negative feedback of IGF-1 on GH release, IGF-1 is the key mediator of the action of the GH axis on linear growth. The analysis from the present study's cohort found multiple correlations (red arrows, with P-values) consistent with these concepts. hsCRP was higher among children with symptoms of illness and positively associated with stool MPO As expected from the model, hsCRP was positively associated with GH, and negatively associated with IGF-1 and IGFBP-3. IGF-1 and IGFBP-3 were in turn positively associated with HAZ, independent of hsCRP levels. GH, growth hormone; HAZ, height-for-age Z score; hsCRP, high-sensitivity C-reactive protein; IGF, insulin-like growth factor; IGFBP, IGF binding protein; MPO, myeloperoxidase.

of this overall project, a case–control study examining biomarkers of malnutrition and intestinal infection was conducted. The present study represents an ancillary trial of this biomarkers initiative.

The MAL-ED case-control study protocol and consent forms were approved by the local institutional review board (IRB) at Universidade Federal do Ceará, the national IRB, Conselho Nacional de Ética em Pesquisa, Brasília, DF, Brazil, and the IRB at the University of Virginia, VA. Between August 2010 and September 2012, children were recruited for the case-control study at Promotion of Nutrition and Human Development located in Fortaleza, Brazil. Further details including the geographic location, population, demographic characteristics, environmental, and socioeconomic status have been described elsewhere [20]. Malnourished or "case" children were defined as having weight-for-age (WAZ) scores $<\!-2$ and matched "nonmalnourished controls" were defined as having a WAZ >-1. Children who required prolonged hospitalization or had serious health issues, such as HIV, tuberculosis, neonatal disease, kidney disease, chronic heart failure, liver disease, cystic fibrosis, congenital conditions, or enteropathy (e.g., Crohn's disease, celiac disease, ulcerative colitis, or malabsorption disease), diagnosed by a physician; or those with a parent or primary caregiver with cognitive deficits or who was <16 y of age were excluded. For mothers who were ages 16 to 17 y, permission of their guardian or the child's father was required for enrollment in the case-control study. Of 484 children screened, 82 declined or failed to meet enrollment criteria. After obtaining informed consent from the responsible parent or guardian, 402 children ages 6 to 26 mo were enrolled (201 cases and 201 controls). Of these, 321 provided fecal samples within 1 mo of enrollment and 292 provided initial blood plasma specimens. Anthropometry was assessed at study visit 1. Age and anthropometric measures were used to generate Z scores for length, weight, and weight-for-length according to the World Health Organization growth curves; height-for-age Z scores were referred to as HAZ by convention [21]. Stunting was defined as HAZ < -2.

Cases in which blood draw or stool collection were postponed for >1 mo were excluded. Additionally, for all analyses regarding interrelationships between variable categories (anthropometry, survey response, serum measures, and stool measures), only variables obtained <7 d from each other were included.

For the current analysis, cases and controls were compared for variables of interest. With the exception of differences in anthropometry (which was true by design), there were no differences between cases and controls with respect to illness symptoms, hormones, or markers of inflammation. Thus, both groups were combined into a single cohort for analysis.

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