The acute-phase protein response to infection in edematous and nonedematous protein-energy malnutrition

Marvin Reid, Asha Badaloo, Terrence Forrester, John F Morlese, William C Heird, and Farook Jahoor

ABSTRACT

Background: Immune structure and function are more compromised in edematous protein-energy malnutrition (PEM) than in nonedematous PEM. Whether the positive acute-phase protein (APP) response to infection is affected remains unknown.

Objective: We assessed whether children with edematous PEM can mount a general APP response and compared the kinetic mechanisms of the response in children with edematous PEM with those in children with nonedematous PEM.

Design: Plasma C-reactive protein, α1-acid glycoprotein, α1-antitrypsin, haptoglobin, and fibrinogen concentrations and the fractional and absolute synthesis rates of α1-antitrypsin, haptoglobin, and fibrinogen were measured in 14 children with edematous PEM, aged 11.4 ± 2 mo, and 9 children with nonedematous PEM, aged 10.1 ± 1.4 mo, at 3 times: ≈2 d after hospital admission (period 1), when they were malnourished and infected; ≈8 d after admission (period 2), when they were malnourished but free of infection; and ≈54 d after admission (period 3), when they had recovered.

Results: Children with edematous and nonedematous PEM had higher plasma concentrations of 4 of 5 APPs in period 1 than in period 3. The magnitude of the difference in concentration and in the rate of synthesis of the individual APPs was less in the children with edematous PEM than in those with nonedematous PEM. The kinetic data show that the characteristics of the APP response were different in the 2 groups.

Conclusions: These results suggest that severely malnourished children can mount only a partial APP response to the stress of infection and that the magnitude of this response is less in those with edema.

INTRODUCTION

The characteristic response to an infective stress includes increased plasma concentrations of the positive acute-phase proteins (APPs; 1, 2), which play important roles in host defense (3). Although there is general consensus that both immune structure and function are more compromised in the edematous syndromes of protein-energy malnutrition (PEM; 4), it is not known whether this includes the APP response to infection. The finding that the serum interleukin 1 (IL–1) concentration, an important mediator of the acute-phase response (5), is markedly lower in children with infection and kwashiorkor than in those with infection and marasmus or in healthy children (6) suggests that children with kwashiorkor may not be able to mount an APP response to infection. At present, it is not clear from the literature whether persons with either type of PEM can mount an APP response (6–10).

The extent and quality of the APP response are dependent on the host nutritional state and the severity of the infection (11). Severe malnutrition may affect the APP response by reducing the availability of precursors for APP synthesis or by reducing the synthesis of modulating proinflammatory factors such as IL–1 and IL–6. In a previous study of infected children with marasmus, we showed that the kinetic mechanisms used in mounting an APP response included alterations in both the rates of synthesis and the catabolism of the proteins (12). Children with kwashiorkor, however, differ from those with marasmus in having slower rates of whole-body protein breakdown, which may reduce the availability of endogenous amino acids for APP synthesis (13). Furthermore, the concentrations of the APP regulatory cytokines have been reported to be lower in children with kwashiorkor than in those with marasmus (6). Whether children with edematous PEM can mount an adequate APP response to an infective stress and what kinetic mechanisms they might use to mount such a response remain unknown.

The present study was performed in infected children with marasmic kwashiorkor or with kwashiorkor to determine whether children with edematous PEM can mount a general APP response. The purpose was to compare the kinetic mechanisms responsible for the APP response in edematous and nonedematous PEM. Data from most of the subjects with nonedematous PEM were reported previously (12) but are included here for convenience of comparison.

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SUBJECTS AND METHODS

Subjects

This study was approved by the Medical Ethics Committee of the University Hospital of the West Indies and by the Baylor Affiliates Review Board for Human Subject Research at Baylor College of Medicine. The subjects were recruited from children admitted to the Tropical Metabolism Research Unit of the University of the West Indies for the management of severe malnutrition. The eligibility criteria for recruitment into the study were a deficit in weight-for-age ≥ 20% and clinical evidence of infection. Nine children with nonedematous PEM (marasmus) and 14 children with edematous malnutrition [7 with kwashiorkor and 7 with marasmic kwashiorkor diagnosed according to the Wellcome classification (14)] were enrolled in the study, after written informed consent was obtained from their parents. Their ages were 10.1 ± 1.4 mo in those with nonedematous PEM and 11.4 ± 2.0 mo in those with edematous PEM. Their weight was measured on an electronic balance (model F150S; Sartorius, Göttingen, Germany), and their length was measured on a horizontally mounted stadiometer (Holtin Ltd, Cynmych, United Kingdom). The diagnosis of infection required one or more of the following on admission: white blood cell count > 11 × 10^9/L; temperature > 37°C or < 35.5°C; abnormal shadowing on chest X-ray; and positive blood, urine, or stool culture. In addition, diagnosis of the specific subtype of infection or infections was made by the pediatrician on the ward with the use of standard clinical criteria and independently of the study investigators.

Treatment

During hospitalization, the children were managed according to a standard treatment protocol that divided their treatment into phases. The acute resuscitative phase of treatment extended from admission until edema was resolved, infection was cleared, and appetite returned. During this resuscitative phase, the children were anorexic. Restoration of appetite was considered to have occurred when the children spontaneously consumed all food offered them. The mean duration of the resuscitative phase was ≈ 8 d. During this period, fluid and electrolyte imbalances were corrected, and infections were treated with broad-spectrum antibiotics, usually parenteral penicillin and gentamycin, plus oral metronidazole. The children were fed a resuscitative diet that was made with a commercial milk powder (61 g, Nan; Nestlé SA, Vevey, Switzerland), 36 g corn oil, and 903 g water. The energy content of the food was 2623 kJ/kg, and the macronutrient composition per kilogram of food was 7.6 g protein, 47 g lipid, and 31.5 g carbohydrate. The amount of food offered was intended to provide ≈ 417 kJ·kg⁻¹·d⁻¹ energy and ≈ 1.2 g·kg⁻¹·d⁻¹ protein (15). The children were fed with the use of a cup and spoon every 3 h throughout the day or every 2 h if the child was having problems tolerating the food.

The next phase in the clinical management of the children was the rapid catch-up growth phase. In this phase of treatment, the children were fed an energy-dense, milk-based formula that provided ≈ 462–760 kJ·kg⁻¹·d⁻¹ energy and ≈ 2–3.3 g·kg⁻¹·d⁻¹ protein until the growth rate plateaued and the weight-for-length was ≥ 90% of that expected. The children were fed with the use of a cup and spoon every 3 h throughout the day or every 2 h if the child was having problems tolerating the food.

The mean duration of the resuscitative phase was 7.6 g protein, 47 g lipid, and 31.5 g carbohydrate. The amount of food offered was intended to provide (417 kJ·kg⁻¹·d⁻¹ energy and 1.2 g·kg⁻¹·d⁻¹ protein) during each period. The first isotope infusion (period 1) was performed immediately after fluid resuscitation and as soon as the children were clinically stable as indicated by blood pressure and pulse and respiration rates; at this time, they had received the resuscitative diet for 1–2 d. Period 2 began ≈ 8 d after admission, when the children were still severely malnourished but had lost edema, had recovered appetite, and were no longer infected, as indicated by the normalization of temperature and of respiration and pulse rates and by the resolution of the clinical features of infection (e.g., cessation of diarrhea, absence of chest crepitant). At this time, the children had been receiving the resuscitative diet for ≈ 8 d. Period 3 began ≈ 54 d after admission, when the children had recovered, the catch-up growth rate had started to plateau, and weight-for-length was ≥ 90% of that expected. The resuscitative diet was begun again 3 d before this period.

Isotope-infusion and blood-sampling protocols

The isotope-infusion protocol has been described in detail previously (12). Briefly, a sterile solution of [¹³C]leucine (Cambridge Isotope Laboratories, Woburn, MA) was prepared in 9 g saline/L and infused for 8 h for measurement of the rate of synthesis of haptoglobin, α₁-antitrypsin, and fibrinogen. About 40% of the subject’s daily food intake was delivered by constant intragastric infusion during the experiment, starting 2 h before the isotope infusion began. After a 2-mL venous blood sample was drawn, the [¹³C]leucine solution was infused nasogastrically at a rate of 26 µmol·kg⁻¹·h⁻¹ for 8 h. Additional 2-mL blood samples were drawn at 1-h intervals throughout the infusion. The same isotope-infusion and blood-sampling protocols were used for the second- and third-period experiments.

Sample analysis

Blood was drawn into chilled tubes (containing Na₂EDTA and a cocktail of sodium azide, merthiolate, and soybean trypsin inhibitor) and centrifuged immediately at 1000 × g for 15 min at 5°C. An aliquot of the plasma was removed immediately for measurement of fibrinogen concentration as described below, and the remainder was stored at −70°C for later analysis.

The plasma concentrations of C-reactive protein (CRP), α₁-acid glycoprotein, haptoglobin, α₁-antitrypsin, and fibrinogen were measured by radial immunodiffusion (Human RID kits; The Binding Site, San Diego). The concentration of IL-6 was measured by enzyme-linked immunoassay (Human IL-6 Quantikine Immunoassay Kit; R&D Systems, Minneapolis).

Haptoglobin and α₁-antitrypsin were isolated from plasma by sequential immunoprecipitation with antihuman haptoglobin (Behring, Somerville, NJ) and antihuman α₁-antitrypsin (Behring) and purified by sodium dodecyl sulfate–polyacrylamide gel electrophoresis as described previously (16). A standard of the protein (Sigma Chemical...
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TABLE 1
Anthropometric characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (n = 9)</td>
<td>MK (n = 7)</td>
<td>K (n = 7)</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>10.1 ± 1.4</td>
<td>13.0 ± 3.0</td>
<td>9.9 ± 1.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.97 ± 0.22a</td>
<td>4.90 ± 0.27a</td>
<td>6.91 ± 0.44b</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>64.2 ± 1.2</td>
<td>63.1 ± 1.8</td>
<td>67.3 ± 1.7</td>
</tr>
<tr>
<td>Length-for-age (%)</td>
<td>88.5 ± 1.9</td>
<td>83.6 ± 2.7</td>
<td>92.9 ± 1.1</td>
</tr>
<tr>
<td>Weight-for-length (%)</td>
<td>54.5 ± 2.1a</td>
<td>51.6 ± 3.1a</td>
<td>76.1 ± 3.5b</td>
</tr>
</tbody>
</table>

/* Standard errors. There were no significant differences in white blood cell counts or hemoglobin or albumin concentrations between the 3 groups.

/1 Main effects of period, P < 0.005.
/2 Period-by-diagnosis interaction, P < 0.04.
/3 Main effects of diagnosis, P < 0.01.

Co, St Louis) and low-molecular-weight standards (Bio-Rad Laboratories, Richmond, CA) were also included in the gel (16). After being stained with Coomassie brilliant blue R-250 dye, the protein bands were cut out and washed several times. Fibrinogen was isolated as fibrin by thrombin precipitation, and VLDL–apolipoprotein B-100 was isolated by ultracentrifugation and isopropanol precipitation as described previously (16). The dried protein precipitates and gel bands were hydrolyzed in 6 mol HCl/L at 110 C for 12 h. The amino acids were then analyzed by using the precursor-product equation:

\[ \text{FSR} (\% / d) = \frac{\text{E}_{a} - \text{E}_{d}}{\text{E}_{a} + \text{E}_{d}} \times 100 \]

where \( \text{E}_{a} \) is the increase in the isotopic enrichment of haptoglobin, \( \text{E}_{a} \) - antitrypsin, or fibrinogen-bound leucine over 4-8 h (8 - t4) of the infusion, and \( \text{E}_{a} \) is the plateau isotopic enrichment of VLDL–apolipoprotein B-100-bound leucine. In this calculation, the plateau enrichment of VLDL–apolipoprotein B-100-bound leucine in plasma is assumed to represent the enrichment of the intrahepatic leucine pool from which the 3 APPs are synthesized (17).

The intravascular absolute synthesis rate (ASR) of each APP was estimated as the product of FSR and the intravascular mass of the protein:

\[ \text{Intravascular ASR (mg \cdot kg}^{-1} \cdot d}^{-1} = \text{Intravascular } \alpha 1 \text{-antitrypsin (or Hp or Fg) mass} \times \text{FSR} (2) \]

The intravascular mass of \( \alpha 1 \text{-antitrypsin, haptoglobin (Hp), or fibrinogen (Fg)} \) is the product of the plasma volume and the plasma concentration of the protein. The plasma volume at each experiment was based on measurements done in a comparable group of malnourished children at similar time points with the use of the dye-dilution technique described by Gibson and Evans (18).

Statistical analysis

Data are expressed as means ± SEs. The data were analyzed by repeated-measures analysis of variance with the clinical diagnosis at admission as the between-group factor and the measurements done over time (period 1 through period 3) as the repeated-measures factor. Post hoc comparisons were performed by using Tukey’s method. In these comparisons, the error terms were the root mean square error from the repeated-measures analysis of variance with its associated df. Inferential tests were considered statistically significant if \( P < 0.05 \) (two-tailed test).

The Friedman test was used to determine differences in CRP and IL-6 concentrations between periods. If the overall \( P \) value obtained from the Friedman test was < 0.05, then post hoc pairwise comparisons were done with the use of Wilcoxon’s signed-rank test and the Mann-Whitney U test. The STATA software, version 6 for WINDOWS (Stata Corporation, College Station, TX) was used for data analysis.

RESULTS

Subject characteristics

All of the children were severely malnourished at admission; those with marasmus and marasmic kwashiorkor had lower absolute weight, weight-for-age, and weight-for-length in period 1 and period 2 than did the children with kwashiorkor (Table 1). At recovery (period 3), there was no significant difference in mean weights among the groups. However, the children with marasmus and marasmic kwashiorkor still had significantly lower (\( P < 0.05 \)) weight-for-age and weight-for-length (those with marasmus only) indexes than did the children with kwashiorkor. On admission, all the children had an infection, and some had more than one identifiable source of infection (Table 2).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Marasmus (n = 9)</th>
<th>Marasmic kwashiorkor (n = 7)</th>
<th>Kwashiorkor (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/L)</td>
<td>27 ± 2</td>
<td>28 ± 3</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>85.9 ± 2.9</td>
<td>89.7 ± 5.1</td>
<td>90.6 ± 9.2</td>
</tr>
<tr>
<td>White blood cells (( \times 10^9 )/L)</td>
<td>14.5 ± 2.1</td>
<td>13.2 ± 0.5</td>
<td>12.7 ± 0.9</td>
</tr>
<tr>
<td>Type of infection (( n ))</td>
<td>Upper respiratory tract</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory tract</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Scabies</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary tract</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Otitis media</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shigellosis</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

/1 \( \bar{x} \pm SE \). There were no significant differences in white blood cell counts or hemoglobin or albumin concentrations between the 3 groups.

/2 Some children had more than one infection.
There were no significant differences in white blood cell counts or hemoglobin and albumin concentrations between the 3 groups (Table 2).

### Plasma APP concentrations

There was no significant difference in the protein concentrations and kinetics between edematous children with kwashiorkor and those with marasmic kwashiorkor. These groups were therefore combined and compared with the group of nonedematous children. In both groups, the plasma concentrations of all APPs except fibrinogen were significantly greater \((P < 0.05)\) in period 1 than in period 3, when the subjects had recovered (Table 3 and Figures 1–3). In period 2, when the signs and symptoms of infection had cleared but the subjects were still malnourished, the plasma concentrations of CRP and haptoglobin decreased to values that did not change significantly at recovery (period 3). The plasma concentrations of \(\alpha_1\)-antitrypsin, however, remained significantly higher \((P < 0.05)\) in period 2 than at recovery (period 3). In contrast, there were no significant differences in fibrinogen concentrations between the periods. In period 1, the \(\alpha_1\)-antitrypsin concentrations were significantly lower in the edematous group than in the nonedematous group.

### Synthesis rates for \(\alpha_1\)-antitrypsin, haptoglobin, and fibrinogen

The FSR of \(\alpha_1\)-antitrypsin did not differ among groups at any time. However, in both period 1 and period 2, the plasma pools of \(\alpha_1\)-antitrypsin were larger; hence, ASRs were faster (ie, the amount of protein synthesized/unit of time was greater) than in period 3 \((P < 0.05)\); Figure 1). Although the edematous subjects overall synthesized \(\alpha_1\)-antitrypsin only 69% as fast as the nonedematous subjects did in period 1, this difference was not statistically significant.

There was no significant difference in haptoglobin FSR between the groups in each period. However, there was a significant effect of period in that, when the children had recovered (period 3), the FSR of haptoglobin was 80% faster \((P < 0.05)\) than that in period 1. There was a significant period-by-group interaction for haptoglobin ASR \((P < 0.02)\). Thus, the ASR of haptoglobin in the nonedematous group was significantly faster in period 1 than in period 3 and also was faster than the ASR of the edematous group in period 1. There was no significant difference in the FSR or ASR of fibrinogen among periods in either group.

### Plasma IL-6 concentrations

The pooled data from all 23 children show that IL-6 concentrations tended to be higher in period 1 and period 2 than in period 3, but there was no significant difference in concentrations between the edematous and nonedematous groups (Table 3).
DISCUSSION

The present study was performed to compare the magnitude of the APP response to infection and the kinetic mechanisms responsible for the response in children with edematous PEM and in those with nonedematous PEM. Both groups of children had higher plasma concentrations of 4 out of 5 APPs when the children were both infected and malnourished. However, the concentrations of the individual proteins were lower in the edematous group, and the kinetic data show that both the magnitude and the mechanism of the APP response are different in the 2 groups of children. These findings suggest that severely malnourished children mount only a partial APP response to the stress of infection and that the magnitude of this response is even less in those with edema.

As others have also found (4, 19), children with edematous malnutrition had higher plasma concentrations of CRP, α1-acid glycoprotein, haptoglobin, and α1-antitrypsin when the children were both malnourished and infected than they had after recovery. Thus, children with edematous PEM can mount an APP response to infection that is similar to the response of children with nonedematous PEM (12), but the magnitude of the response is less in the children with edematous PEM. For example, the α1-antitrypsin and haptoglobin concentrations in the nonedematous children when they were infected and malnourished were ≈90% and 178% greater, respectively, than the concentrations in those same children at recovery, whereas the concentrations during the same period in the edematous children were, respectively, only 42% and 55% greater. Similarly, the magnitude of changes in synthesis rates of these 2 proteins was greater in the nonedematous group. Hence, although the edematous children mounted APP responses that were similar qualitatively to the responses of the nonedematous children, the magnitude of the response was smaller.

The hypothesis that the increase in pool size of an APP in response to stress represents an increased rate of synthesis (3, 20) is based primarily on in vitro studies showing that rat hepatic APP messenger RNA concentrations increase after burn injury (21) or endotoxin administration (22) and on in vivo measurements of fibrinogen synthesis in injured humans (23) and laboratory animals (24). However, severe malnutrition may affect the APP response by limiting the availability of amino acids and other cofactors necessary for APP synthesis. The greater plasma concentrations of α1-antitrypsin and haptoglobin observed in the nonedematous children when they were both infected and malnourished were associated with higher absolute rates of synthesis of these proteins. Furthermore, both the plasma concentrations of these proteins and their rates of synthesis were lower in period 2 after infections, but not malnutrition, had resolved. These findings suggest
that expansion of the protein pools in response to infection and contraction of the protein pools as the infection resolved were mediated by changes in the rates of synthesis of the proteins. The same was true for α₁-antitrypsin in children with edematous PEM. However, the greater plasma concentrations of haptoglobin observed in these children when they were both infected and malnourished were not associated with a higher ASR than that observed after infection had resolved. In fact, the amounts of haptoglobin synthesized per unit of time were almost identical in children in the infected and malnourished state, in those in the uninfected but malnourished state, and after recovery (Figure 2). This suggests that expansion and contraction of the haptoglobin pool in response to the presence or absence of infection in children with edematous PEM are mediated by a mechanism other than synthesis rate.

The pool size of a plasma protein reflects the balance between its rate of synthesis and its rate of catabolism or loss from the intravascular compartment. Thus, the most likely mechanism by which the haptoglobin pool in persons with edematous PEM expands in response to infection is a reduction in its rate of catabolism relative to the rate of synthesis. An adaptive mechanism whereby the availability of APPs in the severely malnourished person can be increased by a reduction in the rates of catabolism, rather than by an increase in the rates of synthesis, clearly has the advantage of conserving the limited supply of amino acids and other nutrients needed to synthesize APPs.

The weaker APP response in the edematous group was not surprising, because other aspects of host defense, relating to immune structure and function, are more compromised in children with edematous PEM than in those with nonedematous PEM (4). Although the precise reasons for this weaker APP response are not known, data from the literature suggest several possibilities. One proposed explanation for the mechanism is based on the observation that the synthesis of the leukotriene LTB₄ by whole blood is markedly impaired in children with edematous PEM (25). This impairment will result in insufficient chemoattraction of phagocytes as well as decreased cytokine production, which in turn will cause an inadequate inflammatory response (25). Indeed, the serum concentration of IL-1, a cytokine released primarily by phagocytic cells, is markedly lower in infected children with kwashiorkor than in infected children with marasmus or in healthy children (6). IL-1 elicits a wide range of systemic responses characteristic of the acute-phase response (26) and hence is believed to be the primary mediator of the acute-phase response (5). It also stimulates the synthesis of other cytokines, including IL-6, which is believed to be the primary mediator of hepatic APP synthesis (27). We, however, found no difference in plasma IL-6 concentrations between the 2 groups when the children were infected and malnourished. Other investigators have even reported greater IL-6 concentrations in children with kwashiorkor, irrespective of infection (19).

Another reason for the weaker APP response in the edematous group may be a shortage of the precursors needed for APP synthesis. In this regard, there is evidence suggesting that children with edematous PEM may have a greater shortage of endogenously derived amino acids, both from de novo synthesis and from the breakdown of body proteins. For example, Manary et al (13) showed that children with edematous PEM have slower whole-body protein-breakdown rates than do children with nonedematous PEM, and we (28) showed that children with edematous PEM, but not those with nonedematous PEM, have impaired cysteine synthesis. This latter observation suggests that children with edematous PEM may also have a shortage of the co-factors necessary for the synthesis not only of nonessential amino acids but also of APP. Finally, one cannot rule out the possibility that the severity and types of infections the 2 groups experienced may be responsible for the less intense APP response of the group with edematous PEM. We (29) and others (30) showed that both symptomatic acute and asymptomatic chronic viral infections elicit a partial and less intense APP response than do bacterial infections. Although such a possibility cannot be ruled out, the very similar types of infections of the 2 groups (Table 2) make it unlikely.

It is interesting that the plasma fibrinogen concentrations in the children with malnutrition were not significantly different between periods. Because fibrinogen’s major role is in wound healing (31), its limited availability is not likely to affect the malnourished person’s capacity to combat an infection but almost certainly will interfere with such a person’s recovery from surgery or injury. Limited availability of this APP is likely to be related to the skin excoriations that are characteristic of the edematous malnutrition syndromes as well as to the documented delay in postsurgical wound healing of malnourished patients (32).

We are grateful to the physicians and nursing staff of the Tropical Metabolism Research Unit for their care of the children and to Hyacinth Gallimore, Margaret Frazer, and Melanie Del Rosario for their excellent work and support in the conduct of the experiments and analysis of the samples.

REFERENCES


