Glutathione in kwashiorkor

Alan A Jackson

Badaloo et al (1) report on the effects of dietary supplementation of N-acetylcysteine (NAC) on the concentration and rate of synthesis of erythrocyte glutathione in children admitted to the hospital with severe edematous malnutrition. They compared the response of a group who received standard care with that of a group in whom oral NAC increased cysteine consumption by 160% during early treatment and by 65% during rapid weight gain. With supplemental NAC there was an early and more rapid recovery in both the rate of formation and the concentration of glutathione. Also, the supplemented children lost their edema more rapidly and hence recovered sooner. The presence of edema often marks impaired cellular and membrane function and indicates a severe prognosis. These observations provide important insights into the pathophysiologic processes and suggest possible new approaches to effective care.

Physicians who followed the progressive nutritional deterioration of people in the Warsaw ghetto during the Second World War noted an association of cysteine and glutathione with hunger edema (2). A clear differentiation between glutathione status in nonedematous and edematous severe childhood malnutrition (3) formed an important element in the development of the free radical theory of kwashiorkor (4, 5). This conceptual framework has been of value in emphasizing the complex interaction among macronutrients and micronutrients and in highlighting that the condition cannot be represented as a “simple” protein-energy deficiency (6). Impaired antioxidant defenses may underlie the damaged membranes and other aspects of impaired cellular function that are the tissue-level correlates of severe illness. Poor nutritional status is common in developing societies and among some groups in the developed world. The underlying causes may differ, but the fundamental pathophysiology and the understanding required for effective treatment are similar. Every fifth person in the world is malnourished to a degree, and one-half of the deaths in children <5 y of age are related to malnutrition, an estimated 14 000 each day (7). In the developed world ≤50% of persons admitted to the hospital have malnutrition of a degree sufficient to limit the effectiveness of other aspects of care (8).

Given the frequency with which the problem is seen, it might be expected that health care workers would have a general understanding of the principles of care and of the evidence by which effective interventions may be identified. With the use of straightforward low-cost approaches, the case mortality for the most severely malnourished can be reduced to <5% or 10%, even under resource-poor circumstances (6). However, a survey of major centers where severely malnourished individuals are regularly treated showed that the case mortality has remained almost unchanged over 50 y at 30–40% in many centers and as high as 50–60% in some (9). The report by Badaloo et al (1) makes the important observation that cysteine status might possibly be a limiting factor in edematous malnutrition. This carries implications for the way in which we think about the disease process, and there are 3 relevant points that deserve some reflection.

All cells contain relatively high concentrations of the tripeptide reduced glutathione, which plays a critical role in fundamental aspects of cellular regulation: for example, at the heart of cellular antioxidant defenses, in maintaining redox potential, and in calcium homeostasis. Because a low concentration of glutathione appears to be an important trigger for cellular apoptosis, maintaining an adequate status must be a high priority in cellular function. The 3 dispensable amino acids that form glutathione do not usually have to be consumed preformed in the diet and under usual circumstances should be readily available. Any limitation implies extraordinary consumption, unusual losses, or an impairment of the pathways through which the amino acids are formed or made available. The protection of critical pathways for the adequate formation of conditionally indispensable amino acids may play a more important role in maintaining health than has been appreciated.

Cysteine itself is highly reactive, and cellular concentrations of the free amino acid are maintained at low levels. The pathways leading to the formation of cysteine mature relatively late in fetal life, making it conditionally indispensable during early infancy. The availability of cofactors such as vitamin B-6 may be limiting, but the availability of precursors in the form of methionine and serine-glycine have to be considered. That additional cysteine improved glutathione status implies possible down-regulation in its formation but does not exclude increased consumption as part of the stresses experienced by the malnourished individual (5).

Does providing NAC as a supplement make any clinical difference? The authors identify a clear benefit with more rapid loss of edema. If correct this could be of considerable importance, but this is a small study. Assessing the amount and rate of loss of edema is at best crude and is notoriously difficult to do with any precision. Therefore, the present observations should be followed up with carefully structured intervention studies in larger groups of individuals, with close attention given to the rate of progress and the frequency of observations.

It is important that the relative benefit and possible risk of any dietary supplement be clarified in properly structured trials. In the

1 From the Institute of Human Nutrition, University of Southampton, Southampton General Hospital, United Kingdom.
2 Reprints not available. Address correspondence to AA Jackson, Institute of Human Nutrition, University of Southampton (MP 113), Southampton General Hospital, Tremena Road, Southampton SO16 6YD, United Kingdom. E-mail: aaj@soton.ac.uk.
case of severe malnutrition, there were many instances in the past in which enthusiastic correction of abnormal laboratory tests led to increased mortality. The most obvious example is the increased mortality that is seen when oral iron supplements are given to treat mild-to-moderate anemia in severe malnutrition (6). Similar experience comes from the aggressive use of higher-protein diets at an early stage of treatment or in sick individuals (10). Successful management of severe malnutrition recognizes that survival often reflects effective reductive adaptation (6). Hence, the order in which the different aspects of a complex condition are treated can be critical to the outcome: resuscitate, repair, replenish. As a medical emergency, immediate resuscitation with attention to infection, hypothermia, hypoglycemia, fluid and electrolyte disturbances, and cardiovascular stability takes precedence. Cellular function must be restored before the body is required to cope with the demands of net tissue deposition, and this may be absolutely dependent on the effective correction of specific micronutrient deficiencies (10). Net tissue deposition—repletion—is relatively lower on the list of priorities. Abnormal anthropometry is one of the main criteria used to identify individuals in need of treatment, and hence replenishing the tissue that has been lost appears to be the most obvious problem that needs correction, but it has the lowest priority for early aggressive attention. Recommendations for treating severe malnutrition reflect a recognition that in the face of impaired cellular function the ability to handle dietary protein may be impaired.

One important aspect of cellular competence is the ability to achieve adequate synthesis of dispensable amino acids, such as cysteine. There is clearly a potential benefit in providing extra cysteine in the diet if the body’s ability to form a sufficient quantity is impaired. However, if cysteine formation has been down-regulated, there is a possible disadvantage. Free cysteine is normally held at a low concentration in cells, and glutathione acts as an effective storage form. Excess cysteine increases the drive for glutathione formation, which can draw nitrogen from other critical functions, such as protein synthesis (11). If limited availability of cysteine in edematous malnutrition is of functional importance, as suggested by Badaloo et al (1), we will need to determine whether the preferred approach is to supply supplemental cysteine, to limit the unusual demands or losses of the amino acid, or to improve the body’s capability of making adequate amounts for itself.

REFERENCES