A comparison of the pathogenesis of protein-energy malnutrition in Uganda and The Gambia

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Summary

The pattern of growth, biochemical and endocrine development, dietary intake and disease patterns of rural children in Uganda and The Gambia have been monitored during the first three years of life in order to gain a more complete understanding of the reasons why in Uganda kwashiorkor predominates, whereas in The Gambia it is marasmus. Evidence is produced which supports the view that the hormonal balance, particularly cortisol and insulin status, can have a profound influence on which organs of the body are preferentially affected by malnutrition and hence on the type of protein-energy malnutrition which is likely to emerge. There were, however, also important differences in protein and energy intake between the two countries.

Introduction

The term protein-energy malnutrition has been coined to describe a spectrum of pathological conditions ranging from kwashiorkor to marasmus. The cardinal feature of kwashiorkor is the presence of oedema but the degree of body wasting can vary greatly. The main biochemical feature is a very low plasma albumin concentration.

In marasmus there is no oedema but the child is extremely emaciated. In cases of marasmus albumin concentration is not so reduced, indeed it may be quite normal.

Protein-energy malnutrition implies a well established and relatively simple aetiology but we now know that this is far from the truth. It is now generally accepted that many factors other than just a deficiency in dietary protein and energy are involved and perhaps it is more realistic to look upon PEM as an environmental disease; as the environment varies so do the details of the malnutrition which develops.

The textbook explanation for the differences between kwashiorkor and marasmus is that the former arises from the ingestion of a diet rich in energy but poor in protein, whereas the latter is due to an inadequate intake of dietary energy in what otherwise could be a balanced diet. These ideas have been reviewed by McCANCE & WIDDOWSON (1968).

GOPALAN (1968) was one of the first to point out that this explanation was by no means always adequate and he stated quite categorically that in India there was no evidence that either the protein-energy ratios or total food intake had differed in those children who ultimately became clinical cases of kwashiorkor or marasmus. Similar conclusions have since been reported by other nutritional scientists (ARROYAVE, 1975; SCRIMSHAW, 1975; WATERLOW, 1975).

In an attempt to provide an alternative explanation for the difference between kwashiorkor and marasmus, GOPALAN (1968) introduced the term dysadaptation. He postulated that kwashiorkor was essentially a failure of adaptation. He suggested that the biochemical mechanisms which are usually invoked to protect tissues like the liver at the expense of less essential muscle during energy deficit might sometimes fail to operate and that when this occurred the child became prone to kwashiorkor rather than marasmus.

Various biochemical hypotheses (ARROYAVE, 1969; WHITEHEAD, 1971; RAO, 1974) have been produced suggesting the probable nature of this process of dysadaptation and the essence of all these ideas is similar. It has been generally assumed that when muscle wastes under the influence of cortisol it provides the liver with a supply of amino-acids not only for gluconeogenesis but also for protein synthesis. This would reduce the tendency to hypoalbuminaemia and oedema and to hypo-B-lipoproteinaemia and a fatty liver. Should this mechanism fail to be invoked—if, for example, plasma cortisol remains low in concentration and insulin concentration becomes elevated—liver would not be so protected and it is under these circumstances that the child might get kwashiorkor rather than marasmus.

There has, however, been little experimental data presented to support these metabolic explanations and one of the purposes of the work now described was to see how far these could be substantiated.

Basis of the methodology

A major development in our investigative approach came after we had recognized that we were unlikely to obtain the sort of data we needed by confining our studies to severely malnourished children in hospital. The basis of our clinical and biochemical studies thus switched from the ward to children living in their own homes. We
began examining children who were potentially "at risk" regularly during the first three years of their lives. Serial monthly measurements followed changes in the weight and height, plasma albumin, amino-acid patterns, cortisol, insulin and growth hormone concentrations, dietary intake, patterns of infection and alterations in the social circumstances of the family. The first rural community investigated was near Namulonge, about 20 km from Kampala, Uganda, where the predominant form of PEM is kwashiorkor, and this has been followed by a similar study in the region around Keneba, The Gambia, where marasmus is more frequently found.

Epidemiologically orientated studies of this type usually only suggest cause and effect relationships, rarely providing the degree of biological proof necessary to establish a hypothesis. Thus our human investigations have had to be carried out in parallel with animal studies in Cambridge designed to confirm specific points.

Results and discussion

The effect of cortisol on plasma albumin concentrations in malnourished rats

It is convenient to discuss the results of one such animal study at this stage. It was clearly necessary to determine experimentally whether, in animals fed a low protein diet, a change in hormonal balance, particularly a rise in plasma cortisol really could alter the relative concentrations of free amino-acids in favour of the liver and lead to improved plasma albumin concentrations.

Initially it had been demonstrated (Lunn, Whitehead & Baker, 1976) that when low protein diets were fed to weanling rats in amounts sufficient to cause a reduction in growth but no actual loss of weight the concentrations of all essential amino-acids except lysine and threonine were reduced much more in the liver than in muscle. This was associated with a drop in plasma albumin concentration.

The administration of cortisol to such animals, however completely reversed this distribution (Lunn, Whitehead, Baker & Austin, 1976). The free amino-acid content of muscle now exhibited an overall decrease in concentration, whilst that of the liver increased. Furthermore, this resulted not only in an increase in liver protein but also a highly significant rise in plasma albumin concentration from 2.57 to 4.72 g/dl.

These changes occurred without there being any differences in food intake and show how the hormonal pattern on to which the protein deficiency is superimposed can influence markedly the metabolic response to malnutrition and in turn also the probable final form of the PEM. This finding was of course only of relevance if a similar difference in hormonal status could be shown to occur between the children of Uganda and The Gambia.

The pattern of growth in Uganda compared with that in The Gambia

The general pattern of growth of the Ugandan and Gambian children is shown in Figs. 1-4. Fig. 1 illustrates the difference in weight at different ages relative to the modified Boston standards of Jelliffe (1966). Clearly, during the first year weight gain is much more severely retarded in The Gambia than in Uganda. Fig. 2 shows similar differences in growth in height. Fig. 3 and Fig. 4 demonstrate that in Uganda the deposition of subcutaneous fat and the growth of muscle were again much less severely inhibited. On the other hand, throughout the period of study the average child in Uganda had a significantly lower plasma albumin concentration (Fig. 5) than his counterpart in The Gambia, and this was particularly marked around 18 to 24 months when in Uganda there is the greatest incidence of kwashiorkor.

These differences demonstrate that within these two communities subclinical differences started to appear at an early age and were of a type likely to pre-empt the sort of severe malnutrition which might emerge in the second and third years of life. In other words, the final clinical form of the PEM in the two countries was not decided late in the pathogenesis of the protein-energy malnutrition by some acute factor but was probably the product of long term differences in malfunction.

Hormonal changes in the two countries

Were these growth patterns and serum albumin concentrations associated with the sort of differences in hormonal balance about which there has been speculation? Fig. 6 illustrates how plasma cortisol concentration varied with age in the two communities and Fig. 7 shows the corresponding plasma insulin values. In The Gambia it is quite apparent that in the second year of life mean cortisol concentrations were higher than we had previously observed in Uganda (Lunn, Whitehead, Baker & Hay, 1973). At the same time, plasma insulin concentrations became significantly lower.

Thus there was evidence supporting the concept that the two major types of PEM might emerge from a different hormonal background, but what was the reason for these hormonal differences?

At this stage one can only speculate; there are probably various reasons. One of the most common circumstances in which high plasma cortisol concentrations are encountered is during stress associated with certain infections. In the following paper Cole (1977) has analysed the effects of infection on growth in the two village settings and has shown that, in general, infection had more effect in The Gambia than in Uganda. This was particularly the case with gastro-enteritis, and the severe dietary energy deficit and tendency towards hypoglycaemia arising from the diarrhea and vomiting would be an added stimulus for cortisol concentrations to increase. Rao (1974) has suggested from her work in India that kwashiorkor could result from a failure of the adrenals to respond appropriately to such stress. This was said to be because of the tendency for children in hospital with kwashiorkor to have rather lower plasma cortisol concentrations than those with marasmus. The Ugandan serial observations provided no support for this view, however. When malnourished Ugandan children, even those with kwashiorkor, became infected plasma cortisol levels did become elevated, but for most of the time normal or rather low concentrations predominated.

The reason for the differences in plasma insulin concentrations in The Gambia is also not completely understood, but again it is presumably partially due to the different patterns of infection. There is always a tendency for insulin and cortisol concentrations to respond in a reciprocal manner (Lunn et al., 1973).

Recent results are suggesting that the relation between infection and hormonal status in malnutrition might be more complex. We are collaborating with Dr. Newton and Dr. Crompton of the Molteno Institute, Cambridge, in a study of the effect of infection on the development of experimental protein-energy malnutrition in young rats. It is becoming apparent that different types of infection may have different hormonal consequences. Hookworm, for example, is associated with a lowering
of cortisol concentrations rather than an elevation; plasma albumin concentrations also drop more quickly. Worm infestations are much more common in Uganda than in The Gambia and this could be another reason for the tendency to higher insulin and lower cortisol levels in Uganda during the second year of life.

Fig. 1. Growth in weight of Ugandan and Gambian children relative to the international standard (JELLIFFE, 1966).

Fig. 2. Growth in length of Ugandan and Gambian children relative to the international standard (JELLIFFE, 1966).

Fig. 3. Triceps skin-fold of Ugandan and Gambian children. Standard is that of JELLIFFE (1966).

Fig. 4. Mid-upper-arm muscle circumference of Ugandan and Gambian children. Standard is that of JELLIFFE (1966).
Fig. 5. Plasma albumin concentrations in Ugandan and Gambian village children at different ages.

Fig. 6. Plasma cortisol concentrations in Ugandan and Gambian village children at different ages.

Fig. 7. Plasma insulin concentrations in Ugandan and Gambian village children at different ages.

Fig. 8. Plasma alanine concentrations in Ugandan and Gambian village children at different ages.
ever, the fact that a movement of amino-acids from muscle to liver and a consequent high level of gluconeogenesis is occurring to a greater extent in the Gambian children than in the Ugandan was indicated by differences in their plasma alanine concentrations (Fig. 8). Alanine is the major substrate for hepatic gluconeogenesis and uptake of alanine for this purpose is associated with low plasma alanine levels, which is exactly what we found in The Gambia. If there is a greater availability of other amino-acids, as there was in the rats, this could explain why the Gambian children could maintain their plasma albumin levels in spite of their dietary deficiencies.

Dietary differences in the two communities

Although children did thus differ in a manner which supports the metabolic explanation, does this necessarily mean that a dietary contribution to the difference between kwashiorkor and marasmus can be ruled out completely? To answer this we must ask two main questions: was there any difference in the protein content of the diets in the two communities, and did they eat different amounts of food?

Protein intake

When the mean protein:energy ratios in the diets of the two communities were compared they were very similar to those published from other parts of the world. After converting the largely vegetable protein content of the diets to their milk protein equivalents using W10/Fao (1973) factors, and after allowing for unavailable carbohydrate, the mean P:E ratio (%) was 8.15 in Uganda and 8.45 in The Gambia. These values are very similar and would seem to indicate that protein had little to do with the appearance of different forms of PEM in the two countries.

However, a more detailed analysis of the data revealed that by averaging the results in this way the real situation was masked. There were in fact dramatic differences between the protein concentrations of the diets in the two village communities. A different analysis of the results is given in Fig. 9. Because of their non-normal distribution, daily dietary P:E ratios (%) have been expressed in percentile form. Two facts are apparent: whilst there is little difference in 50th centile values there is a much greater variation in P:E ratios in Uganda, secondly there is a marked trend towards a greater proportion of low P:E ratios in Uganda in the second and third years of life. In The Gambia at these ages the situation was actually improving.

One shortcoming of the above comparison is that the Ugandan data are based on 24-hour recall information, whereas that in The Gambia is on weighed intakes. However, Rutishauser (1973) has established that her recall system provided data which fitted closely with nutrient intakes obtained by chemical analysis of duplicate meals collected from the same children.

It could be surmised that a Ugandan child who received a low P:E ratio diet one day might be given a high one the next and thus a poor diet would be balanced by a good one. The fact that this was not so is shown in Fig. 10. This data averages the P:E ratios in the diets of different children during the second two years of life and demonstrates that some children persistently received food from the low end of the distribution range. Those clinic numbers marked with an asterisk are children who eventually merited particular clinical attention.

Food intake

Thus it did seem that the Ugandan child who was at risk to kwashiorkor had been receiving a diet low in protein, but were there any differences in the total amount of food eaten by the children of the two countries? To answer this question we must look at the situation before one year of age separately from that during years two and three.

A comparison of available energy intakes is summarized in Fig. 11, which shows that during the first year of life energy intake is substantially lower in The Gambia than in Uganda and the slower rates of growth found are no doubt partly the result of this deficit.

There are two main reasons for this difference. Although in both countries breast feeding is almost universally practised and continues well into the second year of life, breast milk output is somewhat lower in The Gambia. The mean intake during our study periods before six months of age was 660 ml in Uganda and 500 ml in The Gambia. The Gambian mothers are clearly conscious of this shortfall and introduce supplementary feeding at an earlier stage than in Uganda.

The supplement fed to the children in The Gambia was nutritionally inadequate, being a thin gruel. At four to six months the 50th centile value for available energy concentration in the gruel was only 0.38 kcal/g food and only after 18 months of age did this value rise above 1 kcal/g. In contrast, in Uganda the dietary supplements, when given, had a much higher energy concentration, 0.90 kcal/g food. Thus initially the differences in total energy intake followed the expected pattern; the potential marasmic child was receiving less food than the kwashiorkor case.

On the other hand, in the second and third years of life the over-all energy intake in the two groups of children was of the same order of magnitude, although much less than the WHO/Fao (1973) allowance. However, in interpreting these data it must be remembered that by one year of age the better infant feeding and lower morbidity in Uganda had resulted in a bigger child with, presumably, a greater number of cells to maintain. To some extent it could be argued that a Gambian child who has been lucky enough to survive will be better protected against the worst effects of this energy deficit in the second and third years of life by being small.

Some idea of this protective effect can be obtained by analysing energy intakes relative to body-weight and the results are summarized in Fig. 12. Clearly during the second two years of life, when kwashiorkor becomes the predominant form of PEM in Uganda, the children were, for their size, suffering a much greater degree of dietary deficit. This is true for protein as well as energy intake.

The possibility that kwashiorkor is more frequently encountered in taller children was first suggested from Jamaica by Garrow & Price (1967) and has since been observed by others. Within The Gambia, children who eventually present with kwashiorkor are both taller and older than those who present with marasmus—78 cm and 2:3 years in the former group and 72 cm and 1:6 years in the latter. Again, it is not unreasonable to suppose that part of the problem for the kwashiorkor cases was that their growth had proceeded more normally during early life and thus, like the Ugandan children, they had a greater cell mass to maintain during the dietary inadequacies they must have encountered in the second and third year of life. Naismith (1973), from an analysis of his experiences in Nigeria, has also suggested
Fig. 9. Protein:energy ratios (%) in the diets of Ugandan and Gambian village children expressed as the 50th-3rd per cent. An allowance has been made for unavailable carbohydrate in the energy component. The protein value is the egg/milk equivalent.

Fig. 10. Average protein:energy ratios (%) in the diets of individual Ugandan village children during the second and third years of life. The clinic numbers marked with an asterisk are those who ultimately showed sub-clinical signs of malnutrition.

Fig. 11. Dietary energy intakes at different ages of Ugandan and Gambian children.

Fig. 12. Dietary energy intakes of Ugandan and Gambian children expressed on a body-weight basis.

that children who get kwashiorkor in the second and third year of life have been subjected to even more energy deficiency than those who present with marasmus. At the moment we are unable to explain the over-all significance of these findings, but they certainly merit further investigation.

Conclusion

There is no suggestion that the comparative conclusions we have been able to reach in any way explain the world distribution of the two types of protein-energy malnutrition but the general principles may be relevant. There are obviously many factors other than just dietary energy or protein deficiency conspiring against the children in countries like Uganda and The Gambia and the combination of these can greatly influence the form of PEM which emerges.
References


