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Plasma Cortisol Levels in Protein-calorie Malnutrition

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The two clinical syndromes of protein-calorie malnutrition—kwashiorkor and marasmus, have been widely studied. Striking differences have been observed between kwashiorkor and marasmus, both with respect to the clinical picture and the biochemical profile. One such difference is the exaggerated hyperglycaemic response of the marasmic infant to epinephrine in contrast to the poor response of the child with kwashiorkor (Rao, 1965). The role of the adrenal cortex in determining the full response to epinephrine has been demonstrated by Shafrir and Steinberg (1960). It is possible that some other differences between kwashiorkor and marasmus may also be ascribed to variations in the adrenocortical activity in these two conditions. Indirect evidence for this has been obtained in preliminary studies by the authors, where the development of fatty livers in monkeys maintained on protein-free diets has been appreciably delayed by the simultaneous administration of hydrocortisone.

Available data regarding adrenocortical function in protein-calorie malnutrition are conflicting. Ramachandran, Venkatachalam, and Gopalan (1956) observed lowered urinary excretion of 17-ketosteroids in kwashiorkor. Lurie and Jackson (1962) concluded, on the basis of urinary excretion of 17-hydroxycorticosteroids, that adrenocortical function was not impaired in kwashiorkor; they considered that estimation of urinary 17-ketosteroids was a poor assessment of adrenal function. Plasma cortisol concentration has been claimed to be a better index of adrenocortical function (Bayliss, 1955). In this paper, the results of an investigation of plasma cortisol levels in kwashiorkor and marasmus are presented.

Subjects and Methods

Studies were made on 22 children suffering from kwashiorkor and 8 suffering from marasmus. Their clinical picture and serum albumin levels were similar to those reported earlier (Srikantia, Jacob, and Reddy, 1964). All the children were admitted to hospital, and fasting blood samples were obtained immediately on admission, for estimation of plasma cortisol levels (Mattingly, 1962). To some of these children, 125 μg. of β^{1-24} corticotrophin (Synacthen) was administered intramuscularly, and blood was again obtained 30 minutes later.

The children were then rehabilitated with a diet providing 4 g. protein and 200 cal./kg. body weight daily. The tests were repeated 4 to 5 weeks later, when clinical and biochemical improvement was obvious.

Studies were also made on 12 apparently normal children belonging to the same age-group and the same socio-economic status.

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Results

Mean fasting plasma cortisol levels. *In normal children* the mean fasting level was $19 \cdot 2 \pm 2 \cdot 63$ μg./100 ml. *In malnourished children*, on admission, the mean level was found to be significantly raised in both kwashiorkor ($p < 0 \cdot 01$) and in marasmus ($p < 0 \cdot 001$). The level in marasmus was also significantly higher than that in kwashiorkor ($p < 0 \cdot 001$) (Table).

After clinical recovery, the mean fasting levels in both kwashiorkor and marasmus were significantly lower than they had been at the time of admission, and were not significantly different from the values obtained in the normal children.

Plasma cortisol levels 30 minutes after injections of Synacthen. *In the normal children* the mean level was $48 \cdot 7 \pm 4 \cdot 06$ μg./100 ml., a mean rise of $29 \cdot 5$.

In the marasmic children at the time of admission, the mean level was very high ($70 \cdot 8$ μg./100 ml.), but the *increase* ($39 \cdot 0$ μg./100 ml.) over the fasting level, though somewhat greater than the rise in the normal children, was not statistically significant ($p > 0 \cdot 05$). After nutritional rehabilitation, the mean level following Synacthen was $52 \cdot 5$ μg./100 ml., and the rise over the fasting level ($37 \cdot 7$ μg./100 ml.) was not different from that found in the normal group.

In the children with kwashiorkor two types of response to Synacthen were obtained. 7 of them

TABLE

Plasma Cortisol Levels in Protein-calorie Malnutrition (μg./100 ml.)

	On Admisson		After Rehabilitation	
	Initial	30 min. After Synacthen	Initial	30 min. After Synacthen
Normals	19·2±2·63 (12)	48·7±4·06 (9)	—	—
Marasmus	31·8±5·34 (8)	70·8±10·25 (7)	14·8±3·76 (6)	52·5±8·87 (5)
Kwashiorkor				
(a) With wasting and oedema		57·6±6·91 (7)		41·4±1·19 (4)
(b) Minimal wasting and oedema	24·9±1·95 (22)	38·4 (4)	17·0±2·20 (11)	49·7 (2)

Figures in brackets refer to the number of subjects

had marked muscle wasting and oedema, and conformed to the clinical type generally designated 'marasmic kwashiorkor': in these, the mean cortisol level after administration of Synacthen was 57·6±6·91 μg./100 ml., a response (32·7 μg./100 ml.) not significantly different from that observed either in normal or marasmic children. After rehabilitation, this value was 41·4 μg./100 ml., the response to stimulation (24·4 μg./100 ml.) being not significantly different from that observed at the time of admission. In the remaining 4 patients, muscle wasting and loss of subcutaneous tissue were minimal. In these 4, before recovery, a low response to Synacthen was observed, the increase from the basal levels being 10·0, 5·6, 14·0, and 3·8 μg./100 ml., respectively. In the first 2, who were retested after nutritional rehabilitation, the increase after Synacthen was 34·2 and 14·2 μg./100 ml., respectively.

Discussion

In cases of protein-calorie malnutrition investigated in this study, irrespective of the clinical picture, plasma cortisol levels appear to be raised. Alleyne and Young (1966) have also observed raised plasma cortisol levels in malnourished children with oedema. The results of this study bring out, additionally, the fact that in marasmus the plasma cortisol levels are raised to a significantly greater extent than in kwashiorkor. Within 4–5 weeks of nutritional rehabilitation, the levels came down in all children to values not different from the normals, suggesting thereby an easy reversibility of the underlying functional alteration.

While plasma cortisol concentration indicates the state of adrenal activity at any particular point of time, the reserve function of the gland can be tested by its response to corticotrophin, and synthetic corticotrophin has been found to be reliable for this purpose (Wood *et al.*, 1965). In this study, a synthetic corticotrophin—Synacthen, was employed. Our observations show that, given the same stimulus, the response of children suffering from marasmus and marasmic kwashiorkor was similar to that of normal children. While the increase over the baseline cortisol levels was of similar magnitude in all these children, in marasmus the absolute levels attained after Synacthen administration were very high. Castellanos and Arroyave (1961) observed that, though the urinary 17-hydroxycorticosteroid excretion was initially high in marasmus, this could not be increased any further by stimulation with ACTH, and they speculated that an already hyperactive adrenal gland might not be capable of further stimulation. In contrast, our results show that on stimulation the gland is in fact capable of releasing much greater quantities of the hormone. Najjar and Bitar (1967) have also observed a several-fold increase in urinary 17-hydroxycorticosteroid following stimulation with ACTH.

An interesting observation in this study is the poor response of the four cases of kwashiorkor to β^{1-24} corticotrophin, despite their fasting plasma cortisol levels being high. These cases differed from the cases of 'marasmic kwashiorkor' in exhibiting only a minimal degree of muscle wasting and loss of subcutaneous tissue. This would suggest that though these children are able to maintain their adrenocortical function at satisfactory levels under resting conditions, they are unable to respond to an acute stimulus as well as the normal children or the children with marasmus and marasmic kwashiorkor. This observation runs parallel to an earlier one from these laboratories, where it was found that though the fasting blood sugar

levels were normal in kwashiorkor, the glycaemic response to epinephrine was poor (Rao, 1965).

Recent studies indicate that in population groups susceptible to protein-calorie malnutrition, the diets of children who develop kwashiorkor are not strikingly different from those who develop marasmus, either in their quality or in their protein-calorie ratio (Gopalan, 1967). Moreover, in children subsisting on such diets, there are transitions from the marasmic to the kwashiorkor state. This suggests, contrary to earlier belief, that kwashiorkor and marasmus are not two separate conditions, but two facets of the same, possibly determined by the nature of host adaptation response. As part of the adaptation to stress of protein-calorie deficiency, there may be a hyperactivity of the adrenal cortex leading to muscle wasting, and in extreme cases, marasmus. Should this adaptation process break down, the child may develop oedema and yet present evidence of severe muscle wasting (marasmic kwashiorkor). On the other hand, where the adrenocortical reserve is below par signs of kwashiorkor may appear before significant degrees of muscle wasting have occurred (classical kwashiorkor).

The present observations support this supposition. However, their precise significance cannot be fully interpreted until further information regarding the metabolism of cortisol in protein-calorie malnutrition is also available.

Summary

The fasting plasma corticol levels and their response to β^{1-24} corticotrophin (Synacthen) were investigated in children suffering from kwashiorkor and marasmus. The fasting plasma cortisol levels were raised in both groups and came down to normal levels after therapy. The response to β^{1-24} corticotrophin was of normal order in marasmus. In kwashiorkor, a dual pattern was observed, depending on the degree of muscle wasting in the child. The possible role of the adrenal cortex in the development of the various clinical forms of protein-calorie malnutrition is discussed.

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