



PROSTAGLANDIN E₂ IS RAISED IN KWASHIORKOR

J E Iputo, A M Sammon, G Tindimwebwa

Objective. Infection is a common occurrence in children with kwashiorkor. It has been suggested that infection in kwashiorkor results from immune depression, and that the immune depression of kwashiorkor is caused by a diet-associated elevation of prostaglandin E₂ (PGE₂). The purpose of this study was to determine whether levels of PGE₂ are abnormal in children with kwashiorkor.

Setting and subjects. Plasma PGE₂ and plasma proteins were measured in children admitted with oedematous kwashiorkor, and compared with PGE₂ in children with cerebral palsy.

Results. Plasma PGE₂ was higher in children with kwashiorkor than in control children (7.25 ± 3.5 v. 3.51 ± 1.59 , $P < 0.01$). Within the kwashiorkor study group there was a significant negative correlation between log-transformed serum PGE₂ and total plasma protein ($r = -0.59$, $P < 0.001$), plasma albumin ($r = -0.63$, $P < 0.001$), weight-for-age ($r = -0.37$, $P < 0.05$), and height-for-age ($r = -0.37$, $P < 0.05$). The difference in mean values of PGE₂ in children with kwashiorkor who recovered from the illness and those who died was not significant (7.1 ± 2.6 v. 9.1 ± 4.8 , $P = 0.36$).

Conclusion. Significantly higher PGE₂ levels in children with kwashiorkor provide adequate reason for the depression of immune function known to occur in these children. Elevated PGE₂ levels may also be implicated in other components of the illness.

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Childhood protein-energy malnutrition (PEM) is a major public health problem in underdeveloped Third-World communities. In rural communities in South Africa, up to two-thirds of children in the under-5 age group are undernourished.¹ The most common type of PEM is the underweight-for-age, comprising more than 80% of all PEM cases. More severe forms of PEM — marasmus and kwashiorkor — though less prevalent than the underweight, still present a major clinical

problem. Patients with a primary diagnosis of PEM occupy up to 10% of beds in the children's wards in rural South Africa.

Childhood PEM is a social illness associated with poverty, infection, hunger and deprivation. In Asia and Latin America, where standards of living have substantially improved over the last two decades, the incidence of childhood PEM has dropped significantly. But in Africa where development has at best stagnated, the incidence of childhood PEM has remained high.

The epidemiological association between PEM and poverty and deprivation is universally accepted. The pathophysiology of the oedematous variant of childhood PEM, kwashiorkor, is not clear.

Overwhelming infection is often a terminal event, with a proportion of severely ill children dying within the first 2 weeks of treatment. At least part of the reason for this is immune incompetence, a consistent feature of late-stage disease. It has been suggested that this immune suppression is mediated by excess prostaglandin E₂ (PGE₂).² The fatty acid content of maize is predominantly linoleic acid, and in maize meal much of this may be in the unconjugated form, a precursor of PGE₂.³ A lack of other fatty acids and of riboflavin in the diet strongly favour the overproduction of PGE₂, which is known to be an immune suppressor, principally of cell-mediated immune response. The purpose of this study is to investigate the relevance of the PGE₂ hypothesis in our environment. This study investigates PGE₂ levels in children admitted to hospital with kwashiorkor, and in controls.

SETTING AND SUBJECTS

The study was carried out in Umtata General Hospital, South Africa, and was approved by the ethical committee of the University of Transkei. The study was carried out in August 2000. Children admitted to the nutrition ward with kwashiorkor were recruited into the study on the day of admission. The criteria for admission to the ward are such that only children with morbid protein-energy malnutrition (those who satisfy the Wellcome Working Party definition for kwashiorkor, marasmus or marasmic kwashiorkor⁴) are admitted. The nutritionally normal subjects were selected from children with cerebral palsy attending the paediatric neurology clinic at the hospital. They were systematically sampled with a random start. All clinical details concerning nutritional history, past illnesses (especially diarrhoea), drug history, weight, and signs of malnutrition including oedema, hair and skin changes, were recorded. Children with concurrent illnesses such as pneumonia, diarrhoea and tuberculosis, or who had these illnesses within the past week were excluded from the study. Children who had used non-steroidal anti-inflammatory agents in the past month were excluded from the study. Informed consent was obtained from the parents or guardians of the children.



Subjects were weighed using the Camden Medical Supplies hanging balance (Cambridge, Mass.), which measures in grams and has a known error of 100 g. Weight was expressed as a percentage of the expected weight-for-age and sex, based on the National Centre for Health Statistics (NCHS) standards, with the standard weight being equal to the tenth percentile NCHS value.⁵

Blood samples from each subject were collected in tubes containing EDTA. This was done at the time of recruitment into the study — for hospitalised patients this meant the first day of admission. The blood was centrifuged immediately after collection. The plasma was rapidly frozen to -30°C . Analysis of the plasma samples was carried out within 6 days of sample collection. Plasma protein and plasma albumin were determined, in duplicate, using standard automated procedures. The inter-assay variation was less than 1% for both plasma protein and plasma albumin assays.

PGE2 was measured, in duplicate, using the Amersham-Biotrak PGE2 radio-immunoassay system (Amersham Biosciences, Freiburg, Germany) with magnetic separation. The assay is based on the conversion of PGE2 to the methyl oximate derivative by methoxyamine hydrochloride. The assay then utilises the competition between unlabelled methyl oximated PGE2 and a fixed quantity of ^{125}I -labelled PGE2. The sensitivity of the assay, defined as the amount of PGE2 needed to reduce the zero-dose binding by two standard deviations, is 1.0 pg/ml. The coefficient of variation between duplicate sample values was 4.2%.

The anthropometric and biochemical nutritional variables did not follow a normal distribution pattern. The log-transformed PGE2 values followed a normal distribution pattern. The Mann-Whitney U-test was used to test the mean differences of the log-transformed PGE2 between the kwashiorkor and well-nourished subjects. Interrelationships between PGE2 and the anthropometric and biochemical nutritional variables were examined using Spearman rank correlation coefficients. Statistical analysis was carried out using the Statistical Analysis System (SAS).

RESULTS

A total of 32 subjects were studied — 21 children with kwashiorkor and 11 well-nourished children. The anthropometric and biochemical nutritional parameters of the subjects are shown in Table I.

Plasma PGE2 was higher in the children with kwashiorkor than in the control children (7.25 ± 3.5 v. 3.51 ± 1.59 , $P < 0.01$). Within the kwashiorkor study group there was a significant negative correlation between log-transformed serum PGE2 and total plasma protein ($r = -0.59$, $P < 0.001$), plasma albumin ($r = -0.63$, $P < 0.001$), weight-for-age ($r = -0.37$, $P < 0.05$), and height-for-age ($r = -0.37$, $P < 0.05$). There was no significant

Table I. Anthropometric and biochemical nutritional parameters, and plasma PGE2 levels in kwashiorkor and normal subjects (means \pm standard deviation)

	Kwashiorkor	Well nourished	P-level
Sample size	21	11	
Age (months)	15.6 ± 9.1	14.3 ± 10.2	NS
Weight (kg)	7.9 ± 2.3	9.9 ± 3.8	NS
Height (cm)	71.3 ± 8.1	73.9 ± 10.4	NS
Weight for age	0.87 ± 0.19	1.20 ± 0.31	< 0.05
Height for age	0.95 ± 0.07	1.03 ± 0.05	NS
Total protein	48.5 ± 13.4	62.3 ± 6.3	< 0.01
Albumin	16.8 ± 5.2	34.6 ± 5.4	< 0.001
Globulin	31.7 ± 10.4	26.7 ± 8.1	NS
Albumin/globulin ratio	2.0 ± 0.7	0.80 ± 0.32	< 0.001
PGE2	7.25 ± 3.5	3.51 ± 1.59	< 0.01

NS - not significant.

difference between the mean values of PGE2 for the children with kwashiorkor who recovered from the illness and those who died (7.1 ± 2.6 v. 9.1 ± 4.8 , $P = 0.36$).

DISCUSSION

Normal or control levels for PGE2 assayed using this method have been reported as 4.5 ± 1 ,⁶ which compares well with the normal levels found here. Potentially great variations in 'normal' levels of prostaglandin in plasma⁷ reinforce the need for controls whose plasma samples are analysed using exactly the same method used in the cases.

PGE2 levels in the kwashiorkor group were more than twice control levels and were significantly associated with the degree of undernutrition as measured by serum albumin, weight-for-age and height-for-age. This is the expected result based on the hypothesis described in the introduction, namely that diet causes excess PGE2 production. High PGE2 levels can produce a profound alteration in cell-mediated immune response⁸ and this has been found in children with kwashiorkor.^{9,10} PGE2 exerts its influence at the priming of the naive T cell,¹¹ causing a depression in the number of Th1 cells. A profound depression in cellular immunity is the usual finding in children with late-stage kwashiorkor.¹² While reduction in the plasma PGE2 may be quickly achieved by dietary means, it will necessarily take a significant time to restock with active Th1 cells, and during this period of perhaps 7 - 10 days the child will continue to be predisposed to life-threatening infections.

Kwashiorkor presents similarly in different regions where individual vitamin and other deficiencies vary. This suggests the possibility of a final common pathway of aetiology of the kwashiorkor syndrome. Linoleic acid and/or PGE2 have associations not only with immune polarisation, but also with

diarrhoea, oedema, depression of affect,¹³ and it is possible that the pathogenesis begins with dietary deficiencies that cause PGE2 overproduction. Excess PGE2 in turn could contribute to the pathologies of kwashiorkor.

Williams¹⁴ first described this condition in 1935, and the mainstay of her treatment was cod liver oil. This contains much omega-3 fatty acid, which reduces PGE2 production.¹⁵ Dietary improvement will restore a normal immune balance as PGE2 levels return to normal.

References

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