

Failure to thrive and its relationship to serum vitamin A levels and diet

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Serum vitamin A and retinol-binding protein (RBP) levels were determined in a group of 34 children between 1 and 4 years of age with failure to thrive and in 34 age- and sex-matched controls. Both groups of children were also assessed in respect of anthropometry and diet.

Vitamin A levels in patients (0 - 32,2 µg/100 ml; median 16,9 µg/100 ml) did not differ significantly from controls (6,4 - 47,2 µg/100 ml; median 16,1 µg/100 ml). Fourteen patients (42%) and 4 controls (12%) had vitamin A levels below 10 µg/100 ml. RBP levels in patients (0,45 - 3,50 mg/100 ml; median 2,17 mg/100 ml) also did not differ significantly from those in controls (1,21 - 3,66 mg/100 ml; median 2,06 mg/100 ml). No clinical features of vitamin A deficiency were detected. Weight and height for age, weight for height, mid-upper arm circumference and head circumference differed significantly between patients and controls ($P < 0,0001$ in each instance). Although within the recommendations for intake, patients had a significantly lower intake of the essential fatty acid C 18:2 ($N = 6$) (linoleic acid) and vitamin A.

In view of the current proposed relationship between vitamin A status and infectious diseases, the prevalence of biochemical vitamin A deficiency in children in the Cape Town community studied may contribute to the morbidity and mortality associated with infectious diseases in the area to a greater degree than has been suspected.

S Afr Med J 1995; 85: 373-377.

Monitoring of weight gain in infancy is one of the cornerstones of the policy of promoting growth monitoring, oral rehydration, breast-feeding and immunisation (GOBI) and it is now common practice throughout the world for the weight of children attending child health clinics to be plotted on 'Road to Health' cards.¹ All too frequently in the

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developing world, however, the velocity of weight gain declines from 6 months of age onwards.² At times weight gain ceases for a period or children may actually lose weight. This failure to thrive, while often the result of a complex web of socio-economic conditions, may also result from disease. In this report, we describe our experience with the clinical and dietary evaluation of a group of children who were failing to thrive, in order to determine whether diet, serum vitamin A status or an infectious disease, in particular tuberculosis, could have played a role.

Patients and methods

The study was undertaken in the Cape Town suburb of Bishop Lavis. This area has a relatively low socio-economic status and in 1987, at the time of the study, had a population of approximately 35 000, an infant mortality rate of 18,9/1 000 and a tuberculosis incidence of 550/100 000.³ The area is served by a centrally situated child health clinic which is responsible for the immunisation and growth monitoring of children, family planning and the treatment of tuberculosis in both adults and children. Child health clinics are held each weekday. Other curative services are provided by an adjacent, but separately administered, day hospital.

For the purpose of this study failure to thrive was defined as failure to gain weight or loss of weight over a period of at least 3 months, confirmed on three separate clinic visits. Thirty-four children who met these criteria were selected on a weekday once a week by clinic staff. The first 2 such children who were accompanied by a parent were referred for inclusion in the study.

A control group of children was selected from the same clinic who were matched for age and sex with the cases. These children had to have been gaining weight constantly since birth, and had to be accompanied by a parent.

Evaluation of both patients and controls included clinical examination for obvious signs of disease (cardiac murmurs, abnormal respiratory sounds or hepatosplenomegaly) and measurement of weight, height, mid-upper-arm circumference (MUAC) and head circumference. Blood was drawn for determination of serum vitamin A⁴ and retinol-binding protein (RBP) levels (Paztigen immunodiffusion plates; Behring Institute, Hoechst Pharmaceuticals, Harberg, Germany). In the children with failure to thrive a chest radiograph was taken and a midstream urine specimen collected for microscopy and culture; the parent was requested to bring a stool to the clinic the next day for microscopy. A Mantoux test (5 units PPD) was performed. A chest radiograph of control children was considered unwarranted and it proved impossible to persuade parents to return with a stool specimen for evaluation or for the reading of tuberculin test results.

Dietary intake was determined in 31 patients and controls by means of the quantified food frequency method. A dietitian interviewed the mother of the child and food models, household measures, and a ruler were used as visual aids during the interview for quantification. The data were then computer coded and analysed in the light of the *NRIND Food Quantities Manual* (1986),⁵ and the *NRIND Food Composition Tables* (1986).⁶ Analyses were done of both macro- and micronutrients and data were expressed as intake per day.

Details of birth weight and previous weight gain were available both from the children's Road-to-Health cards and from clinic records. Weight was determined on a beam balance scale (Berkel) correct to the nearest 0,1 kg in children \leq 15 months, and on a bathroom scale in older children. Standing height at ages \geq 15 months and recumbent length (age $<$ 15 months) were determined to the nearest 0,1 cm with locally constructed wooden measuring boards. Left MUAC was measured with a Zervas insertion tape supplied by Teaching Aids at Low Cost.

Anthropometric values were evaluated and the National Centre for Health Statistics (NCHS) data⁷ used as reference. Findings in patients and controls were compared by means of the paired *t*-test. Correlations were sought with the aid of the Spearman correlation test. The Wilcoxon sign rank test was used to determine statistically significant differences in nutrient intake between the cases and controls.

The study was approved by the Ethical Committee of the Faculty of Medicine of the University of Stellenbosch and informed consent was obtained from parents for the inclusion of their children in the study.

Results

The children studied were aged from 1 year to 4 years 2 months (median age 1 year 11 months). There were 18 males (median age 1 year 10 months) and 16 females (median age 2 years 2 months). The age at onset of failure to thrive — the first detectable deviation from the previous growth pattern — varied from 3 months to 30 months (median 8,5 months). Four children experienced actual weight loss.

In Table 1 the distribution of anthropometric findings for weight and height (or length) for age, and weight for height for cases and controls are summarised. All 3 indices differed significantly between cases and controls ($P < 0,0001$ in each instance). Also tabulated is the maximum percentile for weight reached by the patients before the onset of failure to thrive. Twenty (59%) of the children who were failing to thrive had initially been gaining weight on a curve above the 50th percentile of weight for age.

Head circumference in the patients also differed significantly from that in controls ($P < 0,0001$) and was below the 3rd percentile in 18 patients (52%) and 5 controls (15%).

The MUAC in the patients varied from 10 cm to 17 cm (median 15 cm) with 3 values (9%) less than 12,5 cm and a further 6 values (18%) less than 13,5 cm; MUAC was significantly different from that in controls ($P < 0,0001$) which varied from 14,8 to 20,6 cm (median 16,6 cm). The MUAC in both groups was significantly correlated with weight ($r = 0,7969$; $P < 0,0001$), height ($r = 0,49487$; $P < 0,0001$) and head circumference ($r = 0,62868$; $P < 0,0001$).

The birth weights of the patients (1,78 to 4,5 kg; median 2,7 kg) were significantly lower ($P = 0,0089$) than those of controls (1,21 to 5,00 kg; median 3,16 kg). Ten patients (30%) had a birth weight of less than 2,5 kg. Of these 4 subsequently gained weight above the 50th percentile, 3 above the 10th percentile and 1 above the 5th percentile, before failing to thrive. In only 2 of the low-birth-weight children who subsequently failed to gain adequately did weight gain never rise above the 3rd percentile.

Table I. Distribution of anthropometric data in patients and controls

	Percentile achieved							
	< 5th	5th - 10th	10th - 25th	25th - 50th	50th - 75th	75th - 90th	90th - 95th	> 95th
Weight for age								
Patients								
At evaluation	21 (62%)	1 (3%)	12 (35%)	—	—	—	—	—
Premorbid maximum percentile	3 (9%)	2 (6%)	5 (15%)	4 (12%)	10 (29%)	5 (15%)	4 (12%)	1 (3%)
Controls								
	1 (3%)	—	7 (21%)	8 (24%)	9 (26%)	3 (9%)	1 (3%)	5 (15%)
Height for age								
Patients								
	18 (53%)	5 (15%)	5 (15%)	2 (6%)	4 (12%)	—	—	—
Controls								
	2 (6%)	7 (21%)	4 (12%)	9 (26%)	7 (21%)	4 (12%)	1 (3%)	—
Weight for height								
Patients								
	10 (29%)	9 (26%)	7 (21%)	5 (15%)	3 (9%)	—	—	—
Controls								
	—	—	1 (3%)	12 (35%)	6 (18%)	5 (15%)	1 (3%)	9 (26%)

The distribution of serum vitamin A and serum RBP levels in patients and controls is given in Table II. Although there was no significant difference between cases and controls ($P = 0,0909$), 7 of the patients (21%) and none of the controls had serum vitamin A levels below 5,0 µg/100 ml; a further 7 patients (21%) and only 4 controls (12%) had values below 10 µg/100 ml. Twenty-three patients (68%) and 23 controls (68%) had serum vitamin A levels below 20 µg/100 ml. RBP levels also did not differ significantly between cases and controls ($P = 0,3744$). Neither serum vitamin A levels nor RBP levels were significantly related to weight, height, MUAC, head circumference or weight for height.

Table II. Distribution of serum vitamin A and RBP values in patients and controls

	Serum vitamin A (µg/100 ml)		Serum RBP (mg/100 ml)	
	Patients	Controls	Patients	Controls
0 - 5	7 (21%)	—	0 - 1,0	2 (6%)
5 - 10	7 (21%)	4 (12%)	1 - 1,5	8 (24%)
10 - 15	1 (3%)	12 (35%)	1,5 - 2,0	4 (12%)
15 - 20	8 (24%)	7 (21%)	2,0 - 2,5	2 (35%)
20 - 25	4 (12%)	3 (9%)	2,5 - 3,0	2 (6%)
25 - 30	6 (18%)	3 (9%)	3,0 - 3,5	5 (15%)
30 - 35	1 (3%)	2 (6%)	> 3,5	1 (3%)
35 - 40	—	—		2 (6%)
40 - 45	—	2 (6%)		
45 - 50	—	1 (3%)		
> 50	—	—		
Median	16,9 µg/100 ml	16,1 µg/100 ml	2,2 mg/100 ml	2,1 mg/100 ml
Mean	15,1 µg/100 ml	19,1 µg/100 ml	2,1 mg/100 ml	2,3 mg/100 ml

Chest radiography was abnormal in 6 (18%) of the children who were failing to thrive and they were all placed on antituberculosis treatment. One child had 'suspected' tuberculosis — the chest radiograph showed a prominent right hilar area suggestive of adenopathy but the Mantoux test was negative and there was no history of contact. Four children had 'probable' tuberculosis — 2 with unequivocal hilar adenopathy and a strongly positive Mantoux test (> 25 mm induration) and 2 with collapse-consolidation of the right middle lobe accompanied by hilar adenopathy in 1 child and a positive Mantoux test (20 mm induration) in the other. One child had confirmed tuberculosis — a collapsed

right middle lobe and hilar adenopathy and although the Mantoux test was negative (the child was marasmic) *Mycobacterium tuberculosis* was cultured from gastric aspirate. Of the 4 children who had actually lost weight only 1 had an abnormal chest radiograph that showed a prominent right hilum.

Microscopy and culture of the urine revealed a urinary tract infection in only 1 child; despite appropriate treatment and extensive investigation this child nevertheless persistently failed to gain adequate weight.

Ascaris lumbricoides ova were found on stool microscopy in only 4 children who were not thriving and *Trichomonas hominis* cysts in 1 child only.

The mean daily energy, macro- and micronutrient intakes for both cases and controls are shown in Table III together with the difference in intakes as well as the significance of these differences. The mono-unsaturated fat, cholesterol and vitamin A intakes were significantly higher in the controls than in the patients. Although the total polyunsaturated fat intake did not differ significantly between the two groups, the patients had a significantly lower intake of the essential fatty acid C18:2 ($N = 6$) (6,5 v. 9,8 in controls, $P < 0,01$). Mean iron and zinc intakes of both the cases and the controls were very low.

No significant relationships were found between dietary energy, protein and vitamin A intake and the serum levels of vitamin A and RBP.

Discussion

Failure to thrive during the weaning period is a common phenomenon in the developing world and has been ascribed to inadequate energy density of weaning foods associated in many instances with a variety of infections. Once the process of failure to thrive has set in, immunity may be compromised with a consequent susceptibility to infectious diseases such as diarrhoea and respiratory tract infections, including tuberculosis, which themselves may lead to failure to thrive.

Vitamin A is now known to play a major role in the treatment and prevention of infectious diseases,^{9,10} and either directly or indirectly to affect growth.¹¹ With regard to the role of vitamin A in growth, the evidence provided by this study is equivocal as there was no statistically significant

Table III. Energy and nutrient intake of the patients and controls (mean and SD)

Nutrient	Patients (N = 31)		Controls (N = 31)		Difference	P-value
	Mean	SD	Mean	SD		
Energy (kJ)	5 979	1 802	6 646	2 831	668	0,316
Total protein (g)	46,4	15,4	52,1	24,4	5,7	0,436
Plant (g)	14,1	6,1	14,9	7,0	0,8	0,465
Animal (g)	32,2	14,0	37,2	20,9	5,0	0,360
Total fat (g)	55,6	20,5	68,6	30,3	13,0	0,079
Saturated (g)	21,3	9,7	25,8	13,8	4,5	0,104
Mono-unsaturated (g)	18,4	7,4	23,7	10,2	5,3	0,045*
Polyunsaturated (g)	11,3	5,3	14,1	8,3	2,8	0,254
Cholesterol (mg)	189	110	293	159	104	0,009*
Total carbohydrate (g)	182	60	186	85	4	0,833
Sugar (g)	60,6	34,1	60,8	40,9	0,2	0,833
Fibre (g)	10,2	5,7	11,7	5,9	1,5	0,168
Vitamin A (mg)	3 420	1 999	4 655	3 101	1 234	0,023*
Vitamin C (mg)	89	115	73	81	-15	0,584
Niacin (mg)	7,5	3,0	9,3	4,6	1,8	0,085
Vitamin B ₆ (mg)	0,86	0,65	0,94	0,37	0,08	0,292
Calcium (mg)	777	517	836	672	59	0,767
Iron (mg)	5,4	2,0	6,1	2,6	0,7	0,360
Magnesium (mg)	185	71	190	91	5	0,709
Zinc (mg)	6,3	2,2	7,0	2,9	0,7	0,484

*P < 0,05.

difference between the serum vitamin A levels in children failing to thrive and their controls. The lowest serum vitamin A levels (< 5,0 µg/100 ml) were, however, found only among the children with failure to thrive.

This study is the first to document serum vitamin A levels among children in a community in the Western Cape. Previous hospital-based studies more than 20 years ago recorded relatively low serum vitamin A levels¹² but, despite these and our findings, overt clinical signs of vitamin A deficiency are almost unknown locally. Given the wide-ranging role proposed for vitamin A in growth and in the prevention and management of infectious diseases and their complications it is cause for concern that 68% of both patients and controls in this study had serum vitamin A levels of less than 20 µg/100 ml and that 12% of controls and 42% of patients had levels of less than 10 µg/100 ml. The World Health Organisation has proposed that serum vitamin A levels above 20 µg/100 ml are desirable and that vitamin A deficiency is a significant public health problem if the prevalence of serum vitamin A levels below 10 µg/100 ml in preschool children exceeds 5%.¹³ Obviously further community studies are urgently needed in our area and intervention studies to assess the effect of vitamin A supplementation on the prevalence and severity of upper respiratory infections and diarrhoea are warranted.

It is also of interest that the percentage of children with serum vitamin A levels below 20 µg/100 ml is almost identical to that recently reported in a study of preschool children in Turkey.¹⁴

The patients in this study had a lower intake of all the nutrients when compared with the controls, but differences were statistically significant only for some of them. There was no significant relationship between mean dietary intake and serum vitamin A levels. However, in 10% of the patients and none of the controls, vitamin A intakes were less than

67% of recommended daily intakes.¹⁵ Four patients and 7 controls were still taking some breast-milk. This was not quantified, but when the assumption was made that, based on the ages of these children, intake of breast-milk was 200 ml or less,¹⁶ it had no effect on the interpretation of the data. Dietary intake will be discussed comprehensively elsewhere (E. van Staden — manuscript in preparation).

The role of tuberculosis in the development of malnutrition is controversial. On the one hand, some have claimed that childhood tuberculosis occurs mainly among the malnourished,¹⁷ while others have considered the presence of failure to thrive or malnutrition to be of 'little value' in the diagnosis of childhood tuberculosis.¹⁸ In this study 'routine' chest radiography of children not gaining in weight yielded 6 cases (18%) of childhood tuberculosis — 1 suspected case, 4 probable cases and 1 confirmed case. In a community with a particularly high incidence of tuberculosis, routine evaluation for possible tuberculosis in children who are failing to thrive might make a significant contribution to the prevention of complications of childhood tuberculosis. If, for reasons of economy, chest radiography had been limited to the 19 children with a weight below the 3rd percentile of weight for age, 2 of the children with hilar adenopathy would have been missed and the yield would have been 4 cases (12%).

Given the high incidence of tuberculosis in Bishop Lavis it is possible that unsuspected cases of tuberculosis might also have been found among the children who were gaining adequately in weight, had a full assessment been undertaken and had we been able to ensure the reading of tuberculin tests performed on control children.

Socio-economic factors which might have played a role in failure to thrive were not assessed in this study. Children who failed to thrive, however, had a significantly lower birth weight than their controls, suggesting that the two groups

were not comparable at birth. Poorer antenatal or obstetric care or socio-economic status might have played a role in this finding.

The low incidence of ascariasis in the children who were failing to thrive is surprising in view of the known high incidence of parasitic infestation in this area, but can perhaps be ascribed to the fact that one of the first actions of nursing personnel when a child fails to thrive is to administer an anti-helminthic.

For most of the parameters studied, the children who failed to thrive were worse off than the controls but no one factor could be singled out to explain their failure to thrive.

The authors thank the Medical Officer of Health for the Western Cape Regional Services Council and the Medical Superintendent of Tygerberg Hospital for permission to publish, and the nursing personnel of the Bishop Lavis local authority clinic for their considerable assistance during this study, which was supported by the Medical Research Council.

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Accepted 7 June 1993.