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THYROID FUNCTION IN CASES OF ENDEMIC GOITRE IN THE SUDAN

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Abstract Serum thyroid-stimulating hormone (TSH), thyronine (T_4) and triiodothyronine (T_3) levels were measured in 23 children (9 boys and 14 girls) and 18 adults (9 males and 9 females) with goitre from an endemic goitre region of the Sudan. Similar studies were made in 2 girls, 6 women, 2 boys and 6 men who lived in the same region but showed no evidence of goitre. Serum was also obtained from 26 "control" subjects from Khartoum. Low serum T_4 levels were found in the majority of the goitrous subjects. Statistical analysis revealed highly significant differences in T_4 between the control subjects and both the goitrous and non-goitrous subjects from the endemic area. Elevated or high normal T_3 levels were found in the great majority of the goitrous subjects and in a proportion of the non-goitrous subjects from the endemic region, and also in 7 of 26 from Khartoum. There was a statistically significant difference in T_3 levels between the controls and the goitrous subjects but not between the controls and the non-goitrous subjects from the endemic region. T_3/T_4 ratio differed significantly between the controls and the goitrous subjects, and also between the controls and the non-goitrous subjects from the endemic region. Raised TSH levels were found in the majority of the goitrous subjects (in 20 of the 23 goitrous children), in only 2 of the non-goitrous subjects from the endemic area, but in none of the control subjects. The iodine, calcium and fluoride contents of the water from one village in the endemic region were measured. The implications of these results is discussed with particular reference to the metabolic advantages of preferential secretion of T_3 in states of thyroid stress.

Key words Endemic goitre; Sudan

INTRODUCTION

In January 1973 two of us (JHH and JIAO) visited Jabal Marra, a mountainous region of Darfur Province in the western Sudan where goitre is endemic. Travel in this region is both difficult and hazardous so that the population has tended to remain isolated from the principal towns of the province (Nyala and El Fasher), and from modern medical facilities. The inhabitants belong to two tribes called Fur and Masalit who have maintained their identity in small villages scattered about the mountain slopes. No comperhensive survey of the goitre prevalence has ever been made. In the market places of several villages - Dibis, Tur, Martegello, Niartati - we had the chance to examine many children and adults with goitre. Goitres were mostly moderate in size and diffuse in consistency but some were large and nodular. We also noted that some of the subjects showed brown mottling of the teeth which we thought to be due to dental fluorosis. None of the goitrous subjects showed clinical manifestations of hypothyroidism or myxoedema, although in the absence of anthropometric or radiological facilites it is possible that milder degrees were missed. "Neurological" or "myxoedematous" types[1] of endemic cretinism were not observed, and the local medical assistant who had an intimate knowledge of the villages knew of no dwarfed, dear-mute or spastic children.

As part of a more comprehensive survey it was decided to measure the serum thyroid stimulating hormone (TSH), thyroxine (T_4) and triiodothyronine (T_3) levels of samples of goitrous and non-goitrous subjects in the goitre region, and to make similar measurements in "control" subjects in Khartoum which is not regarded as a goitre area.

MATERIAL AND METHODS

In the goitre region serum was obtained in May 1975 from 14 girls and 9 women with goitre, and 2 girls and 6 women without goitre; from 9 boys and 9 men with goitre, and 2 boys and 6 men without goitre. In Khartoum serum

was obtained from 26 subjects (25 adults and one child). None of whom had evidence of an endocrine disease. In Jabal Marra the sera were separated by hand centrifuge and stored in liquid nitrogen. The liquid nitrogen container was despatched to Khartoum from Nyala (the nearest town) by air and from there flown to the United Kingdom.

In Glasgow the specimens of serum were maintained deep frozen until analysis was undertaken. T_4, T_3 and TSH were estimated in duplicate by radioimmunoassay using commercial kits (Abbott Laboratories, Reading, England). With each batch of samples both quality control specimens from commercial sources with assigned values and samples from an inter-laboratory control scheme were assayed. Normal reference values quoted by the manufacturer were respectively: T_4 (51-142 nmol/l), T_3 (1.1-3.2 nmol/l), TSH (0-5 mlU/l). The levels of iodine, calcium and fluoride in the water were also measured from one village (Dibis) by the Sudan Government analyst.

RESULTS

The results of T_4, T_3 and TSH estimations are shown in Table I.

T_4 values. The T_4 levels were below the normal reference range (51-142 nmol/l) in 8 of the 14 goitrous girls; in 7 of the 9 goitrous boys; in 5 of the 9 goitrous women; but in none of the 9 men with goitre. An abnormally low T_4 level was found in only 1 of the 6 non-goitrous subjects from the goitre region (a woman aged 29 years). The T_4 levels lay within the reference range in all 26 subjects from Khartoum (Table II).

T_3 values. In contrast to the T_4 levels, the values for T_3 were above the normal range (1.1-3.2 nmol/l) in 13 of the 14 goitrous girls; in the two non-goitrous girls and in 2 of 6 non-goitrous men. T_3 levels above or at the higher end of the normal range were found in 1 of 2 non-goitrous boys (3.1 nmol/l) and in 2 of 6 non-goitrous women (3.9 and 3.8 nmol/l). It should be noted, however, that raised T_3 values were also found in 6 of the 26 subjects from Khartoum.

Table I. T_3, T_4, T_3/T_4 ratios and TSH in goitrous and non-goitrous subjects from the endemic region

Study groups	No	Age range (years)	T_4 (nmol(l) <51	51-142	>142	T_3 (nmol/l) <1.1	1.1-3.2	>3.2	T_3/T_4 (range)	TSH (mlU/I) 0-5	>5
Girls											
without goitre	2	6- 8	-	2	-	-	-	2	0.030-0.046	2	-
with goitre	14	6-15	8	6	-	-	1	13	0.038-0.390	1	13
Boys											
without goitre	2	7-15	-	2	-	-	2	-	0.025-0.040	-	2
with goitre	9	4-14	7	2	-	-	3	6	0.029-0.400	2	7
Women											
without goitre	6	20-60	1	5	-	1	4	1	0.009-0.084	5	1
with goitre	9	17-35	5	4	-	-	5	4	0.036-0.082	7	2
Men											
without goitre	6	30-79	-	6	-	-	4	2	0.016-0-048	6	-
with goitre	9	21-39	-	9	-	-	5	4	0.020-0.053	8	1

Table II. T_3, T_4, T_3/T_4 ratios and TSH in the control group from Khartoum

Study group (No = 26)	No	Age range (years)	T_4 (nmol(l) <51	51-142	>142	T_3 (nmol/l) <1.1	1.1-3.2	>3.2	T_3/T_4 (range)	TSH (mlU/I) 0-5	>5
Males	20	10 - 15	-	12	8	3	12	5	0.005-0.032	20	-
Females	4	25 - 45	-	3	1	-	3	1	0.020-0.034	4	-
Details unknown*	2	?	-	1	1	-	2	-	0.017-0.033	2	-
Mean+SD			130.6 ± 26.2			2.41 ± 0.89				1.82 ± 1.4	
95% confidence limits			78 - 183			0.63 - 4.2				0 - 4.6	

*The details about the age and sex of two subjects are lacking.

TSH values. The TSH values were above the normal range (0 - 5 mlU/l) to a greater or lesser degree in 13 of the 14 goitrous girls; in 7 of 9 goitrous boys; in 2 of 9 goitrous women; and in 1 of 9 goitrous men. There were only 3 non-goitrous subjects, both from the goitre region, in whom the TSH was well above the normal range (two boys aged 7 and 15; and a 29-year-old woman).

Statistical analysis of T_4, T_3 and TSH results (Table III). The T_4 and T_3 levels in the various groups - goitrous subjects, non-goitrous subjects from the endemic region, and subjects from Khartoum - were compared using the unpaired student's t-test (two tailed). Analysis of the TSH values was accomplished using the Wilcoxon test. The TSH results in the various groups did not form a normal distribution and for this reason the student's t-test was not employed.

There are significant differences ($p<0.001$) in serum T_4 between the controls and both the goitrous and non-goitrous subjects from the endemic region. A similar degree of difference is found between the goitrous and non-goitrous subjects from the endemic region (Table IV). There is no significant difference in serum T_3 between the controls and the non-goitrous subjects from the endemic region ($p<0.10$), but there is a significant difference ($p<0.001$) between the controls and female goitrous subjects, and also a difference ($p<0.005$) between the controls and the males with goitre (Table III). When the non-goitrous subjects from the endemic region are compared with goitrous total a significant difference is found ($p<0.001$); this degree of difference also applies when the females of each group are compared, but when the males of each group are compared the difference ($p<0.10$) is not significant (Table IV). The T_3/T_4 ratio shows a significant difference between the controls and the non-goitrous subjects from the endemic region ($p<0.005$), and between the controls and the goitrous subjects ($p<0.001$; Table III). There is, however, no significant difference in T_3/T_4 ratio between the males with goitre and non-goitrous males in the endemic region ($p<0.10$) but the females show a difference at the 5% level ($p<0.05$; Table IV). There is a difference in TSH values between the subjects in the control group and the non-goitrous females from the endemic region at the 5%

Table III Confidence limits of the differences in T_4, T_3, T_3/T_4 and TSH levels in the various groups

	Controls (non-endemic region); n=26			
	T_4	T_3	T_3/T_4	TSH
Endemic region (non-goitrous)				
a. Females (n=8)				
T_4	$p<0.005$			
T_3		$p<0.50$		
T_3/T_4			$p<0.025$	
TSH				$p<0.05$
b. Males (n=8)				
T_4	$p<0.10$			
T_3		$p<0.20$		
T_3/T_4			$p<0.001$	
TSH				$p<0.10$
c. Group (n=16)				
T_4	$p<0.001$			
T_3		$p<0.20$		
T_3/T_4			$p<0.005$	
TSH				$p<0.10$
Endemic region (goitrous)				
a. Females (n=23)				
T_4	$p<0.001$			
T_3		$p<0.001$		
T_3/T_4			$p<0.001$	
TSH				$p<0.01$
b. Males (n=18)				
T_4	$p<0.001$			
T_3		$p<0.005$		
T_3/T_4			$p<0.001$	
TSH				$p<0.10$

level, and a difference between the subjects in the control group and the goitrous females at the 1% level (Table III). There is, however, no statistically significant difference between the males from the endemic region with or without goitre and the subjects in the control group ($p<0.10$). When the non-goitrous subjects

from the endemic region are compared with the goitrous the whole groups reveal a difference at the 5% level, but there are no statistically significant differences between the males or females when considered separately (Table IV).

Table IV Confidence limits of the differences in T_4, T_3, T_3/T_4 and TSH

	Endemic region (non-goitrous); n=16			
	T_4	T_3	T_3/T_4	TSH
Endemic region (goitrous)				
a. Group (n=41)				
T_4	$p<0.001$			
T_3		$p<0.001$		
T_3/T_4			$p<0.01$	
TSH				$p<0.05$
	Males (non-goitrous)			
	T_4	T_3	T_3/T_4	TSH
b. Males (n=18)				
T_4	$p<0.05$			
T_3		$p<0.10$		
T_3/T_4			$p<0.10$	
TSH				$p<0.05$
	Females (non-goitrous)			
	T_4	T_3	T_3/T_4	TSH
c. Females (n=23)				
T_4	$p<0.001$			
T_3		$p<0.001$		
T_3/T_4			$p<0.05$	
TSH				$p<0.05$

Water analysis

The levels of iodine, calcium and fluoride in the water sample from Dibis village were 0.0025 mg/l, 10.0 mg/l and 0.2 mg/l, respectively.

DISCUSSION

In subjects with endemic goitre the serum T_4 levels were below the normal reference range in the great majority of the children and in 5 of 9 women, but in none of the goitrous men. These findings indicate that certainly in the children and probably in the women, none of whom was manifestly hypothyroid, the thyroid glands were under stress and the subjects remained somewhat precariously euthyroid. Indeed, the euthyroid status of our subjects was presumably related to their elevated or high normal T_3 levels, and other workers in areas of endemic goitre have reported low T_4 levels in association with T_3 levels which were raised[2,3] or normal[4]. T_3 contains less iodine weight for weight and is metabolically four or five times more active than T_4. An alternative explanation for the lower serum T_4 levels in the absence of hypothyroidism could be a deficient concentration of one of the T_4-binding proteins (thyroxine-binding globulin, thyroxine-binding prealbumin or albumin). These were not measured in our subjects but Wellby et al[5] working in the endemic area of Papua-New Guinea found no deficiencies in these proteins. Both raised and normal levels of TSH have been reported by other workers in endemic goitre[3,4,6,7], and it is of note in our subjects that a raised TSH level was found in 20 of 23 goitrous children but only in 3 of the 18 goitrous adults. These findings again indicate developing thyroid inadequacy, particularly in the children, and Kochupillai et al[3] have shown that the degree of thyroid failure correlates with the pituitary output and reserve. It is less easy to explain the low T_4 and the raised or high normal T_3 levels in those goitrous adults with normal TSH values.

The serum T_4 level was low in only one of our non-goitrous subjects for the endemic region in association with a raised TSH, but raised or high normal T_3 levels were found in several non-goitrous subjects unrelated to TSH levels.

Raised or high normal T_3 levels were also found in 7 of the 26 control subjects from Khartoum but these values have to be viewed against the 95% confidence limits determined for the control population (Table II). In none of these controls was the T_4 below or the TSH above the

normal reference range for the method, and in only one subject was the TSH level marginally above the range determined for this group.

The aetiology of the endemic goitre in the Sudan has not been extensively investigated although iodine deficiency seems likely in this mountainous and land-locked region of the largest coutry in Africa. Our findings for TSH, T_4 and T_3 levels would be consistent with this hypothesis. So also would the significant differences in T_3/T_4 ratios between the controls and the goitrous subjects. Green et al[8] have reported an increased T_3/T_4 ratio in iodine-deficient rats. The absence of endemic cretinism in Jabal Marra presumably indicates that the degree of iodine deficiency in the mothers is less severe than in coutries such as Papua-New Guinea, the Belgian Congo or Nepal. The iodine level (0.0025 mg/l) in the water from Dibis is, in fact, more than twice that recorded by Day and Powell-Jackson[9] in Nepal. The fluoride content of the one specimen of water analysed gives no support to our clinical suspicion of dental fluorosis in some of the subjects from the goitre region, nor does it suggest that fluoride played a part in the pathogenesis of the goitre. Th calcium level of the water (10 mg/l) excludes water hardness as an aetiological factor. It would seem also that iodine deficiency was not of a degree sufficient to result in acquired hypothyroidism in either the children or the adults with goitre, although in a considerable number the serum T_4 and TSH values were at the levels commonly found in patients with hypothyroidism. We presume that TSG-mediated thyroid hyperplasia with preferential secretion of T_3 allowed the euthyroid status to be preserved.

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