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Endemic juvenile hypothyroidism in a severe endemic goitre area of Sudan

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Summary

OBJECTIVE The aim of the study was to assess thyroid function, iodine intake and exposure to dietary goitrogens of children living in an area with a high prevalence of goitre, in the region of Darfur, Sudan.

DESIGN In a village where goitre affected approximately 85% of children, a cross-sectional survey of thyroid function was performed in children 0–7 years old.

PATIENTS Twenty neonates and 190 children, aged 1 month to 7 years, were included.

MEASUREMENTS Thyroid hormones, urinary iodide and thiocyanate excretion were measured.

RESULTS Mean ± SD serum T4 was below the normal range at birth (82 ± 50 nmol/l) and in the age group less than 2 years (73 ± 46). Children older than 2 years had even lower serum T4: 37 ± 37 ($P < 0{\cdot}001$) at 3–4 years and 36 ± 38 ($P < 0{\cdot}001$) at 5–7 years. Mean serum TSH was 25·8(6·2–107·7) mU/l at birth, 8·3(2·5–27·8) in the group less than 2 years, 15·3(2·9–79·1) at 3–4 years and 16·4(2·7–98·3) at 5–7 years. The overall prevalence of hypothyroidism (TSH > 50 mU/l) was 24%. Mean urinary thiocyanate was high at birth(107 ± 69 μmol/l), normal in the group less than 2 years and higher in children older than 2 years (126 ± 69 μmol/l) ($P < 0{\cdot}001$). All age groups had a low urinary iodide concentration.

CONCLUSION Hypothyroidism was very frequent in each age group. The higher frequency of hypothyroidism observed in weaned children (> 2 years) was attributed to the combined effects of iodine deficiency and goitrogens (thiocyanate and glycosylflavones) derived from millet.

Darfur is one of the severest endemic goitre regions in Sudan (Kambal, 1969). The prevalence of goitre among schoolchildren reaches 85%. Although the prevalence of endemic cretinism in the region has not been estimated, the cases reported belong to the neurological form (Eltom *et al.*, 1984). The occurrence of hypothyroidism in neonates and children from Darfur is unknown. Several studies from different iodine deficient regions indicate that neonatal hypothyroidism may be extremely high (Thilly *et al.*, 1978; Sava *et al.*, 1984; Kochupillai *et al.*, 1986). However, only one study has focused on thyroid function during childhood (Vanderpas *et al.*, 1984). That study indicated that hypothyroidism was much more frequent in children of 5–7 years than in children of less than one year.

The severity of endemic goitre and the occurrence of hypothyroidism does not depend exclusively on the degree of iodine deficiency (Gaitan, 1980; Ermans *et al.*, 1983). In Darfur the major cause of endemic goitre is iodine deficiency (Eltom *et al.*, 1984). However, epidemiological and experimental observations suggested that the high consumption of millet *(Pennisetum typhoides)*, which is the staple food of the area, may be a contributing factor to the high prevalence of endemic goitre in Darfur (Osman, 1981; Eltom *et al.*, 1985a; Osman & Fatah, 1981; Klopfenstein *et al.*, 1983; Gaitan *et al.*, 1989).

The aim of this work was to assess thyroid function, iodine intake and the exposure to dietary goitrogens of Darfur children from birth to 7 years.

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Subjects and methods

The study was carried out in Wadi-Saleh District, Southern Darfur province. There had been no previous programme of iodine prophylaxis in the district.

To study the evolution of thyroid status with age, cord blood samples were collected from 20 consecutive births and from 190 clinically euthyroid children, aged 1 month to 7 years, recruited in a community survey of one village. The objectives of the study were discussed with village leaders and mothers before children were enrolled. A standard questionnaire on breast feeding history and weaning food was given to the mothers of all the study subjects. All children were examined and clinical thyroid status was recorded. Goitre was assessed by palpation, and classified according to the World Health Organization criteria (Thilly *et al.*, 1980). Where any doubt existed about the stage of goitre, the lower stage was recorded. The clinical criteria used

Table 1 Comparison of the serum levels of T4, FT4, T3, TSH with age

	Age (years)				Belgian controls 0–7 years
	birth	<2	3–4	5–7	
T4 (nmol/l)	82±50 (20)	73±46 (43)	37±38 (81)***†	36±38 (66)***‡	126±13·2 (174)
FT4 (pmol/l)		10·0±7·1 (43)	5·1±5·4 (78)***†	4·9±5·4 (65)***‡	19·4±3·6 (174)
T3 (nmol/l)	1·1±0·6 (20)	2·8±1·1 (43)	2·8±0·9 (80)NS	2·7±1·1 (66)NS	2·96±0·79 (173)
TSH (mU/l)	25·8 (6·2–107·7)(15)	8·3 (2·5–27·8)(43)	15·3 (2·9–79·1)(80)NS	16·4 (2·7–98·3)(66)NS	2·9 (0·6–4·2)(174)

NS Not significant ($P>0·05$); *** $P<0·001$. Number of subjects in parentheses.
Arithmetic mean ± 1 SD or geometric mean ± 1 SD for serum TSH.
† Levels of significance by Scheffé multiple comparison test: <2 years *vs* 3–4 years.
‡ Levels of significance by Scheffé multiple comparison test: <2 years *vs* 5–7 years.

for the classification of endemic cretins were those set out by the Pan American Health Organization (Querido *et al.*, 1974).

Blood and urine samples were taken for determination of serum T4, FT4, T3, TSH, TBG, urinary iodide and thiocyanate. All samples were frozen within 8 hours and kept frozen until time of analysis. Serum TSH concentrations were measured by immunoradiometric assay, using a kit obtained from Diagnostic Products Corporation (DPC, Los Angeles, California, sensitivity 0·03 mU/l). Serum T4, FT4, T3 concentrations were measured by radioimmunoassay in duplicate using commercial kits (DPC, Los Angeles, California; sensitivity T4: 3.86 nmol/l, FT4: less than 0·13 pmol/l and T3: 0·11 nmol/l). Serum TBG was measured by radioimmunoassay by a commercial kit (Behring, Marburg, FRG). Urinary iodide and thiocyanate concentrations were measured in spot samples as previously reported (Vanderpas *et al.*, 1984). The data are presented as the arithmetic mean ± 1 SD. However, serum TSH and urinary iodide are both expressed as the geometric mean ± 1 SD, since the log-transformed value of both parameters better fits a normal distribution. In the figures, data are presented as arithmetic or geometric mean ± 1 SEM.

The normal reference values of the 174 euthyroid children from Belgium are the same as those previously published (Vanderpas *et al.*, 1984). The hormone concentrations in Belgian children were measured by our own radioimmunoassay. There were no significant age trends in this control group for any of the determinations. The iodine intake in Belgium has been recently considered as marginally low (Bourdoux, 1990).

One-way ANOVA, Scheffé's test for comparison of means, and the Chi-squared test for comparison of proportions were performed. All statistical procedures were conducted with the Statistical Package for Social Sciences (SPSSPC+, SPSS, Inc, Chicago).

Results

The overall prevalence of hypothyroidism (TSH > 50 mU/l) in the children studied was 24% (49/205). Table 1 shows the mean serum concentrations of T4, FT4, T3 and TSH

Table 2 Comparison of the frequencies of low T4, low T3 and high TSH in the three age groups

	Age (years)		
	<2	3–4	5–7
A: T4 < 38·6nmol/l (30 μg/l)	30 (13/43)	60 (48/80)**†	65 (43/66)***‡
B: T3 < 1·69nmol/l (1·1 μg/l)	14 (6/43)	6 (5/80)NS	11 (7/66)NS
C: TSH > 50mU/l (50 mU/l)	12 (5/43)	26 (21/80)NS	29 (19/66)*‡
A and B	5 (2/43)	6 (5/80)NS	9 (6/66)NS

NS Not significant ($P>0·05$); * $P<0·05$; ** $P<0·01$; *** $P<0·001$.
† Levels of significance: <2 years *vs* 3–4 years.
‡ Levels of significance: <2 years *vs* 5–7 years.
Frequencies expressed in percentages. Ratio between the number of pathological values and the total number of values in parentheses.

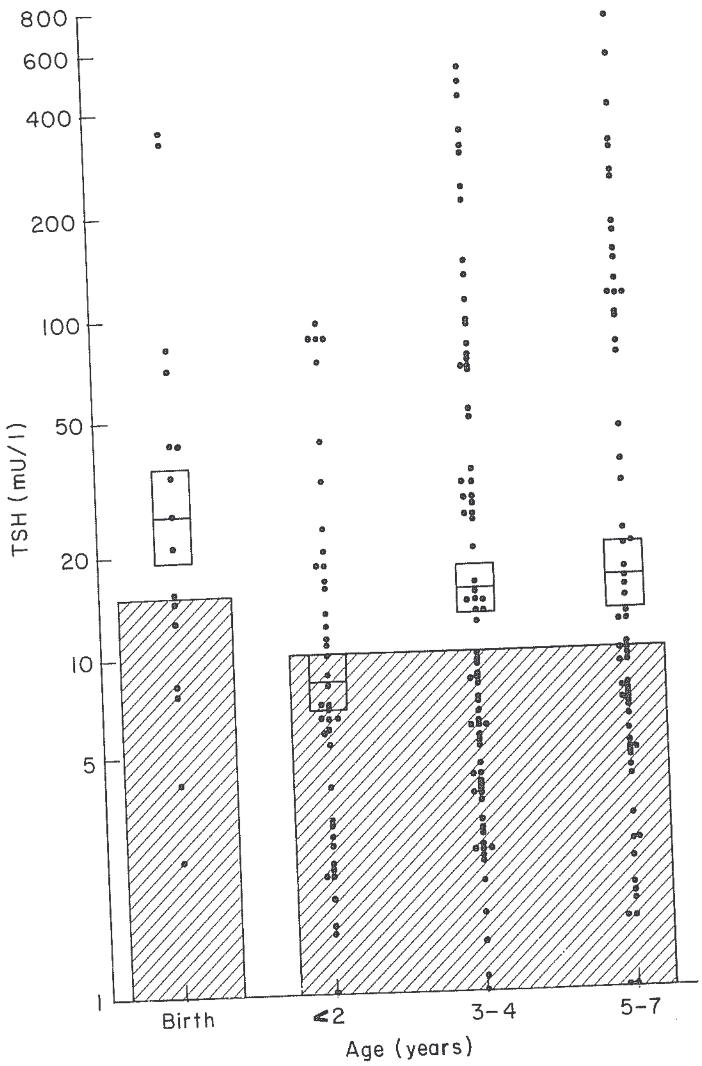

Fig. 1 Serum TSH values in newborns and in children from Darfur, Sudan, divided in three age groups: <2, 3–4 and 5–7 years. ▨, Range of values in normal Belgian children.

measured in the newborn and children across three age groups; less than 2 years, 3–4 years and 5–7 years. Thyroid function in the newborn was characterized by low T4, high TSH and normal T3. Compared to these neonatal values,in the less than 2 years age group, serum T4 remains low, whilst mean serum TSH decreased. A marked deterioration of thyroid function was observed in the next two age groups, characterized by a significantly lower serum T4 and FT4 ($P<0.001$) and higher serum TSH. The one-way analysis of variance (ANOVA) shows that the observed differences in serum TSH were at the limit of significance ($P=0.06$).

Mean serum T3 and TBG (29 ± 7mg/l) stayed within normal ranges and did not change significantly with age.

The mean and the individual values of serum TSH at birth and within the three age groups is illustrated in Fig. 1. This shows the wide variability of TSH values. An increase in the proportion of serum TSH values above 50mU/l was observed in both the 3–4 and 5–7 years age bands. Unlike the other age groups there was no TSH value above 100mU/l in the less than 2 years group.

Table 2 compares the frequencies of low serum T4 and T3 and high TSH in the children of each age group. It shows a significant increase of the frequency of low T4 (<38·6 nmol/l (or 30 μg/l)) and high TSH (>50 mU/l) with age. In the 5–7 years age group, the frequency of low T4, high TSH and simultaneously low T4 and T3 was greater than in the less than 2 years group (65, 29 and 9% respectively).

Figure 2 shows the increasing prevalence of goitre with age ($P<0.001$), and the evolution of urinary thiocyanate and iodide concentration.

Table 3 Serum T4, T3 and TSH of cretins aged 13 to 24 years

Age (years)	Sex	Goitre (stage)	T4 (nmol/l)	T3 (nmol/l)	TSH (mU/l)	Clinical form
24	f	0	1·3	0·53	1000	myxoedematous
13	m	2	1·3	1·58	73	neurological
15	m	2	1·3	0·96	69	neurological
20	m	0	27	2·18	18	neurological

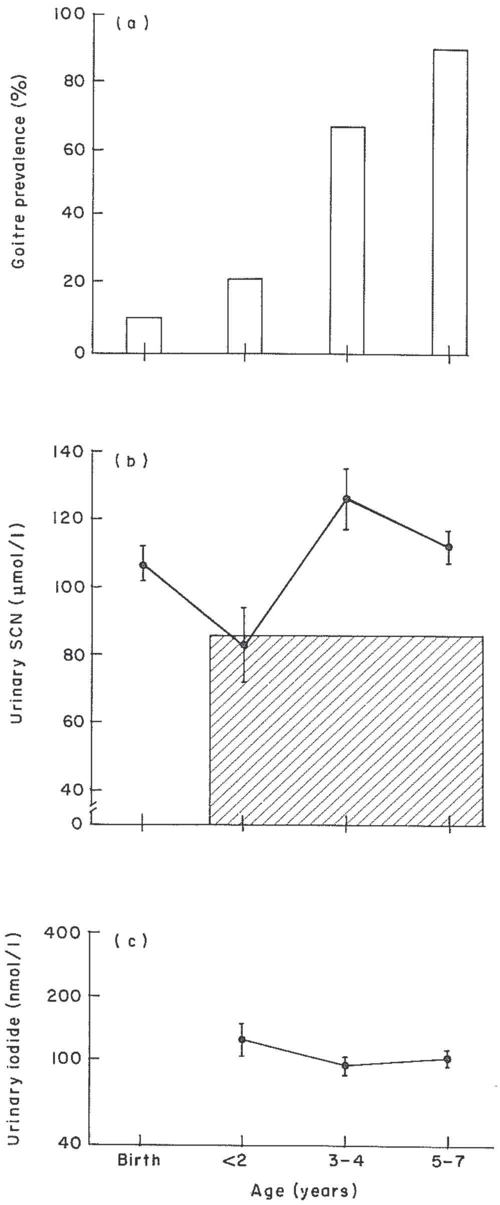

Fig. 2 Evolution with age of a, prevalence of goitre; b, urinary thiocyanate concentration; c, urinary iodide concentration. For the SCN, ▨ represents the range of values in Belgian children.

Two cases of visible congenital goitre were observed among the 20 newborns. The urinary iodide concentration was low, 105(83–133) nmol/l and did not vary significantly with age. By contrast, mean thiocyanate urinary concentration changed significantly with age; at birth it was $107 \pm 68{\cdot}9$ μmol/l, had decreased to 83 μmol/l in the group less than 2 years and then increased to 126 ± 69 μmol/l at 3–4 years ($P < 0{\cdot}01$).

The questionnaire on feeding habits showed that 70% of one-year-old children were still exclusively breastfed, 25% received supplementary food and 5% were fully weaned. At 2 years of age, 70% of children received supplementary food and 30% were fully weaned. At 30 months 80% were fully weaned. The first weaning food used is a porridge prepared with millet and cow's fat.

Table 3 shows the individual values of thyroid hormones of the endemic cretins detected in the village. Three were clinically classified as neurological cretins, one as a myxoedematous cretin.

Discussion

The aim of the present study was to focus on the relationship between iodine deficiency, dietary goitrogens, and thyroid function in children. The main findings of the study were: (1) an extremely high frequency of hypothyroidism at every age group; (2) a higher frequency of hypothyroidism in children older than 2 years.

Our results clearly show an extremely high frequency of hypothyroidism in clinically normal subjects. None of them presented obvious signs of mental retardation, but as no psychometric evaluation was performed, we cannot exclude any minor degree of impaired mental development. Four cases of cretinism were detected. Neurological cretinism was predominant over myxoedematous, and it was associated with biochemical hypothyroidism. These data allow only for a rough estimation of the prevalence of cretinism in Darfur, of 0·5%.

Our data show that hypothyroidism was less frequent during the breastfeeding period than after the age of 2 years. This difference was not associated with changes in iodine intake, as reflected by the stable, low urinary iodine concentrations in all age groups. In normal children living in areas where iodine intake is optimal, a slight decrease with age of serum T4 and T3 without change in serum TSH has been observed (Fisher *et al.*, 1977; Parra *et al.*, 1980). This phenomenon has been attributed to the progressive decrease in serum TBG concentration (Fisher *et al.*, 1977; Hesch *et al.*, 1977) and to a change in pituitary T4 feedback sensitivity with age (Fisher *et al.*, 1977). In the iodine deficient region of Darfur, the significant fall of T4 with age was however accompanied by a similar fall in FT4 and an increase in TSH.

The thyroid hormone or iodine content of human milk is unlikely to protect breastfed children from hypothyroidism. Several studies have shown that the thyroid hormone content of human milk is low (Varma *et al.*, 1978; Vigouroux *et al.*, 1980; Möller *et al.*, 1983; Glasscock & Nicoll, 1983). The iodide content of the milk of Darfur mothers is likely to be as low as reported in other endemic areas, since the urinary iodine excretion in Darfur lactating women was very low (data not shown).

The deterioration of thyroid function, observed in children older than 2 years, may be explained by the intervention of goitrogenic factors, which represent an additional stress to the iodide-depleted thyroid gland. A higher prevalence of goitre and thyroid anomalies has been observed in rural areas of Darfur where millet consumption is greater than in urban areas, despite a similar degree of iodine deficiency (Osman & Fatah, 1981; Osman, 1981; Eltom *et al.*, 1985a). Indeed, millet has strong antithyroid activity *in vitro* and *in vivo*, and this activity is directly correlated to the flavonoid content of different millet fractions (Gaitan *et al.*, 1989). Millet also contains thiocyanate, whose goitrogenic activity has been well documented (Bourdoux *et al.*, 1978). Thiocyanate overload, from consumption of poorly detoxified cassava, is implicated in the Ubangi area in the genesis of juvenile hypothyroidism (Vanderpas *et al.*, 1984, 1986). Thiocyanate (and probably flavonoids) pass freely through the placenta, but remain low in maternal milk, even when maternal serum levels are high (Funderburk & Van Middelsworth, 1967; Vanderpas *et al.*, 1984). In Darfur, the fetus is thus exposed to thiocyanate and probably flavonoids before birth, whilst infants are protected, as indicated by the low urinary thiocyanate concentration during the breastfeeding period. The goitrogenic activity of goitrogens in the Darfur diet is however unlikely to induce goitre by itself. As has been previously shown, the correction of iodine deficiency in Darfur prevents the development of goitre and normalizes thyroid function (Eltom *et al.*, 1985b). Flavonoids and thiocyanate act on iodine metabolism at different sites. Thiocyanate inhibits the iodine concentrating mechanism while flavonoids prevent the oxidation of iodine by inhibiting the thyroid peroxidase (Gaitan *et al.*, 1989).

Very few studies have been conducted to monitor thyroid function of children in iodine deficient areas, and it is therefore difficult to compare these data with other endemic goitre areas, though a comparable evolution of thyroid function with age in Ubangi, Zaire, has been reported (Vanderpas *et al.*, 1984).

In conclusion, our data indicate that iodine deficiency and the goitrogenic action of millet were likely to be responsible for the higher frequency of hypothyroidism in children older than 2 years of age. The very high frequency of children with hypothyroidism, and the prevalence of endemic cretinism in Darfur, obviously represent a major public health problem and justify the programme of iodine supplementation with iodized oil implemented since 1989.

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