Iodine deficiency, hypothyroidism, and endemic goitre in Southern Tanzania*

A survey showing the positive effects of iodised oil injections by TSH determination in dried blood spots

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SUMMARY The Ukinga and Uwanji regions, located in the southern highlands of Tanzania, were studied for the degree of iodine deficiency and the incidence of goitre and hypothyroidism, respectively. A urinary iodine excretion as low as $17.6 + 9.3 \mu\text{g/g}$ creatinine was observed in Wangama village. The mean goitre prevalence in 27 villages in Uwanji ranged between 65 and 96% ($n=3031$ schoolchildren). Of 681 pregnant women from Ukinga 79.6% had goitre. The prevalence of cretinism as estimated on clinical criteria was 3% in Magoye (Uwanji). A normal serum TSH (below 2.1 mU/l) was observed in only 12 out of 66 school children before iodine prophylaxis, whereas the T_4/TBG ratio was decreased in 36 of 63 cases. Blood spot TSH levels in newborn infants ($n=219$) from mothers without iodine supplementation were above 12 mU/l in 45%. In contrast, only 20.3% of the newborn ($n=118$) had elevated blood spot TSH ($p<0.002$) when the mothers had received an iodised oil injection during pregnancy. Most of the newborn ($n=18$; 75%) of the latter group with elevated TSH ($n=24$) came from mothers who had received the iodine injection only 1–25 days before delivery. Maternal iodine prophylaxis in late pregnancy does not increase the rate of neonatal hypothyroidism.

Conclusions: (1) It has been confirmed that severe iodine deficiency resulting in endemic goitre, cretinism, and hypothyroidism is prevalent in the regions studied. (2) Dried blood spot TSH determinations may serve as an index for the efficiency of iodine prophylaxis programmes. (3) Such a programme was carried out with relatively little expenditure and effort on a large scale basis.

Numerous areas of endemic goitre and cretinism throughout the world^{3 12 13} have been studied. Unfortunately, both diseases have not yet been eradicated, although preventive programmes have been convincingly suggested and introduced in many countries known to have areas of endemic goitre and iodine deficiency.^{3 8 12} Two different areas of the southern Highlands of Tanzania, Ukinga, and Uwanji, having a mean altitude of 2000 m were surveyed for the prevalence of endemic goitre. Iodine was measured in urine specimens from

schoolchildren, in samples of drinking water, and in non iodised salts in order to confirm iodine deficiency in this area. Target populations such as pregnant women, newborn, and schoolchildren were also studied for the incidence of hypothyroidism before and after iodine supplementation.

The aims of this study were (1) to confirm the areas of Ukinga and Uwanji as areas of endemic goitre and cretinism due to iodine deficiency, according to the PAHO-criteria;³ (2) to perform a preliminary study with iodine prophylaxis in order to show its effectiveness in decreasing hypothyroidism; (3) to explore to what extent a decrease in blood spot TSH as compared to serum TSH may serve as an

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indicator of the effectiveness of iodine prophylaxis in areas with limited technical facilities; and (4) to convince the authorities of the need to install an effective preventive programme.

Methods

POPULATION STUDIED

In both areas, Uwanji and Ukinga, Cassava² is only a minor constituent of the diet but exact data are lacking for these regions.

Uwanji Altogether 3031 schoolchildren aged 6 to 18 years, 118 pregnant women (table 1), and 29 children under the age of 6 years were examined for thyroid enlargement by palpation. The goitres were graded according to the WHO classification of endemic goitre¹² with the modification that grade OB was included in grade I.

Table 1 Gradation of thyroid enlargement in young women (n=681) in Ukinga and schoolchildren (n=3031) in Uwanji.

Grade	Women		Schoolchildren	
	n	%	n	%
0	139	20.4	255	8.4
I	225	33.0	1591	52.5
II	287	42.2	752	24.8
III	30	4.4	433	14.3
I-III	542	79.6	2776	91.6
Total	681	100	3031	100

In one village (Magoye), 700 inhabitants were investigated for signs of deaf mutism, growth and mental retardation in an attempt to estimate the prevalence of clinically overt cretinism.

Ukinga In 1979, 371 pregnant and 221

non-pregnant women attending Consolata Fathers' Hospital in Ikonda were investigated for goitre. All the newborn as well as all babies up to 4 months of age brought to the Maternity and Child Health Clinics (MCH) were included in the survey, which comprised physical examination of the thyroid and determination of TSH levels.

IODINE SUPPLEMENTATION

Iodised oil injections were given intramuscularly in doses of 1 ml each (Lipiodol^R, Byk-Gulden, Constance FRG), which contained 480 mg iodine bound to the ethyl ester of oleum papaveris. This dose was reported to provide adequate iodine supplementation for approximately three to five years.⁸ Iodised oil injections were given to all 371 pregnant women from Ukinga 1 to 230 days before delivery, where the injections were recorded in the antenatal records, and to approximately 12 000 inhabitants of Uwanji, including 8000 schoolchildren 6-18 years of age, representing approximately 60% of all schoolchildren in this area.

Iodised salt was distributed in a pilot study to all families in Wangama village (Uwanji) with the advice to use only this salt (50 mg KI/kg NaCl).

BLOOD SPOT TSH SAMPLING IN BABIES AND NEONATES

Blood spot samples for TSH analysis were taken by heel-prick from 224 babies up to age 4 months and from 304 newborn in the first four days of life (Uwanji and Ukinga; table 2). Because the mothers usually leave the Maternity Unit early, it was not possible to perform a sampling for neonatal TSH on day 5 as optimal.¹

In 191 cases the mothers had received iodine prophylaxis during pregnancy whereas 219 mothers had not received iodine because they attended the MCH clinic only late in pregnancy (table 2).

Table 2 Distribution of elevated blood spot TSH levels in children of mothers without and with iodine supplementation during pregnancy, compared with two Munich control groups.

The mean calculated iodine intake of adults is $32 \pm 15 \mu\text{g/d}$ in Munich.⁷

Blood samples taken on:	Children of:						Munich control group			
	Untreated mothers			Treated mothers						
	n	TSH>12 mU/l	%	n	TSH>12 mU/l	%	n	TSH>12 mU/l	%	
Newborn										
Day zero	13	8	61	40	12	30	18	9	50	
1	42	19	45	55	8	15	65	11	17	
2	6	2	33	17	3	18	20	0	—	
3	8	2	25	5	1	20	—	—		
Total	69	31	45	117	24	21	103	20	19	
Babies										
5 days to 4 months	150	4	2.7	74	0	—	127	0	—	

TSH DETERMINATION IN DRIED BLOOD SPOTS

The radioimmunological TSH determination in dried blood spots on filter paper (filter paper method, FPM) was performed by modification of a published radioimmunological determination for serum TSH.^{4 14 16} The interassay coefficients of variation were 14.3% for 54.2 mU TSH/l (n=12) and 16.7% for 34.8 mU TSH/l (n=16). The lower limit of detection was 6.4 mU/l, the 50% inhibition of tracer binding 31.3 mU/l (n=15). WHO 68/38 TSH standard, dissolved in TSH-free human blood, was used as material for the standard curve.

STABILITY OF TSH IN DRIED BLOOD SPOTS ON FILTER PAPER AND IN SERUM

Blood spots on filter paper with a known TSH content were subjected to different storage conditions and then measured in a serial assay. The storage time was four months at -20°C , one week, two and six weeks at room temperature, and one week at $+37^{\circ}\text{C}$ (fig 1). TSH remained almost stable at -20°C over four months but the activity decreased by approximately 25% after one or two weeks at room temperature and by about 75% after one week at $+37^{\circ}\text{C}$. In order to investigate the loss of activity during transport from Tanzania to Germany, freshly dried blood spots with a known TSH content were transferred by air directly to Tanzania and returned by the usual postal service. The delivery from Tanzania to Munich took six weeks, the decrease of TSH activity being approximately 50% (fig 1).

Fig 1 Dependence of TSH recovery on storage time and temperature.

The level (100%) ranged from 31 to 200 mU/ml.

The fall of TSH reactivity is based on the TSH measurement of seven filterpapers, each in triplicate ($\pm$ SD). TSH recovery after storage of the samples under different temperature conditions (dotted line) and after transport from Tanzania to Munich (solid line).

Furthermore, serum samples of eight patients with serum TSH levels from 1.0 to 41.0 mU/l stored at $+20^{\circ}\text{C}$ on day zero and at 1, 2, and 6 weeks showed no loss of hormonal activity when measured serially in a routine TSH radioimmunoassay.

Filter paper samples collected in Tanzania were dried and stored at 4°C until the transfer by air to Munich, where they were stored at -20°C before determination. Thus losses of TSH immunoreactivity as described above have to be taken into consideration, and an underestimation of the prevalence of hypothyroidism in the Tanzanian children may be possible.

The analysis of thyroxine (T_4), triiodothyronine (T_3), thyroxine binding globulin (TBG), and thyrotrophin (TSH) in serum samples as well as the determination of iodine in urine, salt, and drinking water were performed by published methods.^{4 6 7 10 16}

Results

IODINE DEFICIENCY IN UWANJI

The iodine content in seven local non iodised salt samples from different Uwanji villages was found to be in the range 0.7–9.4 mg iodine/kg salt with the exception of one sample which inadvertently contained as much as 85 mg iodine/kg salt.

Urinary iodine excretion was assessed in 23 individuals before iodine supplementation in Wangama village and found to be $17.6 \pm 9.3 \mu\text{g}$ (mean $\pm$ SD) per g creatinine.⁷ After replacement of the local salts by the iodised salt the mean iodine excretion increased to $93.3 \pm 59.0 \mu\text{g}$ iodine/g creatinine in 13 reinvestigated subjects.

PREVALENCE OF ENDEMIC GOITRE AND CRETINISM IN UWANJI AND UKINGA

The goitre prevalence was 79.6% in 681 young women during pregnancy or shortly after delivery (table 1). Among the 3031 schoolchildren examined, the mean goitre prevalence was 91.6%; the mean values for 27 villages ranged from 65 to 96.5%.

The clinical investigation of approximately 700 inhabitants of Magoye village led to a rate of assumed cretinism of 3%. The 23 individuals with the clinical diagnosis of cretinism had normal TBG levels, the serum thyroxine was decreased in 20 cases, and the serum TSH levels were raised in 12 (range 4–60 mU/l).

HYPOTHYROIDISM IN SCHOOLCHILDREN; COMPARISON OF T_4 /TBG RATIO AND TSH BEFORE AND AFTER IODINE SUPPLEMENTATION

The blood spot TSH levels were elevated (range 20–200 mU/l) in 10 out of 101 schoolchildren before iodine oil injections. In contrast, TSH levels were

below 12 mU/l in all 123 investigated subjects three months after iodine injection.

The situation appeared more dramatic when the serum TSH levels were determined. Before iodine injection only 12 out of 66 children had normal TSH levels below 2.1 mU/l, whereas the levels were moderately elevated (range 2.1–10.0 mU/l) in 29 and markedly elevated (range 10–200 mU/l) in 25 of the children. The T_4 /TBG ratio was decreased in 36 out of 62 investigated children (fig 2).

Three months after iodine injection, the TSH levels were moderately elevated in 16 and grossly elevated in only 1 out of 69 children. The T_4 /TBG ratio was decreased in only 2 out of 71 children. An elevated T_4 /TBG ratio, suggesting hyperthyroidism, was found in one child before and in four children after iodine supplementation.

A special group of 23 pupils in Wangama with goitre grade III and a marked growth retardation was assumed to have borderline cretinism (fig 3). Whereas the TSH levels were increased in all but two, the T_4 /TBG ratio was low in 15, the T_3 levels being elevated in nine of this group. However, the increases in T_3 levels did not compensate for the thyroxine deficiency as concluded from the elevated TSH levels. The urinary iodine excretion was below 45 $\mu\text{g/g}$ creatinine in all but one, who seemed to have an exogenous iodine contamination, as the urinary iodine excretion was 239 $\mu\text{g/g}$ creatinine. Of these 23 children, 17 were reinvestigated three months after the distribution of iodised salt. The TSH levels were found to be in the range 1.5–5.0 mU/l in 16 cases. The T_4 /TBG ratio was normal in all except two (fig 3).

Fig 2 Serum TSH levels and T_4 /TBG ratio in schoolchildren before and three months after iodised oil injection. The upper limit of the normal range of serum TSH is 2.1 mU/l; the normal range of T_4 /TBG ratio is 1.8–5.7.

Fig 3 Thyroid function and urinary iodine excretion in 23 selected schoolchildren with goitre grade III and growth retardation in Wangama.

T_4 /TBG and TSH levels on the left represent the data before, the respective value on the right side the data three months after the use of iodised salt.

T_3 levels could be determined in only 22 serum samples.

BLOOD SPOT AND SERUM TSH LEVELS IN WOMEN BEFORE AND SHORTLY AFTER DELIVERY AND BLOOD SPOT TSH IN THEIR BABIES

The blood spot TSH levels were below the limit of detection both in pregnant women from Tanzania ($n=66$) and in the Munich control group ($n=26$). In contrast, the serum TSH levels were found to be above 2.1 mU/l in 24 (72.9%) out of 33 pregnant women and in 6 (33.3%) of the 18 women after delivery in Ukinga. The serum TSH levels and the T_4 /TBG ratio of 29 mothers were compared with the blood spot TSH levels of their babies on days 11 to 93 after birth. No significant correlation could be shown between the individual maternal T_4 /TBG ratio and the blood spot TSH levels of their babies; however, 14 of 29 babies with an elevated TSH were born to mothers with a subnormal T_4 /TBG ratio and thyroid enlargements grade I–III.

BLOOD SPOT TSH LEVELS IN THE NEWBORN AND BABIES: EFFECT OF IODINE PROPHYLAXIS IN THE MOTHERS

The TSH values of babies born to mothers without iodine supplementation were elevated in 45% of the 69 newborn (range 12–200 mU/l) and in 2.7% of the 150 older babies (table 2). In contrast, the TSH levels

of babies born to mothers after iodised oil injection during pregnancy were above 12 mU/l in only 21% of the 117 newborn and in none of the 84 older babies (table 2). The difference between the TSH levels of the children of iodine treated and untreated mothers was highly significant ($p < 0.001$).

For comparison, the blood spot TSH levels of two Munich control groups of newborn from mothers living in the iodine deficiency area of Munich were determined. In this region the mean calculated iodine intake of adults is $32 \pm 15 \mu\text{g/d}$.⁷ On zero to 5 days of age ($n=103$) and on day 5 ($n=127$) TSH levels were above 12 mU/l but below 50 mU/l in only 20 of the 103 newborn in the first two days of life. All TSH levels were found to be below 12 mU/l in Munich after the second day of life.

The date of iodine injection in relation to the gestational age was found to influence the prevalence of elevated TSH in the newborn. Iodine injection given at the end of the last trimester was accompanied by an elevation of TSH level in 33.9% of the babies, range 12–70 mU/l (fig 4). In contrast, iodine supplementation given earlier during pregnancy resulted in only 9.2% of cases with elevated TSH. In other words, 75% of the newborn with elevated TSH levels were born to mothers who

had received iodine supplementation only shortly before delivery.

Discussion

This survey shows the persistence of severe goitre endemicity in the southern highlands of Tanzania documented earlier by Latham,¹¹ which is due to the lack of a systematic iodine prophylaxis programme. Concomitantly, the prevalence of hypothyroidism was deduced from elevated serum TSH levels in 82% and decreased T₄/TBG ratios in 58% of the schoolchildren.

In one village (Magoye), cretinism was suspected in 3% of the inhabitants. In another village, a group of

23 schoolchildren was assumed to have borderline cretinism because of marked growth retardation, goitre grade III, and hypothyroidism (fig 3). Although these data allow only a rough approximation of the prevalence of cretinism in these regions, they indicate the significance of iodine deficiency for the regional public health.

In this study, the simple method of TSH determination in dried blood spots was used for an approximate estimation of severe hypothyroidism. The filter paper cards are easily transportable to laboratories capable of performing the TSH radioimmunoassay. However, using the filter paper method, a loss of TSH immunoactivity¹⁵ due to prolonged storage of the filter paper and to environmental temperature and humidity has to be taken into account. This problem was not discussed in another publication⁵ describing severe iodine deficiency goitre prevalence of 86% and elevated blood spot TSH above 7.5 mU/l in 40% of schoolchildren in a mountain area in Spain. In this study, clearly elevated TSH levels were found in 10% of the schoolchildren, in 45% of the newborn, and in 2.7% of babies up to the age of 4 months born to mothers without iodine prophylaxis. In addition, it could be documented that the prevalence of elevated TSH levels decreased after iodine supplementation. Undoubtedly, however, blood spot TSH levels below 12 mU/l do not necessarily exclude moderate and mild hypothyroidism under the conditions of our study. By shortening the transport time and introducing a more sensitive TSH assay this method could become even more useful for epidemiological investigations in areas of severe iodine deficiency and limited technical facilities.

The use of iodised oil has already been shown to be superior to iodised salt wherever economic and geographical obstacles are the dominant factors in developing countries.^{3,8,12} Nevertheless, special attention was again given to this problem:

(1) Determination of the iodine content of locally produced salts which were said to be "valuable for goitre patients" showed a sufficiently high iodine content in only a single sample. This salt, however, originated from an area where endemic goitre was not noted by the local health authorities; it was produced in only small amounts for a fairly high price. As a result, this local salt preparation cannot be used as an effective permanent prophylaxis in this region.

(2) The regular salt was replaced completely by a reliably iodised salt over a period of several months in a rather isolated village (Wangama) within the mountain region. Serum TSH levels were investigated in a group of grammar schoolchildren

Fig 4 Comparison of the blood spot TSH levels in the newborn.

Left: newborn of mothers who received iodine only 1 to 25 days before delivery.

Right: newborn of mothers who received iodised oil injection 25 to 183 days before delivery.

before and after the introduction of this salt. The efficiency of this kind of prophylaxis could be documented in this village. However, a regular distribution of iodised salts is not feasible in these remote areas due to the insufficient road network and the lack of local salt factories.

In contrast, iodine supplementation using an oil preparation led to both a significant decrease of elevated serum TSH levels and an increase in T₄/TBG ratios in schoolchildren and in young women. Moreover the incidence of elevated TSH levels in the newborn and in older babies could be lowered by iodine supplementation of the mothers during pregnancy. The prevalence of elevated TSH levels in the newborn was lower when iodine was given during early pregnancy. Further, it should be recognised that neither the prevalence nor the range of elevated TSH of the newborn from mothers who received iodine late in pregnancy were higher compared to that of the newborn from untreated mothers. Thus, there is no aggravation of neonatal hypothyroidism by a large amount of iodine administered to the mother. These results demonstrate again the undeniable advantage of iodised oil for prophylaxis of endemic goitre and cretinism in remote areas.^{2 8 13 14}

The data in this paper document the fact that iodine deficiency is a serious public health problem in the highlands of Tanzania. The extent of physical and mental handicap related to iodine deficiency cannot be expressed fully in this investigation. It is evident that the institution of an iodine supplementation programme will result in regression of thyroid hormone deficiency and associated disorders. It can be foreseen that endemic cretinism will decrease and may even vanish. We therefore recommend iodine supplementation using iodised oil injection in pregnant women in the first and second trimesters in under-5s and pre-school age children, in schoolchildren, and in younger women during the fertile decades of life. Using this method of prevention, the prevalence of endemic goitre in young adults should be reduced from the present 90% to hopefully about 3%. Such a programme is in accordance with the recommendations of the Pan-American Health Organization of 1974.³ This committee has pointed out that iodised oil prophylaxis together with correctly organised follow-up programmes should be conducted by local public health authorities. Our study supports Hetzel's postulation⁹ for eradicating iodine deficiency disorders throughout the world.

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