

Thyroid function in thalassaemia major

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SUMMARY Serum concentrations of T4, T3, rT3, and TSH were measured by radioimmunoassay in 45 patients suffering from β -thalassaemia. A TRH stimulation test was performed and the binding capacity of TBG and TBPA for T3 and T4 measured by reverse flow zone electrophoresis in a group of these patients. Mean T4 serum concentration was lower in thalassaemic patients than controls; T3, rT3, TSH levels, and the pituitary response to TRH were normal. TBPA binding capacity for thyroxine was greatly decreased, probably due to iron overload impairing the liver function. The decreased circulating total thyroxine might be explained by the reduced TBPA capacity, serum free thyroid hormone concentration values being normal. It is concluded that thalassaemic children are euthyroid, despite often having low-normal or subnormal thyroxine levels.

Several authors have reported a high incidence of endocrine abnormalities in children, adolescents, and young adults suffering from thalassaemia major. These abnormalities can be related to the iron overload¹ caused by frequent blood transfusions, and mainly affect the pituitary-gonadal axis.² The growth retardation, noted by all authors, does not seem to depend on a pituitary defect, since growth hormone concentration, even after stimulation, is generally normal.³⁻⁶ No evidence of altered pituitary-thyroid function was found by Zaino *et al.*³ or Canale *et al.*⁴ An increased TSH response to TRH was reported by Lassman *et al.*⁷ in 4 out of 7 patients studied, and in one the results were consistent with slight primary hypothyroidism. In a more recent study, Flynn *et al.*⁵ reported decreased serum thyroxine levels with raised TSH, compatible with subclinical primary hypothyroidism.

As none of these conclusions seemed to agree, we studied thyroid function in a group of 45 patients with thalassaemia major.

Subjects and methods

45 patients aged between 1.1 and 20.4 years with β -thalassaemia (one also with sickle-cell anaemia) and 26 normal children (aged 0.6-12 years) were

studied. The diagnosis of thalassaemia major was established by clinical examination and haemoglobin electrophoresis. Most of the patients were being given blood transfusions and were also being treated with desferrioxamine. They were all followed as outpatients.

Biochemical investigations were performed immediately before each blood transfusion and at least 15 days after the previous one. The controls were healthy, prepubertal children, and only two of them (one 17-year-old girl and one 20-year-old man) had reached sexual maturity. The normal range of response of TSH to TRH stimulation in children has been established for the purpose of detecting early signs of hypothyroidism in children with goitres who live in areas where iodine deficiency is endemic.¹⁴

Abbreviations:

FT3:	free triiodothyronine
FT4:	free thyroxine
T3:	triiodothyronine
T4:	thyroxine
rT3:	reverse T3
TSH:	thyroid stimulating hormone (thyrotropin)
TBC:	thyroid binding capacity
TBG:	thyroxine-binding globulin
TBPA:	thyroxine-binding prealbumin
TRH:	thyrotropin releasing hormone

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Serum total T4, T3, and TSH were determined by specific radioimmunoassays on unextracted serum. Details are reported elsewhere.⁸⁻¹⁰ Reverse T3 (rT3) serum concentration was determined by radioimmunoassay on unextracted serum using an anti-rT3 antiserum (1:5000), raised in rabbits by injecting an rT3-bovine serum albumin conjugate, 0.2% ANS (8-anilino naphthalene-sulphonic), and DCC (Dextran-coated charcoal) (32 mg/ml), in order to achieve bound free separation.¹¹ Free thyroid hormone concentration was determined by a commercial system (Dow-Lepetit Laboratories). TSH response to intravenous TRH (5 µg/kg) was assessed by taking blood samples 15 min before, immediately before, and 15, 30, and 60 min after TRH. Binding capacity of TBG for T3 and T4 and of TBPA for T4 was determined by reverse flow-zone electrophoresis, by the method of Robbins and Rall¹² in 10 of the patients. Iron serum concentration was determined by the Weippl *et al.*¹³ method. Serum protein concentration and electrophoretic pattern were also established. Statistical analysis was performed by Student's *t* test. All values are expressed as mean ± SD.

Results

The mean T4 value (7.54 ± 2.64 µg/100 ml; 97.04 ± 33.98 nmol/l) was slightly lower in patients with thalassaemia than in the control group (9.71 ± 3.22 µg/100 ml; 124.97 ± 41.44 nmol/l) ($P < 0.05$), but was within the normal range. Only 3 patients had T4 values below the lower limit, and no clinical or biochemical evidence of hypothyroidism was found. One patient had low T4 (2.5 µg/100 ml; 32.17 nmol/l) and normal TSH (1.45 µIU/ml). The T4 values of 2 patients were slightly reduced, 3.6 and 3.4 µg/100 ml (46.3 and 43.8 nmol/l), and their T3 values were at the lower limit (60 ng/100 ml; 0.92 nmol/l). TSH concentration in both these patients was slightly raised (5.5 and 6.2 µIU/ml) but their TSH response to TRH was normal (Fig. 1).

T3 values in thalassaemic patients (160.5 ± 61.7 ng/100 ml; 2.46 ± 0.95 nmol/l) were similar to those in controls (159.2 ± 35.8 ng/100 ml;

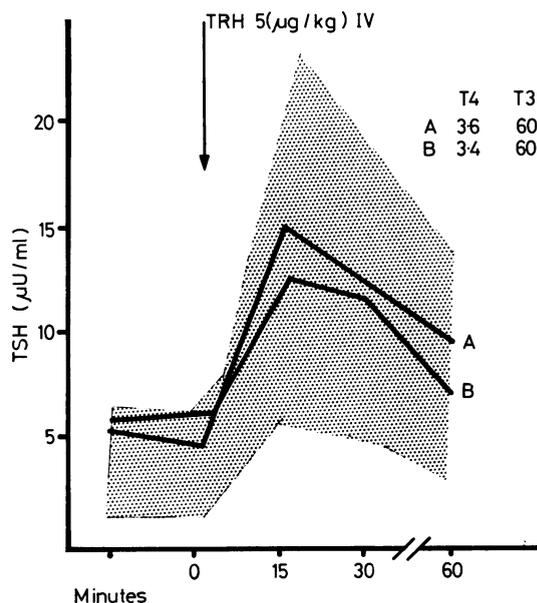


Fig. 1 TSH responses to intravenous TRH in two thalassaemic patients (A, B) with low T4 and T3 levels as shown. Normal range shown shaded.

2.44 ± 0.55 nmol/l). The mean values of FT3 and FT4 serum concentrations (FT4 11.3 ± 7.64 pg/ml; 14.46 ± 9.83 pmol/l, FT3 4.31 ± 1.69 pg/ml; 6.6 ± 2.6 pmol/l) did not differ from those of the controls (FT4 11.8 ± 6.28 pg/ml; 15.19 ± 8.0 pmol/l, FT3 4.52 ± 1.45 pg/ml; 6.9 ± 2.2 pmol/l).

The mean value of TSH was of 2.58 ± 1.66 µIU/ml in patients with thalassaemia, and 2.36 ± 1.5 µIU/ml in controls. All the baseline values, and the TSH response curves to TRH, were within the normal range (maximum peak 25 µIU/ml).

The rT3 concentration (36.7 ± 13.7 ng/100 ml; 0.56 ± 0.21 nmol/l and 37.9 ± 11.98 ng/100 ml; 0.58 ± 0.18 nmol/l) was similar in both groups. The biochemical results are summarised in Table 1. No correlation was found between T4 or TSH and age, sex, number of blood transfusions, or serum iron concentration in the thalassaemic patients.

Table 1 Circulating thyroid hormones, TSH, and rT3 in thalassaemia major (means ± SD)

Group	T4 (µg/100 ml)	T3 (ng/100 ml)	FT4 (pg/ml)	FT3 (pg/ml)	TSH (µIU/ml)	rT3 (ng/100 ml)
Thalassaemic children (n=45)	7.54 ± 2.64	160.5 ± 61.7	11.3 ± 7.64	4.31 ± 1.69	2.50 ± 1.66	36.7 ± 13.7
Controls (n=26)	9.71 ± 3.22	159.2 ± 35.8	11.8 ± 6.28	4.52 ± 1.45	2.36 ± 1.53	37.9 ± 11.9
P	<0.05	NS	NS	NS	NS	NS

Conversion: traditional to SI units—T4: 1 µg/100 ml ≈ 12.87 nmol/l. T3: 1 ng/ml ≈ 1.536 nmol/l. FT4: 1 pg/ml ≈ 1.287 pmol/l. FT3: 1 pg/ml ≈ 1.536 pmol/l. rT3: 1 ng/ml ≈ 1.536 nmol/l.

Table 2 T4 binding capacity and T3 binding capacity in thalassaemia major (means \pm SD)

Group	T4 binding capacity		T3 binding capacity
	TBG	TBPA	TBG
Thalassaemic children (n = 10)	19.72 \pm 2.02	68.47 \pm 12.75	4.88 \pm 0.39
Controls (n = 10)	21 \pm 3.5	110 \pm 18	5.5 \pm 0.6
P	NS	<0.005	NS

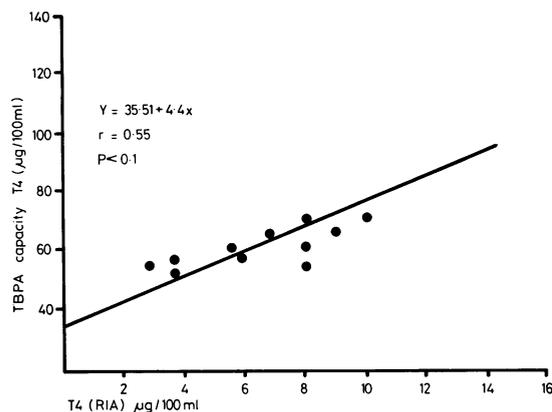


Fig. 2 Relation between T4 levels and TBPA capacity in 10 thalassaemic patients.

Finally, the TBG and TBPA binding capacity for thyroid hormones was evaluated in 10 patients whose T4 was in the lower range. TBG capacity was close to normal, unlike TBPA capacity which was greatly reduced (Table 2). A positive correlation between T4 serum concentration and the binding capacity of TBPA was observed ($r = 0.552$, $P < 0.1$) (Fig. 2). All the patients had low total serum proteins. The electrophoretic pattern generally showed hypoalbuminaemia with hypergammaglobulinaemia.

The iron concentration in most of the patients was >200 $\mu\text{g}/100$ ml (>35.8 $\mu\text{mol}/\text{l}$).

Discussion

The primary hypothyroidism ascribed to iron overload at thyroid level reported by Flynn *et al.*⁵ was not confirmed in this study. Specific biochemical tests of thyroid function showed no abnormalities of the pituitary-thyroid axis in our patients with β -thalassaemia. T3, T4, and TSH values were well within the normal range, while lower levels of T4 were not associated with any increase in TSH levels. In 2 patients both T3 and T4 concentrations were below the normal range, and TSH baseline values were slightly increased; nevertheless TRH stimulation did not elicit an abnormally large pituitary

response, and so gave no indication of increased pituitary reserve. This pattern is in keeping with the observation of normal concentration of free thyroid hormones and a sharply reduced TBPA binding capacity.

The metabolic pathways of thyroxine deiodination seemed to be unaffected. T3:T4 ratio was similar in both groups, while 3, 3', 5' triiodo-L-thyronine concentration was no different in patients and controls. This was despite apparently impaired liver function in the majority of patients, as shown by a consistently low serum plasma protein and low albumin/globulin ratio.

We think the slightly lower levels of T4 can be attributed to the abnormality in T4-binding capacity for TBPA (T4- and T3-binding capacity for TBG was normal). The greatly reduced TBPA binding capacity may induce the slight but significant decrease of T4 levels without affecting the euthyroid status, maintained by the normal levels of free thyroid hormones.

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