HYPERTHYROXINAEMIA DUE TO DECREASED PERIPHERAL TRIIODOTHYRONINE PRODUCTION

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Summary Two patients, a boy of 8 and a woman of 60 years of age, had higher than normal levels of serum total thyroxine (T_4), free T_4 (FT_4), FT_4 index, and reverse triiodothyronine, but normal serum triiodothyronine (T_3) levels. The pituitary-thyroid axis could be normally stimulated by thyrotropin-releasing hormone, suggesting euthyroidism at the pituitary level. High levels of serum T_4-binding globulin decreased during T_3 treatment in the boy. Studies show that in these patients a raised serum FT_4 is necessary to produce in the peripheral tissues sufficient amounts of T_3 for biological action. Two possible mechanisms for a basic defect underlying this newly recognised syndrome are proposed: inhibition of T_4 transport into tissue cells and reduced intracellular 5'-deiodinase activity catalysing T_4 to T_3 conversion.

Introduction

HYPERTHYROXINAEMIA is usually caused by hyperfunction of the thyroid gland. In this disorder free thyroxine index (FT_4I) and levels of total (T_4) and free thyroxine (FT_4), triiodothyronine (T_3), and reverse T_3 (rT_3) are raised, and the pituitary-thyroid axis is suppressed, as indicated by an absent serum thyrotropin (TSH) response to TSH-releasing hormone (TRH). Hyperthyroxinaemia can also exist in the presence of euthyroidism—e.g., when T_4-binding-globulin (TBG) levels are raised and when there is peripheral resistance to thyroid hormones.[1] In the first case levels of free thyroid hormones are normal and in the latter the biochemical pattern is that of thyrotoxicosis, with all parameters of serum iodothyronines above normal. We have described[2,3] another cause of euthyroid hyperthyroxinaemia—in familial euthyroid T_4 excess. In this syndrome serum T_4 and FT_4I are raised owing to the presence of an additional T_4-binding protein in the albumin fraction. Subjects with this syndrome are euthyroid and serum FT_4, T_3, and rT_3 are normal. We now report another hitherto unrecognised syndrome, encompassing hyperthyroxinaemia in two euthyroid subjects.

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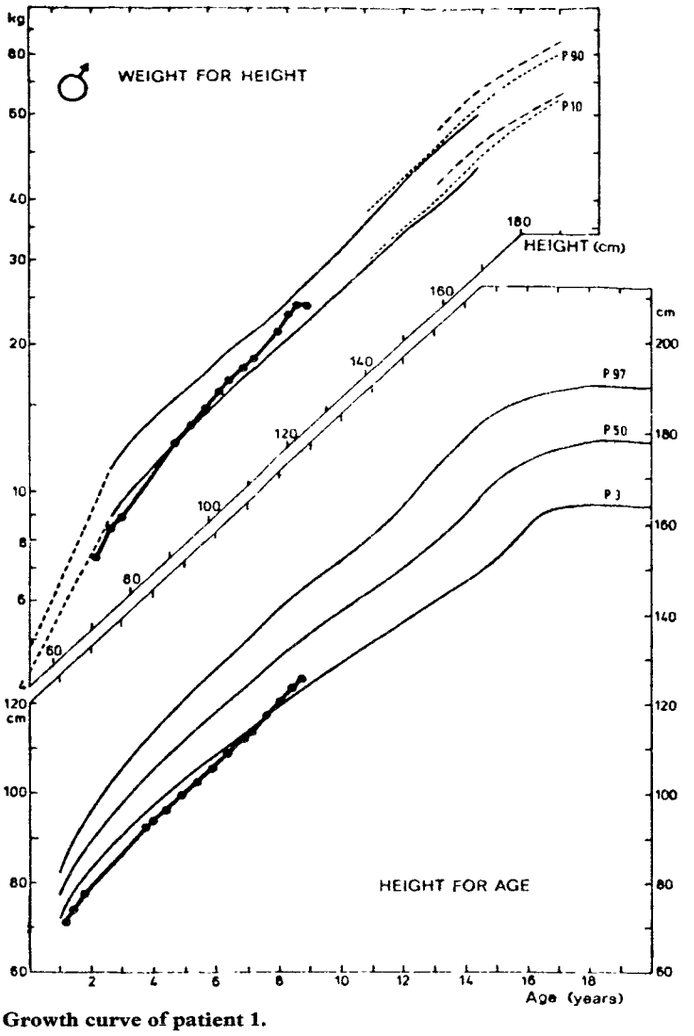

Growth curve of patient 1.

Methods

T_4,[4] T_3,[5] rT_3,[6] and TSH (Calbiochem Zürich, standard MRC 68/38) were measured with specific radioimmunoassays. T_3 resin uptake (T_3RU) was measured with the 'Triobead' kit (Abbott Laboratories, Chicago). FT_4I was calculated as serum $T_4 \times T_3RU$ (%)/100. Serum FT_4 was estimated with a commercial kit (Corning Medical, Medfield, Massachusetts) and with equilibrium dialysis. Results obtained with the former method are reported since both gave values in the same range in the two patients. Serum TBG and thyroxine-binding prealbumin (TBPA) capacities were determined by agar-gel electrophoresis[3,7] as were antibodies against T_4, T_3, and rT_3.[3,8]

Case-reports

Patient 1

This boy, born in 1973, is the first child of healthy, unrelated parents. He was born at term after a pregnancy complicated by toxaemia and was asphyxiated owing to umbilical-cord strangulation and amniotic-fluid aspiration. Birthweight was 2740 g (1·9 standard deviations below the mean) and length 47 cm (2·1 standard deviations below the mean). The neonatal period was uneventful except for pronounced muscular hypotonia. There was no long-term neonatal jaundice. At the age of 1 year the child was referred to a paediatrician because of muscular hypotonia, constipation, and slow psychomotor development. These symptoms could be attributed to the perinatal asphyxia, and the normal growth velocity (see accompanying figure) made hypothyroidism very unlikely; however, for completeness thyroid function was examined.

Serum T_4 was higher than normal and T_3RU was normal; FT_4I was therefore high. These findings were confirmed several times in

TABLE I—THYROID-FUNCTION PARAMETERS AND THYROID-HORMONE-BINDING PROTEINS IN PATIENT 1 AND FAMILY MEMBERS

—	T_4 (nmol/l)	T_3RU (%)	FT_4I	FT_4 (pmol/l)	T_3 (nmol/l)	rT_3 (nmol/l)	TSH (mU/l)	TSH (mU/l) after TRH i.v. 20 min	60 min	120 min	TBG (nmol T_4/l)	TBPA (nmol T_4/l)
Patient 1												
1·0 yr	238	23·1	55	..	..	..	2·9	..	..	..	..	..
5·1 yr	285	..	..	..	1·80	..	4·1	12	9·5	5·4	..	..
6·8 yr	>320	28·2	>90	43·1	1·38	..	..	..	..	..	..	..
7·8 yr	348	30·1	105	49·4	1·86	2·20	3·2	..	..	..	432	2352
8·5 yr*	362	32·4	117	40·6	1·40	1·48	2·8	9·7	5·5	..	470	2795
Father	106	30·7	33	20·2	1·98	0·55	2·1	..	..	..	265	3388
Mother	128	23·1	30	18·1	2·20	0·20	..	..	..	..	..	..
Brother	156	22·0	34	24·5	2·90	0·29	..	..	..	..	..	..
Normal range	60–160	22–33	18–38	13·5–25·7	1·23–3·15	0·15–0·52	<1–5	5–25	5–20	1–10	193–321	2548–3951

i.v. = intravenous.
*Before T_3 treatment.

the ensuing years (table I). In addition we found that FT_4 and rT_3 levels were persistently higher than normal, while T_3 and TSH remained within the normal range. The increase in TSH after intravenous (table I) and oral (table II) administration of TRH was normal, as were the increases in T_4 and T_3 after oral TRH (table II). TBG capacity was greater than normal, and TBPA capacity varied between subnormal and normal. Antibodies against T_4, T_3, and rT_3, which could falsely raise total, but not free, hormone levels, were not found, and abnormal thyroid-hormone-binding proteins were not present.

TABLE II—RESPONSE TO AN ORAL DOSE OF 20 mg TRH IN PATIENT 1 AT THE AGE OF 2 YEARS

—	Hours after intake 0	3	7
TSH (mU/l)	4·6	27	19
T_4 (nmol/l)	320	370	445
T_3 (nmol/l)	2·1	2·7	4·7

These findings are consistent with an intact pituitary-thyroid axis without suppression of TSH by the high T_4 level. Some suspicion of hypothyroidism remained, however, in view of the patient's persistent chronic constipation, muscular hypotonia, and clumsiness and his slow psychomotor development (verbal I.Q. approximately 66, performance I.Q. approximately 86 at 5 years of age). Height and weight gain progressed normally, however, although his height curve was slightly below the normal centiles for Dutch children with some catch-up growth (figure). The bone age was delayed but was in accordance with height age. This combination is consistent with the clinical picture of so-called constitutional delay in growth and development (mean parental height, 167·5 cm: mean for Dutch parents, 172 cm). The child was otherwise healthy and the thyroid gland has never been found to be enlarged. Studies in family members revealed no abnormalities except a slightly high rT_3 level in the father.

In a recent study thyroid-hormone levels were estimated after 2 weeks' T_3 administration, 3×5 μg/day, followed by another 2-week period of 3×10 μg/day (table III). There was a transient increase in psychomotor activity which, however, had disappeared after 4 weeks. Obstipation was unchanged. Pulse rate increased from 80/min to 100/min. Important changes in thyroid-hormone levels were seen (table III). Serum T_4, FT_4, and FT_4 I fell to normal by the end of the second 2-week period. T_3RU also fell, while TBG capacity and rT_3 also decreased but remained slightly above normal until the end of the study. Serum TBPA capacity decreased slightly but the change was no greater than the spontaneous changes in TBPA observed before T_3 treatment. Serum T_3 values increased during T_3 treatment to higher than normal levels; no significance may be attributed to this rise, since the time between the intake of T_3 and blood sampling for T_3 estimation was 2 h.

Patient 2

This woman, born in 1922, underwent subtotal thyroidectomy for Graves' disease in 1965. In 1969 a relapse was diagnosed, and she was treated with carbimazole. No thyroid-function results from this time are available. In September, 1970, she was referred to our hospital and carbimazole treatment was discontinued. 2 months later serum T_4 was 117 nmol/l: from that time serum T_4 and T_3 remained within the normal range until her second relapse in 1974. In 1973 we noted several times that she had some symptoms and signs of hypothroidism, but no action was taken because T_4 levels were normal. In June, 1974, serum T_4 and T_3 were still normal but her relapse in October, 1974, was clinically definite and confirmed by high levels of T_4, FT_4I, and T_3 (table IV).

Because of progressive eye signs, iodine-131 treatment was postponed and she was treated with carbimazole and thyroid hormone. In April, 1977, she was given 4 mCi ^{131}I but less than 1½ years later, despite raised T_4 (162 nmol/l) and normal T_3RU (resulting in a raised FT_4I, 48), serum TSH rose slightly. The latter finding was not appreciated and the patient was given 10 mCi ^{131}I for supposed relapsing hyperthyroidism. She then became clinically hypothyroid: basal serum TSH and TSH after TRH were definitely increased, indicating primary hypothyroidism, and T_4 and FT_4I were within the normal range, while serum T_3 was very low.

In December, 1978, following the diagnosis of primary hypothyroidism, substitution was started with L-T_4 in increasing doses to a maintenance dose of 125 μg/day. Under this dose serum T_4, FT_4, FT_4I, and rT_3 rose to higher than normal levels, while TSH remained slightly elevated. Serum T_3 increased to the low-normal range in December, 1980, but when the patient was treated with propranolol (in combination with chlorthalidone and triamterene) for hypertension it fell again to a subnormal level. TBG and TBPA capacities (measured in December, 1980) were within the normal range (246 and 3091 nmol T_4/l, respectively). No serum antibodies against T_4, T_3, and rT_3 were present and nor were abnormal thyroid-hormone-binding proteins. Serum T_4 and T_3 levels were normal in the daughter and four sisters of the patient.

TABLE III—EFFECT OF T_3 TREATMENT ON THYROID-FUNCTION PARAMETERS AND THYROID-HORMONE-BINDING PROTEINS IN PATIENT 1

—	T_4 (nmol/l)	T_3 RU (%)	FT_4I	FT_4 (pmol/l)	T_3 (nmol/l)	rT_3 (nmol/l)	TSH (mU/l)	TBG (nmol T_4/l)	TBPA (nmol T_4/l)
Before treatment (age 8·5 yr)	362	32·4	117	40·6	1·4	1·48	2·8	470	2795
After 2 weeks T_3 (3×5 μg/day)	267	25·8	68	33·5	4·9	1·27	<1·0	457	2679
After further 2 weeks T_3 (3×10 μg/day)	160	22·6	36	23·2	6·9	0·77	<1·0	378	2390

TABLE IV—STUDIES ON THYROID-FUNCTION PARAMETERS AND THYROID-HORMONE-BINDING PROTEINS IN PATIENT 2

Date	T_4 (nmol/l)	T_3RU (%)	FT_4I	FT_4 (pmol/l)	T_3 (nmol/l)	rT_3 (nmol/l)	TSH (mU/l)	TSH 30 min after TRH
Nov. 1970	117	..	..	..	..	..	..	..
June 1974	152	..	..	..	2·00	..	..	..
Oct. 1974	362	50·6	183	..	8·10	..	..	..
Aug. 1978	162*	29·8	48	..	..	..	7·4	..
Dec. 1978	136	22·6	31	..	0·96	..	30·4	117·3
March 1979	191†	24·4	47	..	1·41	..	8·9	31·3
Oct. 1981	194‡	26·5	51	32	0·98	1·64	6·3	25·6

*3×80 mg propranolol, 50 mg chlorthalidone, and 2×50 mg triamterene daily.
†125 μg L-T_4, 50 mg chlorthalidone, and 2×50 mg triamterene daily.
‡3×40 mg propranolol, 125 μg L-T_4, 50 mg chlorthalidone, and 2×50 triamterene daily.

Discussion

The abnormal pattern of thyroid-hormone levels in patient 1 is similar to that of patient 2 when she was on thyroxine substitution. Both patients had high serum levels of total T_4 and FT_4 with a raised FT_4I, in combination with serum T_3 levels in the normal range. Although the elevation in serum TBG may partly explain the high serum total T_4 level in patient 1, it cannot be the full explanation because T_3RU would have been low and FT_4I and FT_4 normal. It is also interesting that, despite the TBG elevation, serum T_3 was not raised but was in the lower normal range, making the dissociation between serum T_4 and T_3 even more striking.

A similar pattern of thyroid-hormone levels was found in patient 2 when she was on thyroxine substitution (table IV, March, 1979): T_4 parameters were high in combination with a low-normal T_3. The T_4/T_3 ratio was significantly higher ($p<0·001$) than the normal range (61–97) in L-T_4-substituted subjects. The fall in T_3 between March, 1979, and October, 1981, is probably due to the use of propranolol which lowers serum T_3 without affecting T_4 levels.[9] (Chlorthalidone and triamterene are not known to influence serum iodothyronine levels.)

Although FT_4I and FT_4 were raised, the patients were not hyperthyroid: basal TSH and TSH response to TRH were normal in patient 1 and slightly elevated in patient 2 (March, 1979) suggesting slight undersubstitution with thyroxine. Furthermore, the thyroid responded normally (increase in serum T_3 and T_4) to TSH (patient I, table II), and serum TSH could be suppressed by T_3 and T_4 in patient 1 and patient 2, respectively. In both subjects serum rT_3 was very high. In patient 2 the high level could be due only partly to propranolol treatment, since only moderate elevations are seen under comparable doses of this β-blocking agent.[9]

The abnormal findings in these two patients suggest that a high extracellular FT_4 level is necessary to ensure normal intracellular availability of biologically active thyroid hormone. At present, two possible explanations of the abnormal findings can be put forward. One is that transport of T_4 through the cell membrane into target cells is reduced, so that sufficient T_4 can enter the cells only if extracellular FT_4 is higher than normal. Only then can normal amounts of T_3 be produced by conversion from T_4 for biological action. The increased serum rT_3 could be explained by an impaired cellular uptake of rT_3 after it has left the intracellular compartment where it has been produced. A single defect could explain the impaired transport of both T_4 and rT_3, since there is evidence that they share a common active-transport mechanism through the cell membrane in rat liver cells.[10,11] The transport mechanism for T_3 is different, which would also explain the normal T_3 values in our patients. The other possible explanation is that intracellular 5′-deiodinase activity is reduced, resulting in decreased T_4 to T_3 conversion and deiodination of rT_3.[12] To compensate for this defect a high intracellular, and therefore also extracellular, FT_4 concentration has to be built up to achieve normal T_3 production. Since T_4 to rT_3 conversion is catalysed by 5-deiodinase, the intracellular elevation in FT_4 will automatically lead to increased production of rT_3 and (in combination with its diminished breakdown) to increased serum rT_3 concentrations.

TBG capacity was elevated in patient 1 and fell substantially during T_3 treatment. TBG capacity may be elevated in hypothyroidism[13] and, although no other definite signs were present, the decrease of TBG during T_3 treatment may point to thyroid-hormone deficiency in this respect. This aspect raises the possibility of a different expression of the basic abnormality in different organ systems.

No information about the prevalence of this syndrome is available at present. Our investigations in the families of both patients have not yet disclosed whether the disorder is hereditary.

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