

High serum thyroxine-binding globulin—an important cause of hyperthyroxinaemia

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Summary

Four patients are described who had a significant elevation of serum thyroxine-binding globulin (TBG). Review of these patients indicated that inappropriate therapy for thyrotoxicosis had been given in three cases. A study of our laboratory records revealed that significant TBG elevation was a relatively common phenomenon which occurred in approximately 0.45% of our hospital population. Patients with this abnormality have serum thyroxine levels which are comparable to those with clinical thyrotoxicosis. Tri-iodothyronine is frequently elevated though less so than in patients with clinical thyrotoxicosis. Measurement of TBG is indicated in all cases of hyperthyroxinaemia in which the clinical features of thyrotoxicosis are doubtful. The TRH test was found to be most useful in evaluating the thyroid status of these patients.

KEY WORDS: hypothyroidism, TRH test.

Introduction

Familial elevations in thyroxine-binding globulin (TBG) have been known since the original report of Beierwaltes and Robbins (1959). In 1967 Jones and Seal presented evidence for the transmission of the trait as an X chromosome-linked abnormality. The condition is well described but estimates of its incidence are not available. Physiologically marked increases of TBG are found in pregnancy and early childhood. A recent review by Cavalieri and Pitt-Rivers (1981) indicated that well-documented increases in TBG caused by drugs are restricted to oestrogen-containing medications including oral contraceptives. Small but significant increases in TBG are found in myxoedema which fall to normal on thyroxine replacement (Harrop, Hapton and Lazarus, 1981). In thyrotoxic patients small decreases in

TBG are found which rise to normal as the condition is corrected (Harrop *et al.*, 1981; Burr *et al.*, 1979).

In euthyroid patients with elevated TBG levels serum thyroxine is also high. Attempts to compensate for marked increases in TBG by the use of T_3 -resin uptake tests may lead to the misclassification of such patients as thyrotoxic (Burr *et al.*, 1979). The advent of direct assays has permitted patients with elevated TBG levels to be identified accurately (Hesch *et al.*, 1976; Bradwell *et al.*, 1976). From the analysis of our laboratory data we have attempted to gain information on the incidence of significantly elevated TBG levels in our hospital population. We present these data and four case histories to exemplify some practical management problems encountered with affected patients.

Materials and methods

Thyroxine was measured by radioimmunoassay using 8-anilino-naphthalene sulphonic as blocking agent and polyethylene glycol to separate free and bound ligand (Nye *et al.*, 1976). The reference range in our hospital population with this method is 43–131 nmol/l. Thyroxine-binding globulin was measured by the method of Hall and Laing (1982). This method is similar to the widely used Corning Immophase® kit method against which it is standardized. The laboratory reference range is 14–30 mg/l. Tri-iodothyronine (T_3) and thyroid stimulating hormone (TSH) were assayed by conventional double antibody radioimmunoassays. The reference range for T_3 was 1.1–3.9 nmol/l and for TSH 0–8 mu/l.

Patient survey

TBG was measured in 777 consecutive patients in whom thyroid function tests were being carried out in the Clinical Biochemistry Department at Manchester

Royal Infirmary. In addition TBG levels were measured in 291 patients with serum thyroxine levels of greater than 130 nmol/l from a further 3,000 thyroid function tests.

Case reports

Patient 1

This patient, a woman, was admitted to hospital in May of 1981 at the age of 66 years with an acute myocardial infarction. She had lacked energy for several months but there was no history of angina pectoris nor any serious illness.

Examination revealed her to be obese; no other abnormalities were found. The myocardial infarction was complicated by an episode of ventricular tachycardia and she was treated with intravenous and then oral disopyramide.

Serum total thyroxine (T_4) was measured as 205 nmol/l and serum tri-iodothyronine as 3.9 nmol/l during her admission to hospital. As her clinical state did not suggest thyrotoxicosis, she was later readmitted for a thyrotrophin releasing hormone (TRH) test—this showed a basal TSH of 34 mu/l, rising to greater than 50 mu/l at 20 min and 60 min, these findings being suggestive of hypothyroidism. Thyroxine binding globulin was measured as 61 mg/l. Thyroid microsome antibodies were positive 1:6400. Thyroglobulin antibodies were negative.

Disopyramide therapy was discontinued in August of 1981 and the level of thyroxine binding globulin and serum total thyroxine did not change significantly suggesting that their elevation was not drug-induced.

Treatment with L-thyroxine was started in January of 1982. This was followed by improvement in the patient's sense of well-being. After 4 months treatment with 0.1 mg L-thyroxine per day, T_4 rose to 350 nmol/l, TSH fell to 2.7 mu/l, TBG was not significantly changed at 57 mg/l.

Patient 2

The second patient, a 57-year-old woman, presented with symptoms of depression in April 1980. She complained of excessive sweating and difficulty sleeping but clinical examination showed no evidence of thyrotoxicosis. Serum thyroxine was measured as 295 nmol/l and T_3 as 4.8 nmol/l. A two hour radioiodine uptake test was performed and this was low at 10%. However, the patient was given ^{131}I therapy (7,500 cGy) in July 1980 because of the raised T_4 .

She returned in September 1980 again complaining of depression, sweating and difficulty sleeping. T_4 was measured as 390 nmol/l and a further dose of ^{131}I therapy was given. By February 1981 her symptoms

were unchanged but T_4 had fallen to 219 nmol/l and T_3 to 0.6 nmol/l. In July 1981 TBG was measured for the first time and was found to be 68 mg/l.

The patient returned in June 1982 complaining of lassitude and weight gain. Clinical examination revealed her to be hypothyroid. A TRH test was performed, basal TSH being 47 mu/l, rising to 171 mu/l at 30 min and 123 mu/l at 60 min, confirming the diagnosis of hypothyroidism. Serum T_4 at that time was 290 nmol/l, T_3 4.2 nmol/l, TBG 91 mg/l and 'Free T_4 ' 13 pmol/l (NR 11–28 Amerlex¹² kit).

She was treated with L-thyroxine, 0.1 mg per day. By August 1982, T_4 was 400 nmol/l, TSH had fallen to 7.3 mu/l, but despite her biochemical improvement, the patient's many emotional symptoms remained unchanged. She decided that thyroxine therapy was not helping her, stopped therapy and she has become hypothyroid again.

Patient 3

The third patient, a 37-year-old woman, also presented with psychiatric symptoms. She was experiencing panic attacks and depersonalization, together with symptoms of depression. When seen first in March 1977, it was felt that she was euthyroid and that the only abnormality on examination, namely a tachycardia (pulse 124 per min), was related to her anxiety. T_4 measurement at that time was 201 nmol/l and T_3 5.8 nmol/l. The intention was to treat the patient with carbimazole but she failed to collect the tablets.

The patient was seen again in November 1978 with symptoms of anxiety. Examination again revealed a sinus tachycardia but no other evidence of thyrotoxicosis. T_4 was 249 nmol/l and T_3 4.8 nmol/l in March 1979 and she was given ^{131}I therapy.

In March 1980 the patient returned with complaints of feeling hot and irritable, her weight was steady and clinical examination suggested she was euthyroid. T_4 was 110 nmol/l, T_3 4.9 nmol/l, TSH was found to be 45 mu/l and TBG was measured for the first time as 86 mg/l—these investigations suggesting that the patient had become biochemically hypothyroid.

She subsequently defaulted from further surveillance.

Patient 4

This patient, also female, was first seen at the age of 44 years with non-organic neurological symptoms and was found to have mild aortic stenosis. At this time, in 1978, she was felt to be clinically euthyroid but T_4 was measured as 303 nmol/l and carbimazole was prescribed. At the start of 1979, clinical examination again suggested she was euthyroid but T_4 was

measured at 226 nmol/l and T_3 3.5 nmol/l and she was treated with ^{131}I .

At review at the end of 1979 the clinical status was unchanged. Investigation revealed T_4 300 nmol/l, and TBG was measured as 63 mg/l. Despite the absence of clinical evidence of thyrotoxicosis, she was treated with further ^{131}I .

In July 1982 the patient returned with symptoms and signs of frank hypothyroidism. T_4 was 99 nmol/l, T_3 3.7 nmol/l and TSH 48 mu/l. TRH test revealed basal TSH 45 mu/l, TSH at 20 min and 60 min greater than 50 mu/l.

The patient was treated with thyroxine replacement therapy.

Results

For the purposes of this study a significant elevation in TBG is defined as being greater than 38 mg/l by our method. This is equal to the patient mean plus four standard deviations. From the 777 patients studied initially, significant TBG elevations were found in 10 patients. Three of these were pregnant and three were neonates. Four female patients remained in whom no cause for a raised TBG was found. TBG measurements carried out in the patients with high serum thyroxine levels yielded another thirteen patients, 11 female and two male, with elevated TBG levels. (Neonates, pregnant women and patients on oestrogen therapy were excluded). The total was seventeen patients in all. TBG concentrations in these patients ranged from 38–64 mg/l (mean 49.5, s.d. 7.1) and T_4 levels were from 133–269 nmol/l (mean 183, s.d. 41.9). T_3 ranged from 2.0 nmol/l to 5.8 nmol/l (mean 2.82, s.d. 0.66). The overall incidence of raised TBG in the patients studied was 17 in 3777 or 0.45% of the total. For comparative purposes the T_4 levels in our laboratory for patients with clinical thyrotoxicosis are 201 ± 47 (s.d.) nmol/l and for T_3 4.4 ± 1.6 nmol/l ($n=39$).

Discussion

Three of the four cases we describe received inappropriate treatment for hyperthyroidism on the basis of hyperthyroxinaemia. The high T_4 levels were the main factor in the decision to instigate treatment in the absence of a clear clinical picture of thyrotoxicosis. In the first case a TRH test was carried out which indicated that the patient was biochemically hypothyroid in spite of a clearly elevated serum thyroxine level. Appropriate treatment was given in this case. In the second case no TRH test was carried out before ^{131}I therapy was instituted which caused her to become hypothyroid. Additionally radioiodine uptake was low in this patient before treatment when clear clinical indications of hyperthyroidism were absent. The result of ^{131}I therapy in the third patient

was to reduce thyroid reserve without producing clinical hypothyroidism, whilst in the fourth patient frank clinical and biochemical hypothyroidism followed radioiodine treatment.

The reason for misinterpretation of the T_4 results in these four patients was clearly the elevation in circulating TBG. Had TRH tests been performed in the last three cases when the clinical findings were at variance with the T_4 results a diagnosis of hyperthyroidism would not have been made. The T_4 /TBG ratio is undoubtedly useful as an index of thyroid function. We have refrained from using it in our patients because the normality of this index is related to the absolute level of serum TBG (Cusick, 1981). Few patients are available with high TBG levels from whom to construct reference ranges. In view of the fact that T_4 levels of 290, 110 and 99 nmol/l were found in three cases when the patients were clinically hypothyroid with clearly elevated TSH levels it is obvious that clinical assessment is of paramount importance when TBG levels are high. The measurement of free T_4 might prove to be useful in cases of raised TBG but in the only case where it was measured a normal value was obtained with a raised TSH when the patient was clinically hypothyroid. In the four cases described the reason for the elevated TBG was not formally established though a familial cause seems most probable due to the negative drug histories.

The patient survey carried out gives useful working information on the incidence of TBG elevation in our hospital population. The incidence observed of 0.4% may be a slight underestimate for our population because of the biased selection of the majority of patients studied on the basis of a raised T_4 . The low incidence of male patients is probably accounted for by the lower incidence of thyroid disease in men and the requesting procedures of our colleagues. We have established that high TBG levels are an important cause of hyperthyroxinaemia in clinical practice and that the thyroxine levels are of the same order as patients with clinical thyrotoxicosis. The T_3 levels are also elevated but less so than in clinical thyrotoxicosis and do not allow an adequate distinction of the conditions to be made due to the high overlap with the reference range.

There are a number of additional causes of hyperthyroxinaemia without hyperthyroidism. These include familial euthyroid thyroxine excess, an albumin abnormality (Stockigt *et al.*, 1981), increased thyroxine binding to prealbumin (Moses *et al.*, 1982), the presence of circulating antibodies to thyroid hormones (Premachandra *et al.*, 1980) and thyroid hormone resistance (Jansen, Trenning and Oostwitt, 1982). These have all come to light as the result of raised T_4 levels being found.

We are concerned as to the cause of misinterpreta-

tion of thyroxine results in our patients. Some indication may be given by the incidence of hyperthyroidism in different populations. This varies from 38% in a thyroid clinic (Toft *et al.*, 1973), to 1.1% in a general practitioner population (Tunbridge, Evered and Hall, 1977). Thus endocrinologists viewing a highly selected population are more likely to believe their T_4 results. If tests are indiscriminately applied to a healthy population a significant number of elevated T_4 levels can be expected to result from raised TBG and not hyperthyroidism.

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