EUTHYROID HYPERTHYROXINEMIA: A CASE REPORT

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SUMMARY

This report deals with the problems of a young man who was clinically euthyroid but biochemically hyperthyroid. The possibility of peripheral resistance to thyroid hormones to explain this paradoxical state is discussed. The importance of recognising this condition to avoid the erroneous diagnosis of thyrotoxicosis and inappropriate therapy is stressed.

INTRODUCTION

The measurement of serum thyroxine (T_4) concentration is the most commonly used test to diagnose hyperthyroidism in clinical practice. However there are a number of other conditions besides thyrotoxicosis which could give rise to an elevated serum thyroxine level. One such condition is peripheral resistance to thyroid hormones as illustrated by the case under discussion.

CASE HISTORY

A 27-year-old construction site worker was referred to the hospital for thyrotoxicosis. He presented with a history of having noticed a goitre for a year which had remained static in size.

He volunteered a vague history of heat intolerance and occasional palpitation for about three months prior to seeking medical advice. He had no other symptoms of thyrotoxicosis. His past medical history was unremarkable; he denied abuse of alcohol, drugs or tobacco. There was no family history of thyroid disorders.

On examination he had a diffused soft non-tender goitre with no bruit. The physical examination was otherwise normal and in particular there was no other signs of thyrotoxicosis. He had no tremor. Pulse rate was 80/minute and regular. There was no muscle wasting or evidence of proximal myopathy.

Routine investigations including haemoglobin, random blood sugar, blood urea, serum electrolytes, chest X-ray and ECG were within normal limits. Serum thyroxine (T_4) and triiodothyronine (T_3) done by his general practitioner were noted to be high but the actual results were not available.

These measurements were therefore repeated: Serum thyroxine (T_4) – 169 nmol/l (normal range 60 – 130 nmol/l); Serum triiodothyronine (T_3) 5.71 nmol/l (normal range 1.23 – 3.38 nmol/l).

He was treated as a case of thyrotoxicosis with carbimazole 45 mg daily and propranolol 20 mg three times a day and reviewed after eight weeks. He reported that he had stopped the medications a week before the follow-up as he felt that they were doing him "no good".

He had developed severe intolerance to cold, change in voice and lethargy about a month after being on treatment. He had also gained 10 kg over this period.

On examination, his pulse was 55/minute, regular and reflexes were normal. It was felt that he had developed drug induced hypothyroidism and his medications were stopped completely.

His thyroid function tests done a week later were as follows: Serum thyroxine (T_4) 86 nmol/l (normal range 60 – 130 nmol/l); Serum triiodothyronine (T_3) 5.3 nmol/l (normal range 1.3 – 3.2 nmol/l); Serum TSH 6.1 mIU/l (normal range $>$ 7.3 mIU/l.

He was reviewed after six weeks and was found to be clinically euthyroid but serum free

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thyroxine done at this stage was noted to be high at 31 pmol/l (reference range 9.4 – 25.0 pmol/l Amerlex-M Free T_4 RIA kit). Since then, he has been reviewed periodically for the past one year and is euthyroid clinically. His pulse rate during this period was between 70 – 85 beats per minute and regular. His weight has remained constant at 67 kg. The goitre has not increased in size and there is no bruit.

DISCUSSION

This patient was initially treated for thyrotoxicosis based on the clinical history and a reportedly-raised thyroid hormone level. He had only minimal (and vague) complaints to suggest hyperthyroidism but these may be consistent with early thyrotoxicosis or T_3-toxicosis. A repeat thyroid hormones assessment showed raised serum T_3 with borderline raised T_4 level supporting the diagnosis of early thyrotoxicosis.

After about seven weeks on the anti-thyroid therapy, the patient noted features suggestive of hypothyroidism. The clinical impression at this stage was that this (iatrogenic) hypothyroidism was related to the rather high dose of carbimazole (45 mg daily) prescribed for the patient considering that he had only minimal symptoms and the serum T_4 was only slightly raised. However, thyroid function tests done two weeks after stopping treatment showed normal serum T_4 and more surprisingly an above-normal serum T_3 concentration. Serum free T_4 done subsequently when the patient was clinically euthyroid was also found to be raised.

This development of hypothyroidism and the results of tests showing normal T_4, high T_3 and high serum free T_4 while the patient was clinically euthyroid even after periodic reviews would suggest that the patient may not be thyrotoxic even though the serum thyroid hormones were raised.

There was no history to suggest acute illness, drug ingestion or liver disease to account for the raised thyroid hormones.

A condition referred to as euthyroid hyperthyroxinemia has been described and is associated with a number of clinical situations (Table I).

TABLE I
CAUSES OF ELEVATED SERUM TOTAL THYROXINE

Hyperthyroidisim
Increased serum protein binding
Increased TBG concentration
Non-Thyroidal illnesses
Liver disease
Acute intermittent porphyria
Drugs
5-Flurouracil
Clofibrate
Amphetamines
Amiodarone
Iodinated radio contrast dyes
Transient hyperthyroxinaemic states
Acute medical illness
Acute psychiatric illness
High altitude exposure
Peripheral tissue resistance to thyroid hormones

(Modified from Ladenson P.W.):[1]

One of the common causes of raised serum T_4 in euthyroid patients is related to serum albumin or thyroid-binding pre-albumin abnormalities.[1] This familial dysalbuminaemia hyperthyroxinemia (FDH) is unlikely in this patient as the condition is an autosomal dominant syndrome[3] and there was no history of similar thyroid disease in the patient's family (though thyroid hormone levels should be assessed to be certain). In the FDH syndrome usually only serum T_4 is raised while serum T_3 is within normal range.[1] This is because in this disorder the abnormal albumin molecule has an increased affinity for T_4 but not for T_3.[2] In this patient, serum T_3 was raised on several occasions.

One cause of euthyroid hyperthyroxinemia is related to peripheral tissue resistance to thyroid hormones. This syndrome was first described by Refetoff in 1967 in three siblings of consanguinous parents.[2] Subsequently a number of sporadic as well as familial cases with autosomal dominant inheritance were reported.[2]

Patients with this syndrome typically present with a goitre but with no clinical evidence of thyrotoxicosis. Serum thyroid hormones (both the total and free concentrations) are classically raised. The case under discussion who presented with a goitre and raised thyroid hormone levels

but with minimal symptoms of thyrotoxicosis may fit into this rare syndrome.

The exact defect leading to peripheral resistance to thyroid hormones is not known. Some authors postulate an abnormal T_3 binding to tissue receptors with postbinding defects.[2] While others have suggested qualitative defect of nuclear T_3 receptors and/or a defect in the transport of thyroxine across the plasma membrane.[4] It is likely that there are several different defects which collectively lead to the "common clinical endpoint of peripheral resistance to the thyroid hormones".[2]

Confirmation of this syndrome in a patient would depend firstly on the exclusion of other causes of raised thyroid hormones in a patient who is clinically euthyroid and secondly on hormonal response at cellular level. The latter would entail the use of receptor assays and the assessment of postreceptor events such as cyclic-AMP generation after exposure to thyroid hormones. Since these specialised tests are not generally available in routine laboratories, diagnosis of tissue resistance to thyroid hormones as in this patient would have to be by exclusion of other causes of euthyroid hyperthyroxinemic state and on clinical observations over a period of time.

In conclusion, this case illustrates a possibility of peripheral resistance to thyroid hormones in a clinically euthyroid patient with raised serum thyroid hormones. This rare syndrome should be considered in a patient presented with a goitre and raised serum thyroid hormone levels but with minimal or no clinical features of thyrotoxicosis. As a corollary, one should be wary of treating a patient for thyrotoxicosis based solely on thyroid hormone levels without collaborative clinical features suggestive of hyperthyroidism.

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