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Rare disease

Resistance to thyroid hormone – an incidental finding

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Summary

A 16-year-old female with mild hirsutism was noted to have a small, smooth, non-tender goitre. A resting peripheral tremor, but no other symptoms or signs of thyroid dysfunction were present. Her only medication was the contraceptive pill. There was no family history of thyroid disease. Investigation showed elevated free thyroxine (28 pmol/l) and total triiodothyronine (3.4 nmol/l) with non-suppressed thyroid stimulating hormone (1.4 mU/l). Radioiodine uptake scan of the thyroid showed bilateral increased tracer uptake, suggestive of Graves' disease, however thyroid peroxidase and antithyroid stimulating hormone (TSH) receptor antibody testing was negative and sex hormone binding globulin concentration was normal. Laboratory analyses excluded assay artefact or abnormal circulating thyroid hormone binding proteins. Genetic analysis identified a thyroid hormone receptor gene mutation (T277I), making a diagnosis of resistance to thyroid hormone (RTH). RTH is a disorder characterised by elevated thyroid hormones, failure to suppress pituitary TSH secretion and variable refractoriness to hormone action in peripheral tissues.

BACKGROUND

The syndrome of resistance to thyroid hormone (RTH) is an uncommon disorder characterised by elevated circulating thyroid hormones, failure to suppress pituitary thyroid stimulating hormone (TSH) secretion and variable tissue refractoriness to thyroid hormone action. The majority of patients are asymptomatic, requiring no treatment. In such patients, abnormal thyroid function tests, undertaken on account of a goitre or non-specific symptoms, may lead to identification of the disorder. In contrast, a subset of patients exhibit greater peripheral tissue responsiveness to thyroid hormone action and develop clinical features of hyperthyroidism such as palpitations, anxiety, tremor and weight loss.[1–3]

Recognition of the disorder is important as its management differs from that of other, more common forms of thyroid dysfunction. Current management of RTH aims to avoid inappropriate treatment of asymptomatic individuals or alleviate hyperthyroid symptoms when present. In the majority of cases, genetic testing to identify defects in the thyroid hormone receptor β (TRβ) gene confirms the diagnosis.

CASE PRESENTATION

A 16-year-old female with mild, non-progressive hirsutism was investigated and found to have abnormal thyroid function tests (TFTs), showing an elevated free thyroxine (fT4) of 28 pmol/l (reference range: 9–21 pmol/l) with a non-suppressed TSH of 1.4 mU/l (reference range: 0.35–5.0 mU/l) (table 1).

On examination, she had some coarse hair on the chest, with no abnormal hirsuties elsewhere or virilisation. In addition, a small, smooth, non-tender goitre was noted. She had a slight peripheral tremor, but a normal, regular pulse rate (60 beats per min) with no other signs or symptoms of thyroid dysfunction or dysthyroid eye disease. Her menstrual periods had always been light and irregular. Apart from recent commencement of the oral contraceptive (Microgynon 30), she was not taking any other regular medication. Her medical history was unremarkable except for recurrent otitis media in childhood and there was no family history of thyroid disease.

INVESTIGATIONS

Repeat TFTs confirmed the original results, but documented raised total triiodothyronine (T3) (3.4 nmol/l; reference range: 0.9–2.5 nmol/l) levels as well. Thyroid peroxidase and anti-TSH receptor antibody measurements were negative (table 2).

As the patient remained clinically euthyroid on follow-up, with persistently abnormal TFTs, the possibility of assay interference causing spuriously abnormal test results was considered. TSH, fT4 and T3 were measured by chemiluminescent microparticle immunoassay on the Abbott Architect ci8200 analyser. Heterophilic antibody interference in these assays was subsequently excluded (table 3). The validity of the results was further confirmed

Table 1 Initial biochemistry results

Analyte	Concentration	Reference range
LH	3.3 U/l	
FSH	6.3 U/l	
E2	94 pmol/l	
Prolactin	332 mU/l	<630 mU/l
Testosterone	2.9 nmol/l	1.0–3.2 nmol/l
SHBG	76 nmol/l	20–155 nmol/l
FAI	3.8	<7.0
fT4	28 pmol/l	9–21 pmol/l
TSH	1.4 mU/l	0.35–5.0 mU/l

E2, oestradiol; FAI, free androgen index; FSH, follicle-stimulating hormone; fT4, free thyroxine; LH, luteinising hormone; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone.

Table 2 Cumulative thyroid function test results

Analyte (reference range)	fT4 (9–21 pmol/l)	T3 (0.9–2.5 nmol/l)	TSH (0.35–5.0 mU/l)	TPO (<6 IU/ml)	TRAB (0–15 U/l)
25/05/10	28		1.4		
11/06/10	28		2.0	<1	
15/07/10	27	3.4	1.2		
06/09/10	28	3.2	1.5		
28/10/10	27	3.7	1.1		<3
03/03/11	29	3.4	1.1		

fT4, free thyroxine; T3, triiodothyronine; TPO, thyroid peroxidase antibody; TRAB, TSH-receptor antibody; TSH, thyroid-stimulating hormone.

Table 3 Thyroid function test results before and after treatment of sample with heterophilic antibody blocking reagent (performed on Abbott Architect ci8200 analyser)

	Pre blocking reagent	Post blocking reagent
fT4 (pmol/l)	27	26
T3 (nmol/l)	3.7	3.2
TSH (mU/l)	1.1	1.0

fT4, free thyroxine; T3, triiodothyronine; TSH, thyroid-stimulating hormone.

Table 4 Thyroid function test results analysed by dissociation-enhanced lanthanide fluorescent immunoassay

Analyte	Concentration	Reference range
Free T4	32.9	9–20 pmol/l
Total T4	267.0	69–141 nmol/l
Free T3	11.0	3.0–7.5 pmol/l
TSH	1.27	0.40–4.0 mU/l
TBG	29.3	14–31 μg/l

T4, thyroxine; T3, triiodothyronine; TSH, thyroid-stimulating hormone; TBG, thyroxine binding globulin.

by measurement of TFTs using an alternative analytical methodology (dissociation-enhanced lanthanide fluorescent immunoassay) (table 4). TSH and fT4 measurements were linear to dilution and showed good recovery following treatment of the serum with polyethylene glycol. Normal thyroxine binding globulin levels excluded hyperthyroxinaemia due to raised circulating binding proteins.

A radioiodine scan of the thyroid showed markedly increased tracer uptake, with diffuse bilateral enhanced activity in both lobes (figure 1). The elevated tracer uptake suggested that hormone synthesis from the gland was genuinely increased, with the pattern of activity being compatible with Graves' disease. However, non-suppressed TSH levels and negative thyroid antibody measurements were against this diagnosis. Furthermore, serum sex hormone binding globulin (SHBG) levels, a hepatic marker of thyroid hormone action, were normal (table 1).

Elevated fT4 and T3 with non-suppressed TSH levels suggested either a TSH-secreting pituitary tumour or central resistance to thyroid hormone (RTH) action, both rare conditions. The normal SHBG concentration suggested hepatic refractoriness to elevated thyroid hormones, thereby favouring the latter diagnosis.[4 5] Accordingly, sequencing of the TRβ gene was performed. This identified a single nucleotide change (830C>T) corresponding to a threonine to isoleucine change at codon 277 (T277I) in the predicted protein. This mutation, located in the receptor hormone-binding domain, is functionally deleterious and has been documented previously in RTH,[6] thus confirming this diagnosis at a molecular level (figure 2).

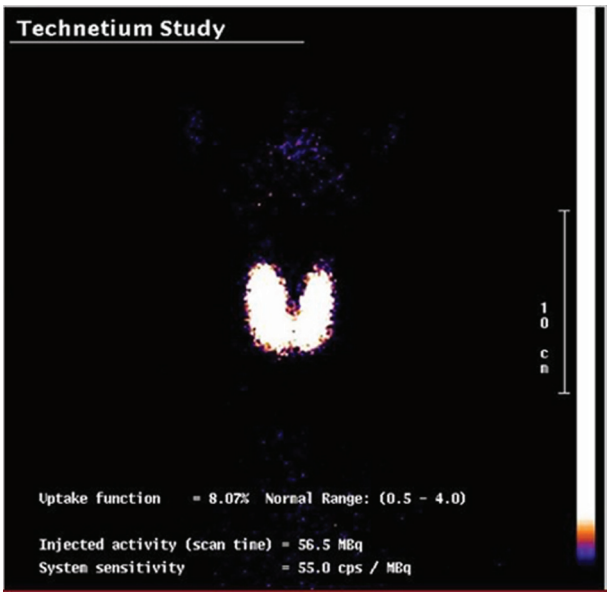

Figure 1 Thyroid uptake scan: thyroid scan shows intense tracer uptake in both thyroid lobes with suppressed background activity.

As TRβ gene mutations are usually dominantly inherited, screening was offered to the patient's first degree relatives. The T277I TRβ mutation was not detected in either parent, both of whom had normal TFTs, and the patient has no siblings. It was therefore concluded that the TRβ gene mutation arose de novo in the patient.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of raised free T4 with 'inappropriately' non-suppressed TSH levels includes the following diagnostic possibilities:

- Thyroxine replacement*
- Intercurrent acute illness*
- Drugs (eg, amiodarone, heparin)*
- Assay interference – heterophilic antibodies/autoantibodies to T4 (and T3)
- Genetic albumin variants (dysalbuminaemic hyperthyroxinaemia)
- RTH
- TSH-secreting pituitary tumour

(*Most common causes).

OUTCOME AND FOLLOW-UP

As the patient remains asymptomatic, no intervention was required. She continues to be followed up in the endocrine clinic.

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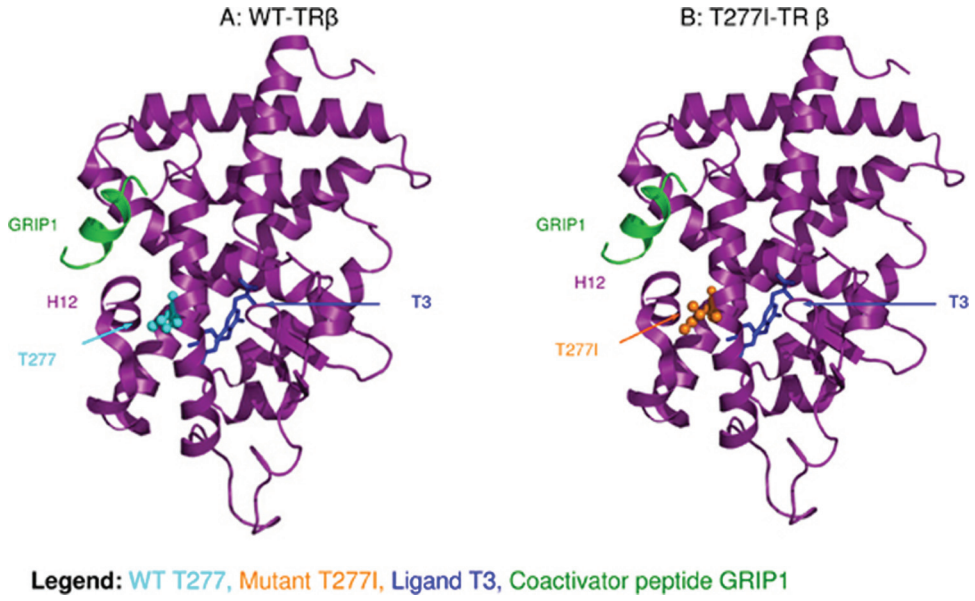

Figure 2 Crystallographic modelling of T277I TRβ mutation. Modelling of TRβ ligand binding domain bound to T3 (blue) and coactivator peptide (green). The position of wild type T277 (cyan) and mutation T277I (orange) relative to helix 12 is shown. Based on the crystal model the T277I mutation is predicted to affect the correct orientation of helix 12 resulting in changed ligand binding affinity and coactivator interaction.

DISCUSSION

The syndrome of RTH is characterised by elevated circulating thyroid hormones and failure of feedback suppression of TSH.

The prevalence of the disorder is approximately 1 in 40 000 live births.[6 7] 85–90% of cases are due to mutations in the TRβ gene, resulting in impaired hormone binding and/or transcriptional activity of mutant receptors. Mutations are usually inherited in an autosomal dominant manner, although approximately 25% arise de novo.[2 8 9]

Clinical features of the disorder are quite variable. The majority of individuals are asymptomatic and have few clinical signs other than goitre. This clinically euthyroid state is often referred to as 'generalised RTH', in which the defect appears to be adequately compensated for by the high endogenous levels of thyroid hormones. Goitres are usually small, unobstructive and require no intervention.

In a subset of cases however, similar thyroid hormone abnormalities are associated with thyrotoxic features, suggesting that peripheral tissues are less refractory to thyroid hormone action than the pituitary. This phenotype of the disorder is termed 'pituitary RTH'.

There does not appear to be any clear correlation between clinical phenotype and the nature or location of the receptor defect. Indeed Adams *et al* report the same mutation in association with either a generalised or pituitary RTH phenotype in different kindreds.[2] Different clinical features have also been observed in affected individuals within a kindred harbouring the same TRβ mutation.[1 2]

In childhood, RTH is associated with failure to thrive, growth delay, short stature, recurrent ear infections, attention deficit hyperactivity disorder and learning difficulty.[1 10–12] It is interesting to note that recurrent childhood otitis media was a feature in our patient.

RTH is sometimes misdiagnosed as Graves' disease due to the presence of a goitre with high iodine-123 thyroid uptake and high levels of total and free thyroid hormones.[1 9] In contrast, anti-TSH receptor antibody testing is usually negative in RTH. Furthermore, serum SHBG, a hepatic marker of thyroid hormone action, is typically normal signifying hepatic resistance in RTH, whereas it is elevated in patients with thyrotoxicosis or TSH-secreting tumours with normal hepatic sensitivity to elevated circulating thyroid hormones.[4 5]

TSH-secreting tumours can be further distinguished from RTH by assessment of the response to thyrotrophin-releasing hormone administration. In RTH, TSH typically increases, while in subjects with TSH-secreting tumours, no response is seen. Similarly, administration of T3 will lead to suppression of fT4 and TSH in RTH, whereas levels are unaffected in tumour patients. Raised serum concentration of the α-subunit of TSH may be seen with TSH-secreting tumours. Tumour size is assessed by MRI scanning. A diagnosis of RTH is confirmed in most cases by genetic analysis of the TRβ gene.

Currently, there is no specific treatment available to correct the receptor defect in RTH. Current management is aimed at alleviating hyperthyroid symptoms (eg, with β blockade), if present. Most importantly, recognition of the correct diagnosis in asymptomatic RTH patients is crucial, avoiding inappropriate antithyroid drug treatment or thyroid ablation in such cases.

Theoretically, chronically elevated TSH levels in RTH could lead to the development of autonomous TSH-secreting pituitary tumours. To date, however, only a single case of pituitary adenoma has been reported in association with RTH.[13] Likewise, the incidence of thyroid malignancy within the goitres of these individuals is not increased.

Learning points

- RTH is characterised by elevated thyroid hormones with 'inappropriately' normal non-suppressed TSH levels.
- Most patients are asymptomatic, with few clinical signs other than mild goitre, although a subset may exhibit thyrotoxic features.
- RTH may be misdiagnosed as Graves' disease due to the presence of goitre and elevated thyroid hormone levels with increased thyroid gland radioiodine uptake.
- The disorder should be suspected in individuals with characteristic TFTs, which remain unchanged over time, after exclusion of assay interference.
- A definitive diagnosis is important to avoid inappropriate antithyroid drug treatment or thyroid ablation in asymptomatic individuals.

Competing interests None.

Patient consent Obtained.

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