CASE REPORT

Puzzling thyroid function test

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Accepted 20 November 2017

SUMMARY

A 13-½-year-old boy was referred to the Department of Endocrinology as a case of thyrotoxicosis for initiation of antithyroid medication. His chief complaint was a swelling in front of the neck, which was incidentally noted by his mother 2 weeks prior to presentation. He denied any history of symptoms suggestive of hyperthyroidism or ophthalmological involvement. His physical examination was unremarkable except for a grade 2 goitre. Thyroid function test revealed elevated free triiodothyronine and tetraiodothyronine in the face of an unsuppressed thyroid-stimulating hormone level. Technetium-99 uptake scan showed increased uptake indicating enhanced thyroid activity. However, he was clinically euthyroid. This raised the possibility of resistance to thyroid hormones, which was confirmed by documenting similar thyroid function test abnormalities in other members of his family and genetic testing. The family was reassured of the benign nature of the condition.

BACKGROUND

This case illustrates the importance of clinical examination and also emphasises the importance of a lucid understanding of basic physiological processes.

CASE PRESENTATION

A 13-½-year-old boy was referred to the Endocrinology outpatient department as a case of thyrotoxicosis for initiation of antithyroid medication. He had presented with a complaint of neck swelling for 1 month. The swelling was noticed incidentally and moved with swallowing. He did not have any compressive symptoms or any symptoms to suggest thyrotoxicosis. He was developmentally normal and has been growing on par with his peers. His scholastic performance was good. He was not on any long-term medications and did not suffer from any chronic medical illness. He was the third child of a non-consanguineous marriage. His parents and two elder brothers (16 and 20 years old) did not have any history of neck swelling or symptoms suggestive of hypothyroidism or hyperthyroidism.

On examination, he was noted to have grade 2, diffuse, soft, non-tender goitre. No bruit or thrill was present. His general physical examination was otherwise unremarkable and vital parameters were also within normal limits. His

weight (30 kg) was between the 3rd and 10th percentile and height (148 cm) was between the 10th and 25th percentile, according to Indian Academy of Paediatrics growth charts for Indian children. His systemic examination was also normal.

INVESTIGATIONS

On further evaluation, he was found to have deranged thyroid function tests with elevated serum free tetraiodothyronine (T4) and free triiodothyronine (T3) but normal thyroid-stimulating hormone (TSH) levels (table 1). Antithyroid peroxidase antibody (55.56 IU/mL; normal, <35 IU/mL) was positive but antithyroglobulin antibody (15 IU/mL; normal, <40 IU/mL) was negative. Serum ferritin (29.2 ng/mL; normal, 20–200 ng/mL) was normal but sex hormone binding globulin (71.9 nmol/L; normal, 12–70 nmol/L) was borderline high.

Ultrasound (USG) of the thyroid gland revealed altered echogenicity with increased vascularity. ^{99m}Tc-pertechnetate thyroid scan showed diffuse increased uptake of 7.7% (N: 0.5 to 4.5). His bone age corresponded to his chronological age. Baseline ECG and echocardiography were normal.

DIFFERENTIAL DIAGNOSIS

Although thyroid hormone levels were elevated in our patient, he was asymptomatic raising the possibility that hyperthyrotoxaemia was erroneous and due to laboratory measurement artefact. However, the presence of goitre in USG and increased radioisotope uptake on thyroid scan suggested that thyroid hormone synthesis was genuinely increased, prompting further investigation.

At this stage, taking his clinical and biochemical features into account, two diagnostic possibilities were considered: resistance to thyroid hormone due to defective thyroid receptor β (RTHβ) or a TSH-secreting pituitary adenoma (TSH-oma). Neurological signs and symptoms, if present, suggest TSH-secreting macroadenoma. Neurological examination was normal in our patient. An elevated α-subunit of TSH with raised α-subunit/TSH molar ratio are indicative of TSH-oma. However, this was not feasible in our setting. Further, sex hormone binding globulin (SHBG) and serum ferritin levels are peripheral markers of thyroid function and are elevated in TSH-oma, whereas in

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To cite:

Lakshmana Perumal N, Sahoo JP, Kamalanathan S, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222712

Table 1 Thyroid function tests in index case

Parameters	Normal range	1st reading	Repeat 1	Repeat 2
Serum TSH	0.35 to 5.5 µIU/mL	2.44	2.23	3.5
Free T4	0.89 to 1.76 ng/dL	2.87	2.40	1.91
Free T3	2.3 to 4.2 pg/mL	6.53	6.32	6.75

T3, triiodothyronine; T4, tetraiodothyronine; TSH, thyroid-stimulating hormone.

Table 2 Thyroid function tests in other members of the family

TFT	Father	1st sibling (16 years)	2nd sibling (20 years)
TSH (N: 0.35 to 5.5 µIU/mL)	3.34	2.45	4.07
Free T4 (N: 0.89 to 1.76 ng/dL)	2.25	2.34	2.34
Free T3 (N: 2.3 to 4.2 pg/mL)	5.24	6.14	5.77

T3, triiodothyronine; T4, tetraiodothyronine; TFT, thyroid function test; TSH, thyroid-stimulating hormone.

resistance to thyroid hormone, the levels are normal or in the low range. In our patient, SHBG and ferritin were within the normal range. MRI scan of the pituitary was also normal. The possibility of RTHβ was favoured and other members of his family were evaluated. They were clinically euthyroid and did not have goitre on clinical examination. Thyroid function tests in his mother were normal, whereas the father and two elder brothers showed a similar picture

Figure 1 Genetic analysis of thyroid hormone receptor beta showing heterozygosity for a single nucleotide substitution corresponding to an alanine to threonine substitution at codon 234 (A234T) in the predicted protein sequence. TSH, thyroid-stimulating hormone.

with elevated thyroid hormones and normal TSH levels, supporting the diagnosis of an inherited disorder (table 2).

Sequencing of the thyroid hormone receptor beta gene confirmed heterozygosity for a single nucleotide substitution corresponding to an alanine to threonine substitution at codon 234 (A234T) in the predicted protein sequence (figure 1).

TREATMENT

Since our patient was clinically euthyroid, he was reassured about the benign nature of his condition, with no further intervention being required.

OUTCOME AND FOLLOW-UP

Patient and other members of his family are doing well.

DISCUSSION

Resistance to thyroid hormone due to defective thyroid receptor β, first described by Refetoff and colleagues in 1967,¹ is inherited in an autosomal dominant fashion.² Its prevalence has been estimated to be 1 in 40 000.³ The majority of patients with RTHβ are clinically euthyroid and remain asymptomatic, often presenting with a goitre; a proportion (~15%) of adult and childhood patients can present with signs and symptoms of thyrotoxicosis. Treatment is tailored to clinical presentation and is often not required in many. In patients with features of thyrotoxicosis, therapy with thyromimetic triiodothyroacetic acid suppresses TSH secretion without worsening thyrotoxicosis.⁴ Failure to make the correct diagnosis can result in subjecting patients to unnecessary and harmful medical treatment and surgery.^{5 6}

Learning points

- ▶ Laboratory measures and imaging modalities must be interpreted in the light of patients' clinical examination findings.
- ▶ Inappropriate thyroid-stimulating hormone response to thyroid hormone levels should prompt a search for uncommon clinical diagnoses.
- ▶ In patients diagnosed to have resistance to thyroid hormone, therapy is based on clinical features and may not be needed in those with well-compensated thyroid function.
- ▶ Making the right diagnosis avoids exposing patients to unnecessary and often harmful treatment.

Acknowledgements We acknowledge the contributions of Professor Krishna Chatterjee, Dr Anne McGowan and Dr Odelia Rajanayagam of Metabolic Research Laboratories, Wellcome Trust–MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, for their help in elucidating the genetic basis of RTHβ in this family.

Contributors NLP managed the patient, collected data, drafted the initial manuscript and reviewed and revised the manuscript. JPS and SK supervised the management of the patient and data collection and also critically reviewed the manuscript. CM helped with genetic testing and also critically reviewed the manuscript.

Competing interests None declared.

Patient consent Guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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