Case report

Thyroid hormone resistance in identical twins

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A 62 year man with tablet-controlled type 2 diabetes was referred by his general practitioner to the emergency medical unit with shortness of breath. He was found to be in atrial fibrillation with a heart rate of 130 beats/min and the patient was commenced on sotalol and warfarin. Thyroid function tests were requested and found to be abnormal, with thyroid-stimulating hormone (TSH) 7.75 mU/l (reference range 0.35–4.5), raised serum thyroxine (FT4) 49.3 pmol/l (11–24) and triiodothyronine (FT3) 10.3 pmol/l (3.9–6.8). On re-examination, the patient did not have a goitre or any clinical features of hyperthyroidism other than atrial fibrillation.

A differential diagnosis of assay interference, a TSH secreting pituitary adenoma or thyroid hormone resistance was considered. Samples were sent for repeated analysis in a second laboratory to look for evidence of assay interference; these confirmed a raised TSH with a raised FT3 and FT4. Thyroid antibodies, a thyrotrophin-releasing hormone (TRH) test and pituitary magnetic resonance imaging (MRI) were organized for the patient on an outpatient basis. The patient was discharged from hospital to be followed up by the Endocrine team.

Ten days after discharge, the patient re-presented to the emergency medical unit with headaches, vomiting and slurred speech. Neurological examination revealed dysarthria, horizontal nystagmus, left-sided dysdiakinesis and past-pointing, reduced co-ordination in the left lower limb and ataxia. An emergency computed tomography scan of the head showed a left cerebellar infarction. Warfarin was temporarily discontinued, and the patient was commenced on aspirin and dipyridamole. He remained in atrial fibrillation and was restarted on warfarin 2 weeks later. The patient was switched from sotalol to digoxin for heart rate control. He improved clinically and was discharged home.

The patient was followed up by the Endocrine team. Thyroid peroxidase antibodies were negative. Serum prolactin, follicular-stimulating hormone, luteinising hormone and testosterone were all in the normal range. Random serum cortisol at mid-morning was 301 nmol/l. Glycated haemoglobin (HbA1c) was 6.8%. The pituitary MRI showed no abnormality. The TRH test stimulated TSH release: after a 200 mcg intravenous injection of TRH (Protirelin), TSH increased from 4.32 mU/l at baseline to 23.74 mU/l after 30 min and was recorded at 18.44 mU/l after 60 min, consistent with the diagnosis of thyroid hormone resistance.

It emerged that the subject had an identical twin with a very similar medical history to himself. The twin lived locally and had insulin-treated type 2 diabetes. He had developed atrial fibrillation in earlier life and had also suffered a left cerebellar infarction 1 year prior to his brother. The twin brother was invited to the Endocrine clinic for thyroid function tests and these showed a TSH of 6.67 mU/l, a FT4 of 39.1 pmol/l and a FT3 of 13.1 pmol/l.

Genetic testing in both twins showed the same mutation in the gene encoding the thyroid hormone receptor β (TRβ), with a heterozygous substitution in
Activity to thyroid hormone. Biochemically, patients with thyroid hormone resistance present clinically, and the syndrome is characterized by reduced tissue sensitivity to thyroid hormone. Patients typically have raised FT4 and FT3 with an inappropriately normal or elevated TSH. There can be differential sensitivity to thyroid hormone in the pituitary gland compared with the peripheral tissues, resulting in variable clinical features. It is an uncommon condition with an annual incidence of approximately 1 per 40,000 live births. Reports of this condition in twins are extremely rare. More remarkable is the similarity with which both cases presented clinically, even accounting for the fact that both patients were carrying the same mutation for thyroid hormone resistance.

Thyroid hormone action is mediated by the products of two human genes: thyroid hormone receptor α (TRα) and TRβ. These genes are alternately spliced to generate four nuclear receptor isoforms: TRα1, TRα2 (inactive form), TRβ1 and TRβ2. Mutations in the TRβ gene are the commonest genetic cause of thyroid hormone resistance and result in a receptor with a dominant negative effect on normal thyroid receptor function. The result is a reduction in pituitary and peripheral tissues sensitivity to thyroid hormones. As a consequence, higher concentrations of free thyroid hormone are required for hormone to bind to the receptor. Typically, despite the high serum thyroid hormone levels, TSH release occurs with stimulation by TRH. This is in contrast to a TSH secreting pituitary adenoma, where thyroid function tests show results similar to thyroid hormone resistance (raised FT4 and FT3 with normal or elevated TSH) but TSH response to TRH stimulation is blunted.

Interestingly, both twins showed variable peripheral tissue sensitivity to thyroid hormone, with each having increased pituitary and peripheral tissue resistance to the effects of thyroid hormone except for their hearts, which retained their sensitivity to thyroid hormones and therefore were subject to the hyperthyroid effects of the increased thyroid hormone levels. Differential tissue sensitivity to thyroid hormones has been well described and is thought to be due to the distribution of the nuclear receptor isoforms. The pituitary expresses mainly TRβ2 receptors and mutations in the TRβ gene affect this isoform. This may lead to defective feedback regulation in the hypothalamic–pituitary–thyroid axis and elevated thyroid hormone levels. However, those tissues that continue to predominantly express the unaffected TRα1 will be subject to hyperthyroid effects from raised hormone levels. TRα expression is increased in the heart muscle. This retained cardiac responsiveness by TRα1 in cardiac tissue may explain the predisposition to atrial fibrillation in our twin subjects. Furthermore, it is also likely that atrial fibrillation contributed to cerebellar infarction in the twins.

The majority of individuals with thyroid hormone resistance adequately compensate for their TRβ mutations through increased thyroid hormone secretion, are clinically euthyroid, and require no specific treatment. For patients with clinical features of hyperthyroidism, cardioselective beta-blockers can be effective in the symptomatic treatment of tachycardia. Thyroid hormone analogues Triiodothyronine and D-thyroxine have also been successfully used to decrease serum TSH and thyroid hormone levels but this is not always associated with clinical improvement. Our case highlights that thyroid hormone resistance can be associated with clinically significant adverse events, even if patients appear clinically euthyroid on initial presentation.

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References

