Resistance to thyroid hormone in a Chinese family with R429Q mutation in the thyroid hormone receptor beta gene

The combination of elevated serum levels of free thyroid hormones with non-suppressed thyroid-stimulating hormone suggests the differential diagnoses of resistance to thyroid hormone or thyroid-stimulating hormone–secreting pituitary tumour. Clinical differentiation of these two conditions can be difficult, because patients with thyroid hormone resistance may exhibit various combinations of hypermetabolic and hypometabolic features, and laboratory results have limited sensitivity and specificity. We report a case of resistance to thyroid hormone in a Chinese family that illustrates this difficulty. The diagnosis could only be confirmed by the identification of a known disease-causing mutation in the thyroid hormone receptor beta gene in peripheral leukocytes. Availability of genetic tests will identify more cases in the future and improve our understanding of this condition.

Introduction

Thyroid hormone secretion is stimulated by thyroid-stimulating hormone (TSH), secretion of which is controlled by thyroid hormones by negative feedback. The unusual combination of elevated serum levels of free thyroid hormones with non-suppressed TSH suggests the diagnosis of resistance to thyroid hormone (RTH) or a TSH-secreting pituitary tumour (TSHoma). We report a case of a Chinese family in whom the diagnosis of RTH was confirmed by a codon 429 mutation in the thyroid hormone receptor beta (THRβ) gene, and discuss the differentiation of these two conditions and the treatment of RTH.

Case report

A 39-year-old Chinese man presented in 1990 with palpitations. He had a diffuse goitre (twice of the normal size) but no ocular signs or other...
symptoms of hyperthyroidism. His pulse rate varied from 70 to 100 beats per minute. Investigations showed an elevated total thyroxine (T₄) level (227 nmol/L; reference range [ref], 77-157 nmol/L) and an increased free triiodothyronine (FT₃) concentration (10.03 pmol/L; ref, 3.28-8.2 pmol/L). The TSH level was not measured. Thyroid antibodies were negative.

The patient was treated for thyrotoxicosis with propylthiouracil (up to 600 mg per day), but his FT₃ levels remained elevated (9.65-12.3 pmol/L). In 1993, his TSH level was found to be 16.7 mIU/L (ref, 0.3-4.0 mIU/L) with a free T₄ (FT₄) level of 20.7 pmol/L (ref, 8.5-20.7 pmol/L). This pattern of elevated FT₄ and non-suppressed TSH levels persisted on repeated testing (FT₄, 25.2 pmol/L and TSH, 7.0 mIU/L; FT₄, 23.9 pmol/L and TSH, 7.3 mIU/L). Family history was negative. All family members had normal FT₄ and TSH levels (Table 1).

In 1994, magnetic resonance imaging (MRI) revealed an enlarged pituitary gland with lobulated outline, heterogeneous signal intensity, and mild suprasellar extension. Other anterior pituitary function tests were normal. A tentative diagnosis of TSHoma was made and transphenoidal excision performed. The “tumour” was macerated in the process of removal, histology of the surgical specimen did not show any definite adenoma, and immunohistochemical staining revealed a mixture of cells, compatible with normal pituitary tissue. Postoperatively, his FT₄ and TSH levels remained elevated (23 pmol/L and 6.7 mIU/L, respectively). Propylthiouracil was stopped in 1997 in view of the failure to suppress FT₄ values to normal and the clinical suspicion of RTH. Subsequent post-operative MRI follow-up for 10 years revealed no residual or recurrent tumour.

After stopping all medication for at least 4 weeks, results of other investigations performed between 1994 and 2003 were as follows: thyroid scan showed diffusely increased perfusion and uptake. Thyrrotropin-releasing hormone (TRH) stimulation test showed exaggerated response of TSH to TRH (3.0, 13.2, and 15.2 mIU/L at 0, 15, and 30 minutes, respectively). Administration of exogenous T₄ led to partial suppression of basal TSH and TSH response to TRH stimulation, with basal/post-TRH TSH of 0.5/0.7 mIU/L, 0.07/0.1 mIU/L, and 0.04/0.2 mIU/L after 50, 100, and 200 µg of levo-triiodothyronine (L-T₃) daily, respectively. The alpha-subunit was normal (0.27 and

| Table 1. Biochemical findings* of the index patient and his family members in 2003 |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                   | TSH (mIU/L) | FT₃ (pmol/L) | TT₃ (nmol/L) | FT₄ (pmol/L) | TT₄ (nmol/L) | T-Chol (mmol/L) | SHBG (nmol/L) | CK (IU/L) | Ferritin (pmol/L) |
| Index patient†    | (See text and Table 2) | <5.2 | 13.0-71.0 | 62-328 | 69-920 |
| Father            | 1.87       | 4.4      | 1.26      | 16.0     | 133      | 5.4                | 50.9           | 98          | 1010             |
| Mother            | 1.36       | 2.8      | 1.05      | 19.7     | 110      | 7.2                | 85.2           | 130         | 590              |
| Elder sister      | 3.78       | 4.6      | 1.30      | 15.5     | 119      | 5.4                | 86.4           | 88          | 31               |
| Elder brother     | 1.54       | 4.4      | 1.27      | 15.7     | 111      | 7.0                | 23.4           | 132         | 1286             |
| Son†             | 3.39       | 10.7     | 3.16      | 32.6     | 246      | 5.6                | 57.9           | 183         | 97               |
| Reference range   | 0.27-4.20  | 3.0-6.2  | 0.70-2.10 | 12.0-22.0 | 62-154   | <5.2               | 13.0-71.0      | 62-328     | 69-920           |

* TSH denotes thyroid-stimulating hormone, FT₃ free triiodothyronine, TT₃ total triiodothyronine, FT₄ free thyroxine, TT₄ total thyroxine, T-Chol total cholesterol, SHBG sex hormone binding globulin, and CK creatine kinase
† Both the index patient and his son had increased serum levels of thyroid hormone with non-suppressed TSH

| Table 2. Biochemical parameters* of the patient before and after treatment with 3,5,3’-triiodothyroacetic acid (TRIAC) |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                   | Reference range | Without TRIAC (2 Sept 2003) | Treated with TRIAC (0.35 mg) |
|                   | (20 Oct 2004) | 2 times daily | 3 times daily | 4 times daily |
| FT₃ (pmol/L)      | 3.0-6.2       | >46.1          | >46.1          | >46.1          |
| FT₄ (pmol/L)      | 12.0-22.0     | 28.2           | 30.4           | 27.0           |
| TSH (mIU/L)       | 0.27-4.20     | 0.19           | 0.07           | 0.05           |

* FT₃ denotes free triiodothyronine, FT₄ free thyroxine, and TSH thyroid-stimulating hormone
† FT₄ and TSH levels decreased while FT₃ became markedly elevated, probably due to cross-reactivity of TRIAC with FT₃ assay
0.07 IU/L; ref, <0.8 IU/L) in 1995 and 2003. The red blood cell (RBC) zinc concentration was also normal at 158 μmol/L and 176 μmol/L of RBC (ref, 155-237 μmol/L of RBC) in 1994 and 1998. Results of other biochemical tests for assessing tissue sensitivity to thyroid hormones are shown in Table 1. Dual energy X-ray absorptiometry in 2003 revealed osteoporosis (T score: L1-L4, -2.8; neck of femur, -2.7). The alkaline phosphatase level was normal.

In 2003, the diagnosis of RTH was confirmed by genomic analysis of the THRβ gene. The patient was heterozygous for R429Q, with CGG to CAG missense mutation at codon 429 on exon 10. Screening of his asymptomatic 7-year-old son revealed the same mutation. Thyroid function tests showed inappropriate TSH secretion (Table 1).

After confirmation of the diagnosis of RTH, the patient was prescribed 3.5,3'-triiodothyroacetic acid (TRIAC) 0.35 mg twice per day and then increased to 4 times per day. His palpitations and insomnia improved with twice daily dosing of TRIAC, but dose escalation produced no further improvement. Pulse rate during TRIAC treatment ranged from 70 to 80 beats per minute. Free T₄ and TSH levels decreased, but FT₂ became significantly elevated (Table 2). Echocardiography showed that the calculated cardiac output decreased from 4.90 to 3.84 L/min after TRIAC therapy, primarily due to a decline in heart rate from 100 to 75 beats per minute. Stroke volume, ejection fraction, and diastolic function remained unchanged.

Serum FT₃ was measured by a two-step chemiluminescent microparticle immunoassay (Axysym; Abbott Laboratories, Abbott Park, US). Serum FT₄ was measured by a competitive immunoassay (ADVIA Centaur; Bayer, Abbott Park, US) and serum TSH by a two-site sandwich immunoassay (ADVIA Centaur). The inter- and intra-assay coefficient of variation were less than 10%. Leukocyte DNA was extracted from blood samples using standard methods. The THRβ gene was amplified using primers and conditions developed by Adams et al., and the polymerase chain reaction product was then sequenced by an automatic DNA sequencer (3100 Genetic Analyzer, Applied Biosystems, Foster City, US).

Discussion

Resistance to thyroid hormone is a syndrome of impaired tissue responsiveness to thyroid hormones. Different body tissues may exhibit variable degrees of resistance to the action of thyroid hormones, depending on the number of THRβ they contain. Since the first description of RTH in 1967, more than 600 cases have been reported. Most patients have been identified on the basis of high or inappropriately normal serum TSH in association with elevated free thyroid hormone levels or by family screening.

Clinical differentiation of RTH from TSHoma can be difficult. A positive family history is suggestive of RTH, which is a dominantly inherited condition. Nevertheless, a negative family history does not exclude the diagnosis, as illustrated by our case. Before his son was born, all his family members had normal thyroid function tests. Resistance to thyroid hormone in our patient was probably due to a de novo mutation, which occurs in 16% of RTH cases. Clinical features of hyperthyroidism may appear in both conditions. Some patients with generalised resistance to thyroid hormone (GRTH) exhibit a combination of hyperthyroid and hypothyroid features, or present with predominately hypothyroid symptoms. Patients with TSHoma may have impaired visual fields or features of hypopituitarism. The utility of biochemical tests in differentiating TSHoma from RTH is also limited. Alpha-subunit level is elevated in only 66% of patients with TSHoma, and alpha-subunit to TSH molar ratio is elevated in only 80%. Thyroid-stimulating hormone–secreting pituitary tumour may co-secrete growth hormone (16%), prolactin (11%), and gonadotrophins (14%), but 71% secrete TSH alone. The TSH response to TRH is typically absent or blunted in 87% of patients with TSHoma and intact or exaggerated in subjects with RTH, but the response of some patients with TSHoma may mimic that of RTH patients. This may be due to somatic mutations in the THRβ gene in the tumour cells. Suppression of TSH by exogenous L-T₄ is impaired in both conditions. The presence of a pituitary adenoma on radiological imaging does not necessarily exclude the diagnosis of RTH, because up to 11.3% of adenomas are incidentalomas.

To date, most cases of RTH have been due to mutations in the THRβ gene, and a genomic search for THRβ mutations, if successful, may help differentiate between a TSHoma and RTH, as illustrated by our case. However, RTH without a structural THRβ defect occurs in approximately 10% of the cases. It has been postulated that a cofactor interacting with THR may be responsible for the manifestation of RTH. Subjects with the same mutation may exhibit different phenotypes, suggesting modulation of thyroid hormone actions by other factors.
An intriguing question is whether our patient has concomitant TSHoma and RTH. An example of this type of co-morbidity is a patient with Cushing’s disease and generalised glucocorticoid resistance due to a germline mutation of the glucocorticoid receptor.9 Nevertheless, among more than 600 RTH patients reported in the literature with mutations in the THRβ gene, none developed a TSHoma.1,10,11 A patient with a TSH-secreting microadenoma and pituitary resistance to thyroid hormone (PRTH) has been reported, but no genetic analysis was performed.12 In our patient, while the diagnosis of a concomitant TSHoma remained possible, it was not definitively substantiated by operative or immunohistochemical findings. Alternative explanations for his MRI findings are pituitary incidentalomas or pituitary hyperplasia. Pituitary enlargement compatible with hyperplasia has been reported in a patient with RTH, but only following inadvertent radioactive iodine therapy: regression occurred after supraphysiological doses of thyroxine replacement.13 In our case, there was no prior history of ablative therapy, and his FT3 levels remained elevated despite treatment with propylthiouracil.

In the English medical literature, only one plausibly-case of RTH has been reported among Chinese. The diagnosis was based on compatible thyroid function test results, normal alpha-subunit levels, and non-suppression of TSH by exogenous T4. Family history was negative, and no mutations in THRβ or thyroid hormone receptor alpha genes could be identified.7 The low incidence of RTH in Chinese may be due to underreporting or ethnic differences. The Chinese RTH family we report here is heterozygous for R429Q, with a CGG to CAG missense mutation at codon 429 of the THRβ, leading to replacement of arginine by glutamine. This mutation has been reported to impair co-repressor release in the TSH gene.14

Resistance to thyroid hormone has been subclassified into two phenotypes: GRTH and PRTH. Patients with GRTH are typically euthyroid or hypothyroid, whereas patients with PRTH are usually hypermetabolic. Symptoms of thyroid dysfunction are however relatively non-specific, and there is no good tissue marker for thyroid hormone actions. Differentiation into GRTH and PRTH can thus be difficult. Previous studies have failed to demonstrate an association between clinical features and the nature or location of a receptor mutation.1 More recent studies suggest that specific mutations may be related to the PRTH phenotype.15,16 An example is R429Q mutation. Of three patients with R429Q mutation reported in the literature, two had PRTH1 and one had GRTH.17 Our index patient had palpitations and one had GRTH.17 Our index patient had palpitations and anxiety, osteoporosis, and increased cardiac output—features which are compatible with PRTH.

Treatment of RTH should be based on assessment of tissue sensitivity to thyroid hormones. In most cases of GRTH, tissue RTH appears to be adequately compensated for by the increase in endogenous thyroid hormones, and no treatment is required. For GRTH patients who have features of hypothyroidism, or who cannot compensate by increasing thyroid hormone secretion because of prior erroneous diagnosis and ablative therapy, supraphysiological doses of thyroid hormones are recommended. Patients with PRTH who exhibit hyperthyroid features at tissue levels generally require treatment to reduce the elevated thyroid hormone levels. 3,5,3’-Triiodothyroacetic acid, a physiological metabolite of T3, can reduce TSH and endogenous thyroid hormone levels and alleviate symptoms.3 However, the efficacy of TRIAC is variable,18 and its effect on heart rate is often minimal, probably because the decrease in thyroid hormone levels is offset by the intrinsic thyromimetic effect of the drug. 3,5,3’-Triiodothyroacetic acid also cross-reacts in T3 assays. Glucocorticoids and dopaminergic drugs can suppress TSH secretion, but their side-effects and difficulty in administration preclude long-term use.3 When treatment with TRIAC is unsuccessful, thyroid ablative therapy followed by replacement with physiological doses of thyroid hormone may be required. In our patient, low doses of TRIAC ameliorated his symptom of palpitations and reduced his cardiac output. Assessment of osteoporosis has not been possible because of the short duration of treatment.

References

5. Ando S, Sarlis NJ, Oldfield EH, Yen PM. Somatic mutation of TRbeta can cause a defect in negative regulation of TSH