Published in final edited form as:

Exp Clin Endocrinol Diabetes. 2009 January ; 117(1): 34–37. doi:10.1055/s-2008-1076712.

THYROID HORMONE RECEPTOR BETA GENE MUTATION (P453A) IN A TURKISH FAMILY PRODUCING RESISTANCE TO THYROID HORMONE

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Abstract

Two members of a Turkish family, a mother and son, had thyroid function tests suggestive of resistance to thyroid hormone (RTH). The clinical presentation was, however, different. The mother (proposita) had palpitation, weakness, tiredness, nervousness, dry mouth and was misdiagnosed as having multinodular toxic goiter which was treated with antithyroid drugs and partial thyroidectomy. Her younger son had attention deficit hyperactivity disorder and primary encopresis, but normal intellectual quotient. Both had elevated serum iodothyronine levels with nonsuppressed thyrotropin. A mutation in one allele of the thyroid hormone receptor beta gene (P453A) was identified, providing a genetic confirmation for the diagnosis of RTH.

Keywords

Resistance to thyroid hormone; mutation; thyroid hormone receptor

INTRODUCTION

Resistance to thyroid hormone (RTH) is a dominantly inherited syndrome characterized by decreased responsiveness of target tissues to thyroid hormone. While the presentation is variable, the syndrome is characterized by increased thyroid hormone concentrations in association with normal or elevated thyrotropin (TSH) concentrations. Common presentations are goiter, learning difficulties, attention deficit - hyperactivity disorder and growth delay. Although great majority of patients are euthyroid, some clinical and laboratory findings suggestive of thyrotoxicosis as well as hypothyroidism could be explained by

variable degree of hormonal resistance in different tissues of the same patient (1–3). Myocardium mainly expresses thyroid hormone receptor (TR) alpha, thereby mutations in the TR β gene may maintain cardiac sensitivity to the increased thyroid hormone concentrations, leading to tachycardia (4, 5). Mosaicism for a TR β gene was described for the first time in a Turkish patient, leading to nonuniform sensitivity of various tissues to thyroid hormone (6).

In this study we described a Turkish family with P453A mutation of the TR β gene. The proposita underwent thyroidectomy because of a diagnosis of toxic multinodular goiter. Her 11 year-old son had the same mutation. He had attention deficit-hyperactivity disorder, a normal IQ and, interestingly, primary encopresis.

MATERIALS AND METHODS

Clinical report of the proposita and her two sons

A 37 year-old woman was admitted to our Endocrinology unit with complaints of palpitation, weakness, tiredness, nervousness, dry mouth, and loud speech due to decreased hearing. At the age of 16 years, she was seen elsewhere for weakness. Goiter was found on physical examination. Four years earlier, she underwent subtotal thyroidectomy after one-year treatment with propylthiouracil (PTU) for what was believed to be toxic multinodular goiter. She was then treated with L-thyroxine for a short time interval. Thereafter, hyperthyroidism was thought to recur and she was referred to the Endocrinology Department of Istanbul University. On admission she was still taking PTU 100mg twice daily.

Her menstrual cycles were normal, and she had two children. Her older child was a 15-year old boy. His height was 1.68 m and his weight was 58 kg. His audiometry was normal, IQ was 129. He had mild attention deficit hyperactivity disorder (ADHD). Her younger son was an 11 year-old boy. His height and weight were 1.33 m and 35 kg respectively. His audiometry was normal and IQ was 108 %. He had ADHD and primary encopresis.

The proposita's father died from lung cancer, and her mother had arterial hypertension.

On physical examination the proposita had two nodules of approximately 2 by 1 cm in diameters in the left thyroid lobe. She was 1.60 m in height and 60 kg in weight. Her blood pressure and pulse were 120/80 mmHg and 80/min, respectively. Physical examination was otherwise unremarkable.

Laboratory evaluation revealed normal blood count, renal and hepatic function tests, urinalysis, chest X-ray and audiometry. Electrocardiography showed a heart rate of 90 beats/min. Echocardiography was normal with ejection fraction of 67 %. Results of thyroid function tests, while still on propylthiouracil, showed elevation of all three serum iodothyronine concentrations with no suppression of thyrotropin (TSH). Her younger son (subject III-2 in Fig. 1) had comparable thyroid test abnormalities (Fig. 1) No heterophilic antibodies were detected in the patient's serum. TBG concentration was within the normal limits. TSH and prolactin responded normally to the administration of TSH-releasing hormone (TRH) (Table 1). Magnetic resonance imaging revealed no pituitary abnormalities.

As the clinical and laboratory findings were compatible with RTH, PTU was discontinued in the key case and administration of L-T₄ was planned, because TSH remained elevated (see Fig 1). Metoprolol 12.5 mg twice daily was administered to relieve her symptoms. The patient and first-degree members of her family underwent laboratory and genetic analyses.

Laboratory analyses

Total thyroxine (TT₄), total T₃ (TT₃) and TSH were measured by chemiluminescence using Elecsys 2010 technology (Roche-Boehringer Mannheim GmbH and Hitachi, Ltd). Total reversed T₃ (TrT₃) and thyroglobulin (TG) were measured by RIAs. Free T₄ index (FT₄I) was estimated from the resin T₄ uptake ratio and the TT₄ concentrations. Thyroperoxidase (TPO) and TG antibodies were measured by an agglutination method.

Genomic DNA (gDNA) was extracted from peripheral blood lymphocytes (PBL) of the probanda and immediate members of her family. All coding exons of the TR β gene were sequenced from gDNA extracted from PBLs and using primers and conditions described previously (7, 8). Written informed consent was obtained from the index patient and family members for genetic analysis. The study was approved by the Institutional Review Board of the University of Chicago and written consent was obtained from all family members undergoing laboratory and genetic studies.

RESULTS

The pedigree of the family is shown in figure 1. The probanda (subject II-4 in Fig 1) and her second son (subject III-2 in Fig 1) have elevated serum concentrations of all three iodothyronines and non-suppressed TSH, compatible with RTH (Fig. 1). Other relatives had normal or isolated thyroid test abnormalities. More specifically, a brother (subject II-3) and husband (subject II-5) had mild elevation and reduction of rT₃ concentrations, respectively, which are of trivial significance. The significance of the mild the elevation of serum TSH concentrations of the eldest son and husband is unclear.

Sequencing of the TR β gene identified a mutation in exon 10 of the probanda and her affected child. The identified mutation in the TR β gene is a single nucleotide substitution, a cytosine for a guanine at codon 453 (CCT → GCT), replacing the normal proline with an alanine (P453A). This mutation is located in the hormone-binding domain of the TR β .

DISCUSSION

The P453A mutation found in our cases has been identified in 7 other families (7, 9–12), 2 of which by the senior author of this publication (10 and unpublished). The mutation is reported to produce a TR β with 17 % of the normal binding affinity for T₃ (7, 9). It is of interest that one of these families is also from Turkey (10). In addition the same codon underwent five different mutations; 16 families with P453T (7, 9, 13–19 and Refetoff 6 families unpublished), 12 families P453S (7, 9, 20–22 and Refetoff 4 families unpublished), one family P453N (Refetoff, unpublished data), one family P453Y (9), and four families P453H (14, 20, 23–25 and Refetoff 1 family unpublished).

The clinical presentation was different in mother and the son. The mother was referred to a primary hospital with non-specific symptoms and signs. Hyperthyroxinemia in association with nonsuppressed TSH was detected. The patient underwent subtotal thyroidectomy with a presumptive diagnosis of toxic multinodular goiter. After that she was referred to the Istanbul Medical Faculty for further evaluation of recurrent hyperthyroidism. Nonsuppressed TSH concentrations in association with increased thyroid hormone levels led to additional diagnostic work-up to determine if she had RTH.

Several conditions may be associated with increased serum thyroid hormone concentrations in association with nonsuppressed TSH. Assay interference due to heterophilic antibodies, anti-iodothyronine antibodies and binding protein abnormalities (increased thyroxine binding globulin concentrations, familial dysalbuminemic hyperthyroxinemia) should be excluded (26, 27). Binding protein abnormalities were excluded by measurement of free thyroid hormone concentrations and TBG. The differential diagnosis should also include TSH secreting pituitary adenoma. Presence of a sellar mass, concomitant hypersecretion of alpha-glycoprotein subunit of other pituitary hormones in association with clinical findings, such as acromegaly or galactorrhea, presence of neurological signs/symptoms or visual field defects may be additional clues for a TSH secreting tumor. In patients with TSH secreting pituitary adenoma no TSH response to TRH is expected. In addition T₃ administration fails to suppress TSH in majority of the patients (28). In our patients increased free thyroid hormone concentrations and absence of heterophile antibodies, excluded assay interference or binding protein abnormalities. There was no sellar mass on imaging. In addition results of TRH stimulation test were suggestive for RTH. Genetic analysis confirmed the diagnosis.

The great majority of individuals with RTH are clinically euthyroid. Diagnostic and therapeutic difficulties in patients with RTH may develop after ablative treatment as a consequence of misdiagnosed hyperthyroidism (1). In addition, autoimmune thyroid disease in patients with RTH can obscure the elevation of T₃ and T₄, leading to thyroid gland insufficiency (10). In these situations, elevated serum TSH indicates reduced thyroidal reserve and hypothyroid state at the tissue level. This is the reason for initiating L-thyroxine treatment after thyroidectomy in our patient.

The son had ADHD. Subjects with RTH have a increased frequency of ADHD as compared with their unaffected family members (3, 29, 30). Hearing defects occur in patients with congenital hypothyroidism. Mild forms of hearing impairment were observed in patients with RTH due to recurrent ear infections (2, 3, 31). Although our index patient complained of decreased hearing, no objective finding of impaired hearing could be found. Our patient's sinus tachycardia may be due to the effects of thyroid hormone excess on the TR-alpha mostly expressed in myocardium. In the presence of tachycardia, cardioselective β -adrenergic blockade is advocated and reported to be useful in most of the cases (4, 5).

In childhood, hyperkinetic syndromes, and behavioral disorders were common comorbid abnormalities. Encopresis frequently accompanies psychiatric disorders. It is estimated to afflict 1 to 3 % of the general pediatric population (32, 33). There is no known association of encopresis with RTH. Our patient's son had interestingly primary encopresis accompanying ADHD and RTH.

Mutational analysis of the TR β gene allows definitive diagnosis of RTH, potentially avoiding the need for protracted and expensive pituitary function testing. Mutational analysis also enables family screening and may help to avoid potential misdiagnosis and inappropriate treatment in unsuspected family members.

Acknowledgments

Supported in part by grants DK 15070, DK 07011 and RR 00055 from the National Institutes of Health, USA

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Figure 1.
 Pedigree of the family and results of thyroid function tests. Generations are indicated by Roman numerals and subjects by Arabic numbers. Results of tests are aligned under each symbol representing a family member. Abnormal values are in bold numbers. The proband is indicated by an arrow.

Table 1

Responses of TSH and prolactin (PRL) to TRH stimulation

TEST/TIME(minutes)	0	20	60
TSH (mIU/L)	2.6	25.5	15.9
PRL (ng/ml)	9.5	64.2	24.8

200 µg of TRH were administered intravenously at time 0.

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