Resistance to Thyroid Hormone Accompanied by Graves’ Disease

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Abstract

Resistance to thyroid hormone (RTH) is characterized by elevated serum levels of thyroid hormones and normal or slightly increased serum thyrotropin (TSH) levels. Recently it has been suggested that chronic TSH stimulation in RTH activates intrathyroidal lymphocytes, leading to thyroid damage and autoimmune thyroid disease (AITD). Therefore, individuals with RTH have an increased likelihood of AITD compared to unaffected relatives. We here report a 33-year-old woman in whom we diagnosed Graves’ disease and treated her with thiamazole (MMI). For two years, her TSH levels were suppressed when thyroid hormones were elevated and conversely they were increased when thyroid hormones levels were decreased. These findings were common for a clinical course during treatment for Graves’ disease with anti-thyroid drug. However, three years after the initiation of MMI therapy, she had a normal or gradually elevated serum TSH level even though the level of thyroid hormones never decreased, indicating inappropriate secretion of TSH. We concluded she had RTH clinically, and we demonstrated by direct sequence analysis a mutation of the TRβ gene, causing replacement of a glycine (G) with arginine (R) at codon 251. The finding of an elevated TSH level without decreased thyroid hormones should suggest the presence of RTH during therapy of Graves’ disease.

Key words: resistance to thyroid hormone, TSH level, Graves’ disease, TRβ gene mutation


Introduction

Resistance to thyroid hormone (RTH) is a syndrome involving reduced responsiveness of target tissues to thyroid hormone. Ninety percent of subjects with RTH studied at the gene level have mutations in the TRβ gene (1). The mutant TRβ molecules have either a reduced affinity for thyroid hormone or impaired interaction with one of the cofactors involved in the mediation of thyroid hormone action (2, 3). Elevated serum levels of thyroid hormone in the presence of normal or slightly increased serum thyrotropin (TSH) levels should suggest the diagnosis of RTH (1). Gavin et al proposed that chronic TSH stimulation in RTH activates intrathyroidal lymphocytes, leading to thyroid damage and autoimmune thyroid disease (AITD) (4). Barkoff et al also reported that individuals with RTH have an increased likelihood of AITD compared to unaffected relatives (5). However, most of these cases with both RTH and AITD were autoimmune hypothyroidism. Graves’ disease is also an autoimmune thyroid disorder caused by stimulation by antibodies directed against the TSH receptor (6). Furthermore, Graves’ disease has elevated serum thyroid hormones, as in RTH, but TSH is suppressed, in contrast to the situation in RTH. The clinical course of TSH levels in a patient with RTH accompanied by Graves’ disease might be variable and unpredictable. Here, we report the detailed clinical course of a Graves’ disease patient with RTH.

Case Report

A 33-year-old woman presented with palpitations. Her thyroid gland was diffusely and symmetrically enlarged to twice the normal size without tenderness. Serum FT4 and FT3 levels (3.0 ng/dL and 9.3 pg/mL, respectively) were elevated, and the serum TSH level (0.007 μU/mL) was reduced. Since anti-thyroid receptor antibodies were positive (TBII 80.7% and TSAb 1,832%), she was diagnosed as hav-
ing Graves’ disease, and 30 mg of thiamazole (MMI) per day were administered. For two years, her TSH levels were suppressed when thyroid hormones were elevated and conversely they were increased when thyroid hormones levels were decreased. These findings were common for a clinical course during treatment for Graves’s disease with MMI. However, three years after the initiation of MMI therapy, the serum TSH level gradually rose, even though the levels of thyroid hormones never declined. These findings indicated that she had developed the syndrome of inappropriate secretion of TSH (SITSH), and either RTH or a TSH-producing adenoma (TSHoma) and thus these were considered possible diagnoses. She was admitted to our hospital for further examination.

Her temperature was 35.7°C, resting pulse rate 89 per minute, and blood pressure 143/72 mm Hg. She had goiter, normal skin turgor, no epilation and no edema of the legs. She had never been a smoker or abuser of alcohol. She had a regular menstrual cycle. There was no family history of thyroid diseases. Figure 1 illustrates her clinical course during the period between starting therapy of Graves’ disease and hospital admission. Three years after the initiation of MMI therapy, the thyroid receptor antibody (TRAb) test showed negative (Fig. 1, black arrow). Then, her serum TSH became elevated regardless of an elevated FT4, which was different from the relationship of TSH and FT4 in common Graves’ disease.

We reduced the dose of MMI from 30 mg to 10 mg daily one week before admission. On admission, she had increased levels of FT4 and FT3 (2.0 ng/dL and 5.1 pg/mL, respectively) without suppressed TSH (4.94 μU/mL). TPO antibody and thyroglobulin antibody were positive (14.4 U/mL and 1.5 U/mL, respectively), and TRAb was <1.0 IU/L. α-subunit and sex hormone-binding globulin (SHBG) were 0.4 ng/mL and 12 nmol/L, respectively, within normal ranges. Magnetic resonance imaging of the pituitary gland revealed no tumor in the pituitary gland. Next, before and after 50 μg, 100 μg, or 200 μg of L-T3 administration for consecutive days, the TSH responses to TRH stimulation were examined for differential diagnosis of TSHoma, in which TSH levels were unresponsive to TRH stimulation or T3 suppression tests (7). In this case, TSH responded normally before administration of L-T3, and the peak of TSH responses to TRH after graded doses on L-T3 declined in relation to the L-T3 doses (Fig. 2). SHBG concentration, which is a good marker for peripheral thyroid hormone action (7), was normal at baseline, and not changed after administration of L-T3 (data not shown). On the basis of these findings, we diagnosed her as having RTH clinically.

We received written permission from her for gene analysis of TRβ as approved by ethical committee in Hiroshima University. Genomic DNA was extracted from peripheral whole blood using a Flexi Gene DNA kit according to the manufacturer’s instructions (QIAGEN, Hilden, Germany). Exons 6 to 10 and the flanking introns of the TRβ gene were amplified by polymerase chain reaction (PCR) using the following conditions: one cycle of 95°C for 3 min; 35 cycles of denaturation at 95°C for 30 sec, annealing at 58°C for 30 sec, and an extension at 72°C for 45 sec. The reaction mixture of final volume 20 μl contained 200 ng DNA, 1x Ex Taq Buffer, 0.2 mmol/L dNTP Mixture, 0.5 μmol/L of each primer, and 0.5 U Ex Taq. All the PCR products
Discussion

We described her detailed clinical data of the period between the diagnosis of Graves’ disease and RTH. Although her TRAb had been negative, we could not reduce the dose of MMI due to her elevated thyroid hormone levels. Looking back at her clinical course, she showed elevated serum TSH even though FT4 was elevated (Fig. 1, white arrows). In a patient with common Graves’ disease taking antithyroid drug for the treatment, serum TSH will originally start to elevate after the normalization of FT4. We consider that this finding was different between the present case and common Graves’ disease and it was important for the diagnosis of RTH during therapy of Graves’ disease.

The present case was a RTH patient accompanied by Graves’ disease. Individuals with RTH have an increased likelihood of AITD compared to unaffected relatives (5). A few cases of RTH with Graves’ disease have been previously reported (8-10). The cases of Sato et al and Sivakumar and Chaidarun were similar in symptoms and clinical course of thyroid hormones to the present case but their TRβ gene mutations were different from ours (P435T and G347W, respectively) (9, 10). At the time of the publication of Pillay et al, genetic analysis for TRβ gene mutations was not available, and thus TRβ gene mutation was unclear (8). The prevalence of overt Graves’ disease in individuals with RTH is unclear. Further studies are required in order to clarify the relationship of a RTH patient and Graves’ disease.

In the present case, a missense mutation in exon 8 of the TRβ gene, G251R, was identified by direct sequence analysis. Most subjects with RTH have mutations in the TRβ gene. The gene of TRβ locates in chromosome 3 and consists of 10 exons. Their mutations are located in the exon 7 to 10 which are in three clusters within the ligand-binding domain (amino acids 242-460) and the adjacent hinge domain (amino acids 234-243) of the receptor protein (1, 2, 11-13). If there is a mutation of these three clusters, TRβ function is impaired. No differences were found when the mutations were analyzed within the three different clusters (1). In addition, the severity of the disease is variable among family with TRβ mutations, no clear correlation of phenotype with genotype has been found (14). Same missense mutation in codon 251 of the TRβ gene has been previously defined in the case of 27-year-old Italian male (15). He was complaining of goiter and palpitation. His TPO antibody and thyroglobulin antibody were negative; he had no accompanying AITD, different from the present case. Since the percentage of positive thyroid autoantibody increases with aging in male individuals of RTH (5), the Italian male with RTH may be accompanied by AITD including Graves’s disease in the future.

In conclusion, we demonstrated a patient who was diagnosed as having RTH during treatment of Graves’ disease. If serum TSH gradually begins to elevate even though thyroid levels with similar levels of FT4 and FT3 and TSH.

**Figure 2.** The TRH-stimulation tests after administration of graded doses of L-T3.

**Figure 3.** Direct sequence analysis.

were purified by shrimp alkaline phosphatase (SAP) and exonuclease1 (EXO1), and both strands were sequenced using the amplification primers as sequencing primers and ABI Prism BigDye Terminator v3.1 cycle sequencing reagents according to the manufacturer’s instructions (Applied Biosystems, Foster City, CA). Purified sequencing fragments were separated by capillary electrophoresis and detected by laser-induced fluorescence on an Applied Biosystems 3130X 1 Genetic Analyzer (Applied Biosystems).

We identified a heterozygous G to A transition at nucleotide 1037 of exon 8 of TRβ gene at codon 251, resulting in a glycine (G) to arginine (R), G251R (Fig. 3). After the diagnosis of RTH, we considered that Graves’ disease was in remission from the findings of elevated FT4 and FT3 levels without suppressed TSH, and negative TRAb. Therefore, we decreased the dose of MMI to 5 mg daily for one year along with similar levels of FT4 and FT3 and TSH.
hormone never decreases during therapy of Graves’ disease, we should consider that the patient has associated RTH. In addition, in a patient of RTH accompanied by Graves’ disease, the TSH level and symptomatic improvement of Graves’ disease could be important in order to assess for remission of Graves’ disease.

The authors state that they have no Conflict of Interest (COI).

References