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LETTER TO THE EDITOR

A rare case of resistance to thyroid hormone coexisting with Graves' disease

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To the Editor,

Resistance to thyroid hormone (RTH) is characterized by reduced sensitivity to thyroid hormone, mostly caused by mutation in the *thyroid hormone receptor β (TRβ)* gene. Patients with RTH have increased free triiodothyroxine (FT3) and free thyroxine (FT4) and unsuppressed thyrotropin (TSH) levels [1]. Here, we describe a rare case of RTH coexisting with Graves' disease (GD).

A 17-year-old man presented to the hospital because of fatigue, palpitation, hand tremors, weight loss (6 kg), and a large goiter. His blood pressure and heart rate were 127/76 mmHg and 102 beats/min, respectively. He had no growth or mental retardation. Serum TSH, FT3, and FT4 levels were <0.05 μU/ml (reference 0.541–4.261), 24.5 pg/ml (reference 2.39–4.06), and 6.46 ng/dl (reference 0.71–1.52), respectively. Serum anti-TSH receptor antibody (TRAb) level was >30.0 IU/l (reference <1.0). Titers of anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) antibodies were 402.0 U/ml (reference <0.2) and 8.4 U/ml (reference <0.3), respectively. Ultrasound revealed a diffusely enlarged thyroid gland with no tumor lesion. These findings were consistent with GD. Methimazole (30 mg) therapy was started, with the dose reduced as thyroid function improved. After 3 months, his TSH level became inappropriately high (8.308 μU/ml), and his FT3 and FT4 levels (6.40 pg/ml and 1.91 ng/dl, respectively) and TRAb titer (13.8 IU/l) were also above the reference ranges. These conditions persisted under treatment with 5–10 mg methimazole (TSH and FT3 levels were 2.930–16.16 μU/ml and 5.10–6.05 pg/ml, respectively). Fluctuations in metabolic parameters such as total cholesterol and alkaline phosphatase were relatively small and unrelated to those of thyroid function (163–211 mg/dl and 280–402 U/l (reference 115–359), respectively). Thyrotoxic symptoms were not observed. After 1 year, TSH, FT3, and FT4 levels were 6.46 μU/ml, 6.01 pg/ml, and 2.13 ng/dl, respectively, whereas TRAb titer decreased to 1.9 IU/l. Since the first visit, the patient's body weight had increased by 5 kg. Magnetic resonance imaging was negative for TSH-secreting tumor. RTH was verified by sequence analysis; a heterozygous missense mutation, A234T, was found in the *TRβ* gene [2]. His parents had normal thyroid function.

Because the patient had typical hyperthyroidism due to GD, increased secretion of TSH due to RTH was not clarified until GD improved. The occurrence of GD in a patient with undiagnosed RTH is rare. Sivakumar et al. [3] could identify RTH in a GD patient because a high dose of levothyroxine was required after radioiodine ablation therapy, unlike the case.

In this case, determining the therapeutic target range of the thyroid hormone and methimazole dose was difficult, partly because his thyroid function before the onset of GD was unknown. In addition, hyposensitivity to thyroid hormone varies across tissues within the same patient and across individuals having the same mutation [1]. However, during low-dose methimazole treatment, the absence of apparent thyrotoxic symptoms, weight recovery, and

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fluctuation patterns of metabolic parameters suggested that his thyroid function was maintained almost within the appropriate range. The marked decrease in TRAb titer indicated that his GD is near remission.

Barkoff et al. [4] reported that patients with RTH have higher prevalence of anti-TPO or -Tg antibodies than their healthy relatives. Although the pathogenesis of the coexistence of GD and RTH is unknown, the patient was positive for anti-TPO and -Tg antibodies, suggesting that at least GD occurs in the context of autoimmune thyroiditis. The presence of RTH should be considered if a patient presents with inappropriate hyperthyrotropinemia during GD treatment.

References

1. S. Refetoff, A.M. Dumitrescu, Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract. Res. Clin. Endocrinol. Metab **21**, 277 (2007)
2. J.D. Safer, R.N. Cohen, A.N. Hollenberg, F.E. Wondisford, Defective release of corepressor by hinge mutants of the thyroid hormone receptor found in patients with resistance to thyroid hormone. J. Biol. Chem **273**, 30175 (1998)
3. T. Sivakumar, S. Chaidarun, Resistance to thyroid hormone in a patient with coexisting Graves' disease. Thyroid **20**, 213 (2010)
4. M.S. Barkoff, M. Kocherginsky, J. Anselmo, R.E. Weiss, S. Refetoff, Autoimmunity in patients with resistance to thyroid hormone. J. Clin. Endocrinol. Metab. **95**, 3189 (2010)