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OLGU SUNUMU / CASE REPORT

A rare syndrome: Thyroid hormone resistance

Tiroid hormon direnci: Nadir bir sendrom

Yunus İlyas Kibar [1], Şenay Arıkan [2], Ayşe Çarlıoğlu [2], Yasin Öztürk [1], Ahmet Tay [1], Mehmet Emin Ayhan [1]

[1] Erzurum Bölge Eğitim Hastanesi, İç Hastalıkları, Erzurum, Türkiye

[2] Erzurum Bölge Eğitim Hastanesi, Endokrinoloji, Erzurum, Türkiye

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ABSTRACT

Resistance to thyroid hormone syndrome (RTH) is a rare disorder, usually inherited as an autosomal dominant trait. Patients with RTH are usually euthyroid but can occasionally present with signs and symptoms of thyrotoxicosis or rarely with hypothyroidism. We present a patient with interesting syndrome as RTH but no family history. Goiter, increased weight gain and normal mental status were observed despite high serum thyroid hormones and normal TSH levels.

Key words: Thyroid hormone resistance, obesity, goiter

ÖZET

Tiroid hormon direnci sendromu (RTH) genellikle otozomal dominant kalitim gösteren nadir bir hastalıktır. Tiroid hormon direnci olan hastalar genellikle ötiroid olurlar fakat nadir de olsa tirotoksikoz veya hipotiroidizm belirti ve bulguları ile seyredilebilir. Biz bu yazıda ilginç bir sendrom olarak tiroid hormon direnci olan fakat aile öyküsü olmayan bir olgu sunulmaktadır. Olgumuzda yüksek serum tiroid hormon düzeyleri ve normal TSH düzeylerine rağmen guatr, kilo alımında artış ve normal zeka durumu gözlendi.

Anahtar kelimeler: Tiroid hormon direnci, obezite, guatr

INTODUCTION

Thyroid hormone resistance (RTH) describes as the thyroid hormone levels are elevated with variable refractoriness to hormone action in target tissues but the thyroid stimulating hormone (TSH) level is not suppressed, or not completely suppressed as would be expected.[1] RTH is a rare syndrome, and incidence is variously as 1 in 50,000 or 1 in 40,000 live births.[2] Since the first description of RTH in 1967[3], more than 700 individual with RTH belonging to about 250 unrelated families have been identified up to day.[4-5] The majority of RTH cases that have been described are dominantly inherited with highly variable clinical features.[6]

The genetic studies have shown that most mutations are found in three exons in the thyroid hormone receptor-beta (THRβ) gene on chromosome 3 at"hot spot" regions. Most of the disease-causing mutations are clustered in the ligand-binding domain of THRβ, residues 310-353 (cluster 1), 429-461 (cluster 2), and 234-282 (cluster 3)[7-8] Clinical manifestations are extremely variable, the majority of patients being euthyroid according with a generalized form of RTH while a minority of them presents with thyrotoxic features standing for a less pronounced resistance at the peripheral tissue level. Moreover, there is only one case reported in the literature of isolated resistance to peripheral tissue level, presenting with a severe hypothyroid state.[9]

We herein reported a rare and interesting syndrome in a case with RTH but no family history.

CASE

A man with 44 year-old was admitted to endocrinology department due to fatigue, weakness, constipation, and increased need for sleep. These complaints were continued for one year. He had initially given for two months propylthiouracil because of high

Yazışma Adresi /Correspondence: *Dr. Yunus İlyas Kibar*
Erzurum Bölge Eğitim Hastanesi, İç Hastalıkları, Erzurum, Türkiye Email: Kibar-yunusilyas@gmail.com

free T3 (fT3) and free T4 (fT4) levels in other clinic, but these complaints were increased. When he came to our polyclinics, he had stopped propylthiouracil treatment with his own decision since 6 months ago. He has no prior history of hypothyroidism. There were no chronic illnesses or previous thyroidal operation. In his family history, his father, mother, sisters and brothers do not have any thyroid disease.

Physical examination

The vital signs were blood pressure 120/70 mm Hg, pulse 82/minute, respiratory rate 14/minute, temperature 36.0° Celsius. His height was 165 cm and his weight was 106 kg. He suffered obesity and his body mass index was 39 kg/m^2. He had a nodular goiter (grade II). There was no neck tenderness. Hand fine tremor was not appreciated. Normal deep tendon reflexes were observed. But, there were markedly abdominal obesity and 2 cm hepatomegaly. Bowel sound was hypoactive. Other systemic examinations were normal.

Laboratory values

Free T3 (fT3) and free T4 (fT4) levels were high, but TSH level was not suppressed and, it was inappropriately normal level. Free T3 was found 7.5 pg/mL (normal range 1.8-4.2). Free T4 was found 3.27 ng/mL (normal range 0.8-1.9). TSH was found 3.19 mIU/mL (normal range 0.4-4.0). In spite of the markedly elevated free T4 and free T3, the patient was clinically hypothyroid. TPO antibody was <10.0 IU/mL (normal range 0-35), thyroglobulin was 11.16 ng/mL (normal range 1.15-35.0), antithyroglobulin was 20>IU/mL (normal range 0-40). At thyroid ultrasound, his gland was viewed as a heterogeneous and nodular pattern (5x5.5 mm in right lobe, 6.6x9 mm in left lobe, respectively). In the thyroid scintigraphy, the expected level of involvement and activity in both lobes were homogeneous. The anterior pituitary hormones as FSH, LH, prolactin, growth hormone and fasting morning cortisol levels were normal range. In addition, serum ferritin, total testosterone, free testosterone, dehydroepiandrosterone sulfate, sex hormone binding globulin, and angiotensin-converting enzyme levels were normal. Alpha subunit of TSH level was 0.30 IU/L in normal limit (normal range 0 to 0.80). No pituitary TSH secreting adenoma (TSHoma) was determined in pituitary MR by radiologists. As a result, we considered thyroid hormone resistance and we performed TRH stimulation test. After intravenous TRH injection bolus (400 ug), serum TSH concentration increased from 1,40 U/mL to a peak of 17,6 U/mL at 30 min (Table 1). In evaluation of echocardiography, presystolic ejection time was observed as 52 msec below the normal range (Figure 1). In this state, Refetoff syndrome (thyroid hormone resistance) was considered and, levothyroxine 50 microgram per day was started. Later, his complaints were reduced in the controls.

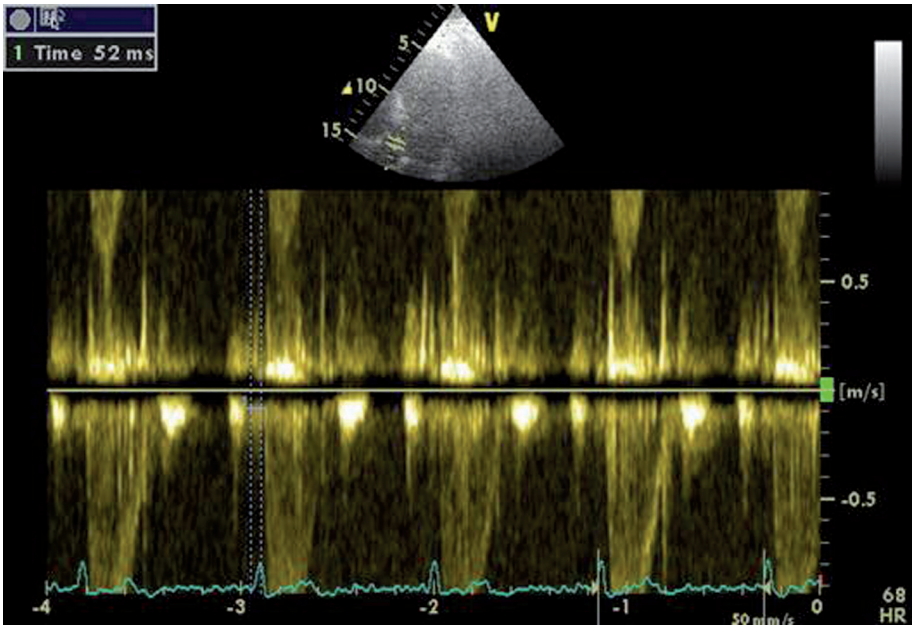

Figure 1. Presistolic ejection time in the patient

Table 1. Summary of pattern associated with elevated TSH during TRH test

Time (min)	TSH (mIU/mL)	f T 3(pg/mL)	f T4(ng/dL)
0	1.40	6.32	2.87
30	17.6	5.90	2.80
60	10.6	5.80	2.92
120	6.05	7.76	2.88

DISCUSSION

Thyroid hormone resistance is a rare disorder and usually dominantly inherited manner with highly variable clinical features. Characteristically, thyroid function tests are elevated free T4 and free T3 concentrations with inappropriately non-suppressed TSH. The clinical expression of this syndrome is heterogeneous. Exacerbate goiter is the most common clinical finding but the classic features include cognitive ability, attention-deficit hyperactivity disorder, poor school performance, delays in growth and development, hypercholesterolemia, signs of hypothyroidism as deaf mutism, nystagmus, epiphyseal dysplasia, and delayed bone age and/or tachycardia are usually diagnosed in childhood. Our patient presented with markedly elevated thyroid hormone and normal TSH levels whereas a mild RTH phenotype. In our case, diagnosis of RTH has remained up to adulthood due to no significantly clinical findings. His clinically features such as goiter, increased weight gain and normal mental status were observed. It is important that many patients with RTH are either asymptomatic or have nonspecific symptoms like our patient. The genetic heterogeneity in patients with RTH is the most likely explanation for variable clinical findings.

Typically most or all tissues are resistant to thyroid hormone, so despite raised measures of serum thyroid hormone the individual may appear euthyroid. Moreover, the severity of hormonal resistance varies among different tissues in an affected individual, and also varies among different subjects carrying the same gene mutation. The reasons for this variability are poorly understood. According to our findings, the only index case presented with elevated TSH and no symptoms of hypothyroidism, but other his family members were asymptomatic and phenotypes were normal. In physical examination, goiter was the most significantly clinical abnormality in our patient. This finding pointed out that high serum TSH levels with increased biological activity might be responsible for the goiter and maintenance of high thyroid hormone levels in RTH. He has normal thyroid hormone levels and normal TSH while taking 100 mg L-T4 per day.

Sinus tachycardia is very common in patients with RTH, some studies reporting frequency as high as 80%[12] One previously study[13] showed mild tachycardia in RTH patients with an average resting heart rate of 83 beats/min (range 57-107). The liver and pituitary express predominantly TRβ1 and TRβ2 respectively, whereas myocardium expresses TRα1. Therefore mutations in the TRβ gene in RTH are associated with pituitary and liver resistance, as exemplified by normal serum sex-hormone-binding globulin and non-suppressed TSH levels seen in patients, while the tachycardia seen in many RTH cases may represent retention of cardiac sensitivity to elevated thyroid hormones acting via a normal TRα.[15] Interestingly, although positive correlations between free T3 and heart rate have been shown in RTH, heart rate was clearly normal range in spite of high free T3 levels in our index case. Moreover, normal presystolic ejection time was demonstrated during echocardiographic evaluation. According to our finding, cardiac affects of RTH were negligible in our case.

Neurophysiological abnormalities such as attention deficit hyperactivity disorder in childhood or language development problems manifested by poor reading skills, dyslexia and problems with articulation have been documented in a large number of patients with RTH.[4,10,11] But, these neurophysiological symptoms were not determined in our patient; his only symptom of RTH was obesity. Obesity was much more pronounce than cases of heterozygous RTH. Moreover, his obesity has worsened due to cessation of LT4 drug treatment over a 6-month period. His weight was increase approximately 12 kg in 6 months. Mitchell CS et al.[14] recently demonstrated that energy intake in RTH subjects was increased by 40%, with marked hyperphagia particularly evident in children. Basal mitochondrial substrate oxidation is increased and energy production in the form of ATP synthesis is decreased in the muscle of RTH patients and that resting oxidative phosphorylation is uncoupled in this disorder.[14]

At least three different molecular alterations may cause reduced sensitivity to thyroid hormones: (a) mutations in the gene encoding TRβ isoform causing RTH, (b) mutations of the specific TH transporter, monocarboxylate transporter 8 (MCT8), and (c) mutations in selenocysteine insertion sequence binding protein 2 (SECISBP2) which reduces the synthesis of selenoproteins, including the TH deiodinases.[16] Kale BK et al.[17] previously demonstrated that a Turkish family with RTH whose proband a 19-year-old male, presented with diffuse goiter, nervousness, and palpitation. Gene sequencing revealed a mutation in one allele of the TRβ gene in the proband, his two brothers, and father. It involved the substitution of the normal cytosine 1642 with a thymidine, resulting in the replacement of the normal proline 453 with a serine (P453S) in the T3-binding domain of the TRβ. Unfortunately, we could not evaluate to genetic mutations in this family because of technical failure.

In conclusion, routine investigation by sensitive TSH may provide to detect a greater number of patients in outpatient's clinics. It is important to remember that the patients with RTH may display only minimal elevation of serum TSH despite high thyroid hormones levels.

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