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Case Report / *Olgu Sunumu*

A case of thyroid hormone resistance

Tiroid hormon direnci olgusu

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ABSTRACT

Resistance to thyroid hormone is a rare syndrome that generally shows autosomal dominant inheritance and characterized by a reduced responsiveness of target tissues to thyroid hormone action. Diagnosis is based on persistent elevations of serum free T_4 and often T_3 levels in the absence of serum thyrotropin suppression and confirmation in most cases is by way of genetic testing. Patients with thyroid hormone resistance usually become euthyroid, but in rare cases, symptoms and findings of thyrotoxicosis or hypothyroidism may appear. Herein, we report a 33-year-old female case with late diagnosis.

Keywords: Autosomal dominant; resistance to thyroid hormone; thyrotoxicosis.

ÖZ

Tiroid hormon direnci sendromu genellikle otozomal baskın kalıtımsal özellik ile hedef dokuların tiroid hormon etkisine azalmış duyarlılık gösterdiği nadir bir sendromdur. Tanı, serum tirotropin baskılanması yokluğunda T_4 ve sıklıkla T_3 düzeyinin kalıcı olarak yükselmesine dayanmaktadır ve bu durum çoğu olguda genetik test yoluyla teyit edilmektedir. Tiroid hormon direnci olan hastalar genellikle ötiroid olurlar, fakat nadir olgularda tirotoksikoz veya hipotiroidizm belirti ve bulguları seyredebilir. Bu yazıda, geç tanı konulan 33 yaşında bir kadın olgu sunuldu.

Anahtar sözcükler: Otozomal dominant; tiroid hormon direnci; tirotoksikoz.

Resistance to thyroid hormone (RTH) is an inherited disease characterized by a reduced responsiveness of target tissues to thyroid hormone action. Since the first description of RTH in 1967, more than 700 individual with RTH belonging to about 250 unrelated families have been identified up to day.[1] Resistance to thyroid hormone is characterized by variable tissue hyposensitivity to 3,5,3'-L-triiodothyronine (T_3), with a persistent elevation of circulating free T_3 (fT_3) and free T_4 (fT_4) levels, along with non-suppressed serum thyrotropin (TSH).[1,2] Resistance to thyroid hormone is associated with mutations in the thyroid hormone receptor beta (THRs) gene which is a nuclear hormone receptor for T_3. Mutations in THRs are associated with thyroid hormone resistance. The mode of inheritance can be autosomal dominant or recessive. The majority of patients are heterozygous for the mutant THRs allele, consistent with the autosomal dominant pattern of inheritance.[3] We present a patient with an interesting case of RTH.

CASE REPORT

A 33-year-old female was referred for hyperthyroidism from another hospital. There was no known history of disease and she had used propitiyourasil several times before we met her There was an operation on thyroid gland at her two children in family history. But we learned that there was not any toxic adenoma on their thyroid glands. A written informed consent was obtained from the patient.

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The vital signs were blood pressure 100/60 mmHg, pulse 70/minute, temperature 36.0 °C. There were not any positive findings in the examinations of her other body systems.

Free T_3 and fT_4 levels were high, but TSH level was not suppressed and, it was at an inappropriately normal level. Free T_3 was found 7.34 pg/mL (normal range 2.0-4.4). Free T_4 was found 1.85 ng/mL (normal range 0.93-1.71). Serum thyrotropin was found 3.80 mIU/mL (normal range 0.27-4.20). Thyroid peroxidase (TPO) antibody was 10< IU/mL (normal range 0-35), antithyroglobulin was <20 IU/mL (normal range 0-40). Other biochemical tests and common blood counts were in the normal range. During the thyroid ultrasound, her gland was normal. The anterior pituitary hormones such as follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, growth hormone and cortisol levels were within the normal range. Alpha subunit of TSH level was in the normal limit. No pituitary TSH secreting adenoma (TSHoma) was determined in the pituitary magnetic resonance imaging. As a result, we considered thyroid hormone resistance and we performed a thyrotropin releasing hormone (TRH) stimulation test.

After intravenous TRH injection bolus (400 ug), serum TSH concentration increased from 1.56 U/mL to a peak of 10.3 U/mL at 30 min. During oral administration of supraphysiologic doses of T_3 (50, 100, 200 ug, were each given for three days), TSH concentrations were not suppressed. Consequently, we performed a gene mutation for diagnosis of TRH. Gene mutation reported that determined rs1667765, rs826381 and CM942145 variations on intron 8-9 and exon 10 areas in THRs gene. CM942145 variation located where exon 10 area on THRB gene.

DISCUSSION

Resistance to thyroid hormone, a syndrome which reduces end-organ responsiveness to thyroid hormone (TH), was identified in 1967.[1] With the recognition of TH receptor (TR) beta gene mutations,[4,5] the term RTH became synonymous with defects of the TR.[1]

Thyroid hormone resistance is a rare disorder and usually inherited in a dominant manner with highly variable clinical features. Thyroid hormone receptor beta is caused by mutations in the thyroid hormone receptor gene that lead to decreased hormone binding affinity and is characterized by elevated serum levels of fT_4 or fT_3, with normal or slightly increased serum TSH concentrations that respond to thyrotropin releasing hormone stimulation.[6] The elevated levels of these thyroid hormones fail to downregulate the hypothalamic-pituitary-thyroid axis as they would in an individual without RTH.

The incidence of RTH is one in 40,000[7] and it occurs with equal frequency in both sexes. More than 2,000 patients with THR have been reported, and in 85-90% of cases, a point mutation or small deletions in the THRB, coding for TR-β, are found.[3] Familial occurrence of RTH has been documented in approximately 75% of cases.[8] Inheritance is usually autosomal dominant and transmission was clearly recessive in only one family.[8,9] The clinical presentation of this syndrome is variable. Some individuals tend to be normal and the syndrome is detected only on routine investigations, whereas others may display features such as goiter, hyper- and hypothyroidism, delayed bone maturation, short stature and attention deficit hyperactive disorder.[10] Goiter is the most common finding, reported in 66% to 95% of patients.[11]

Resistance to thyroid hormone is classified into two phenotypes: GRTH and PRTH. Patients with RTH who appear normal or hypothyroid are considered to have GRTH, and those with thyrotoxic clinical presentation are considered to have PRTH.[6] This classification was based upon clinical findings alone and has no consistent genetic basis. A molecular mechanism to explain these two clinical phenotypes has proven elusive, and many authors have concluded that they are part of a spectrum of the same disorder.[11,12] Accordingly, we would classify our patient as having PRTH, because of the presentations of her hypermetabolic symptoms. One of the most important reasons for recognizing RTH is that its management is different from other types of thyroid dysfunction. Also, it is important to distinguish GRTH from PRTH using clinical criteria as the management of

these two types differ. Patients with PRTH should not be treated with anti-thyroid drugs, as any reduction of the thyroid hormone will aggravate the symptoms, reduce growth and increase goiter size. Patients with this type, similar to our patient, are usually the most difficult to treatment. Patients with GRTH can benefit from thyroxin administration, since it reduces TSH level and the goiter.[13]

The diagnosis of RTH is confirmed if supra-physiologic doses of T_4 or T_3 are required to reduce the TSH secretion or induce the appropriate responses in peripheral tissues, such as an increase in serum sex-hormone binding globulin and reduction in cholesterol concentrations.

To avoid missing the diagnosis and inappropriate treatments, RTH should be considered in all hyperthyroxinemic patients who are clinically euthyroid. We considered thyroid hormone resistance in this patient. So, we performed a gene mutation study. In the patient, CM942145 variation determined on the exon 10 area on the THRB gene. c.1378G>A nucleotide changes reported in literature that caused missense amino acid change (missense mutation, Glu460Lys) on mRNA and associated with thyroid hormone resistance.[14]

In conclusion, RTH is a rare disorder, usually inherited as an autosomal dominant trait. Substantial proportion of discordant results with clinical findings or atypical results possible to come across in the thyroid function tests. Reduced tissue responsiveness to thyroid hormones is the determinating factor for clinical presentation. The assessment of thyroid function tests for to the diagnose hyperthyroidism (thyrotoxicosis) or hypothyroidism does not constitute a nuisance when the clinical suspicion is strong.

Declaration of conflicting interests

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