The Syndrome of Resistance to Thyroid Hormone: Disappearance of a Pituitary Adenoma Following Cessation of Antithyroid Drug Treatment: Case Report

Tiroid Hormonuna Karşı Olan Direnç Sendromu: Antitiroid Tedavinin Kesilmesi ile Kaybolan Hipofiz Adenomu

Melek Eda ERTÖRER, MD,[a]
Okan BAKINER, MD,[a]
Emre BOZKIRLI, MD,[a]
Neslihan BAŞÇIL TÜTÜNCÜ, MD,[a]
Nilgün GÜVENER DEMİRAĞ, MD[a]

[a]Division of Endocrinology and Metabolism, Baskent University Faculty of Medicine, ANKARA

Geliş Tarihi/*Received:* 24.12.2007
Kabul Tarihi/*Accepted:* 05.03.2008

Yazışma Adresi/*Correspondence:*
Melek Eda ERTORER, MD
Baskent University
Faculty of Medicine,
Division of Endocrinology and Metabolism, ANKARA
e_ertorer@yahoo.com

ABSTRACT High serum triiodothyronine (T3) and thyroxine (T4) with non-suppressed thyroid stimulating hormone (TSH), in the absence of accompanying illness, drugs or alterations in thyroid hormone transport serum proteins, are sine qua non requirement for diagnosis of the syndrome of resistance to thyroid hormone (RTH). Reduced tissue responsiveness to thyroid hormones is the determinating factor for clinical presentation. Most cases are asymptomatic. Some may exhibit symptoms of thyroid hormone deprivation, others may show signs of hormone excess. Treatment with antithyroid drugs (ATD) or thyroid gland ablation increase TSH secretion and may result in thyrotroph hyperplasia. Development of true pituitary tumors, even after long periods of thyrotroph overactivity, is extremely rare. Herein, we report a case with generalized RTH exhibiting signs of thyrotoxicosis who had been taking an ATD for 2 years. On admission he was detected to have a pituitary adenoma which was found to disappear after cessation of the medicine.

Key Words: Thyroid gland, thyroid hormones, thyrotoxicosis, nodular goiter

ÖZET Tiroid hormonuna karşı olan direnç sendromu (RTH), eşlik eden hastalık, ilaç kullanımı ya da tiroid hormon taşıyıcı protein sisteminde bir bozukluk olmaksızın, yüksek serum triiodotironin (T3) ve tiroksin (T4) düzeyleri, ve baskılanmamış tiroid uyarıcı hormon düzeyleri ile seyreden bir tablodur. Altta yatan fizyopatolojik sorun, tiroid hormon reseptörü (TR) beta geninde bulunan bir mutasyondur. Tiroid hormonuna karşı azalmış doku yanıtının düzeyi, klinik tablonun belirleyicisidir. Çoğu olgu semptomsuzdur. Bazıları tiroid hormon eksikliği, bazıları fazlalığı, bazıları ise her iki durumun bulgularını birlikte sergileyebilir. Hipofiz düzeyinde ağır direnci olan ve belirgin tirotoksikoz bulguları olan kişilere beta adrenerjik blokaj yapmak gerekebilir. Antitiroid ilaçlar veya tiroid bezinin yok edilmesi, hipofizde tirotrof hiperplazisine neden olabilir. Uzun dönem tirotrof aktivite fazlalığı ile gerçek hipofizer tümör oluşumu literatürde cok nadiren bildirilmiştir. Bu yazıda, tirotoksikoz bulguları sergileyen bir genel RTH olgusu sunulmaktadır. Kabulünde, 2 yıldır aralıksız olarak antitiroid ilaç kullanan olguda hipofizer adenom saptanmış ve ilacın kesilmesi ile adenomun kaybolduğu izlenmiştir.

Anahtar Kelimeler: Tiroid bezi, tiroid hormonu, tirotoksikoz, noduler guatr

Turkiye Klinikleri J Endocrin 2008, 3:77-80

The syndrome of resistance to thyroid hormone (RTH) is a unique clinical entity characterized by elevated levels of serum triiodothyronine (T_3) and thyroxine (T_4) with non-suppressed thyroid stimulating hormone (TSH) levels, in the absence of accompanying illness, drugs or alterations in serum transport proteins.[1] In spite of the fact that it is reported to affect 1 case per 50.000 live births, in literature, only about 1000 cases have been reported that appear to fit this condition.[2] The underlying pathophysiology is a

mutation in thyroid hormone receptor (TR) β gene.[3] The mutation results in either reduced affinity for T_3 or impaired interaction with any of the co-factors involved in the mediation of thyroid hormone action.[3-5] Familial occurrence of RTH has been documented in about 75% of the cases and true incidence of sporadic cases is 21.3%. Current estimate of the frequency of de novo mutations is 22.5%.[6]

Reduced tissue responsiveness to thyroid hormones is the determinating factor for its clinical presentation. Most of the cases are completely asymptomatic. Some may exhibit symptoms of thyroid hormone deprivation, others may show signs of hormone excess. Not uncommonly, some cases may have symptoms of both hormonal deprivation and excess. Cases with RTH that appear to be eumetabolic are usually classified as generalized resistance to thyroid hormone (GRTH). They maintain euthyroidism at the expense of high circulating hormone levels. Some others may exhibit severe signs of hypermetabolism and following analysis, they may be diagnosed as selective pituitary resistance to thyroid hormone (PRTH).[6]

Patients with more thyrotroph resistance and symptoms of thyrotoxicosis may require an adrenergic β blocking agent, preferably atenolol. Treatment with antithyroid drugs (ATD) or thyroid gland increase TSH secretion and may result in thyrotroph hyperplasia. Development of true pituitary tumors, even after long periods of thyrotroph overactivity, is extremely rare.[7]

Herein, we report a case with GRTH who exhibited signs of thyrotoxicosis. He had been taking an ATD for 2 years. On admission, he was detected to have a pituitary adenoma which was found to disappear after cessation of the medicine. He was offered the choice of thyroidectomy at different centers as the final therapeutic option.

CASE REPORT

A 25 year-old man was admitted to our clinic with complaints of palpitation, sweating and tremor in his hands. He was confused about the recommendations of his previous physicians in favor of having a thyroidectomy operation. He had the history of a mass at his neck which he had become aware for 2 years and had been regularly taking an ATD and a β-blocker; propranolol since then. He was a healthy looking, normal-weight (height: 1.64 m, weight: 68 kg) young man with no obvious physical or mental disorder. Nodular goiter and fine tremor in his hands were the only pathological findings at physical examination.

His earliest serum thyroid hormones; both free (fT_3, fT_4) and bound (TT_3, TT_4) fractions, were above the upper reference limits despite normal TSH levels. Such unique laboratory findings persisted all through his medical reports performed at different centers (Table 1). On admission, his thyroid tests, while he was not taking the ATD for 10 days, were: TSH: 4.32 μIU/ml (0.30-4.94), TT_3: 2.7 ng/ml (0.60-1.95), TT_4: 10.97 μg/dl (5.0-11.50), fT_3: 13.57 pmol/L (2.22-5.34), fT_4: 24.48 pmol/L (9.0-25.0). His thyroxine binding globulin level was within normal limits. A TRH (TSH-releasing hormone) test was performed with 200 μg intravenous TRH and his pituitary was detected to respond (Table 2). Alpha subunit of pituitary glucoprotein level was 0.45 mUI/mL (0.05-0.80) with simultaneous TSH; 4.32 μIU/ml. The α-subunit/ TSH ratio was lower than 1.[8] Magnetic resonance imaging (MRI) of his pituitary revealed an adenoma with a size of 4x3 mm at the left side (Figure 1).

He had hypoactive multinodular goiter with negative thyroidal autoantibodies. His cardiac systolic and diastolic performance characteristics were not exhibiting a hyper-dynamic heart and his thyroidal blood flow was within normal limits.

He was hospitalized and an L-T_3 suppression test was performed. Through the test, he was placed on a diet constant in calories and protein. At baseline and at every third day, corresponding to the last 24 h of each incremental L-T_3 dose administered, a 10 ml blood sample was obtained. Tissues were found to respond, as shown in Table 3.

Levels of serum T_3 and/or T_4 with inappropriate TSH levels, accompanying pituitary unresponsiveness to TRH test and an α-subunit/ TSH ratio lower than 1 made the diagnosis of RTH most likely. Depending on the results of the L-T_3 suppression

TABLE 1: A list of the previous thyroid function tests of the patient performed at different centers.

DATE	TT3	TT4	fT3	fT4	TSH
Nov 11th,2003	3.12 nmol/L (1.30-3.10)	202.2 nmol/L (66-181)	10.75 pmol/L (2.80-7.10)	52.97 pmol/L (12-22)	1.27 mU/ml (0.270-4.20)
Feb 19th, 2004			7.4 pg/ml (1.8-4.6)	3.1 ng/dl (0.9-1.7)	
Jul 19th, 2004	2.42 ng/ml (0.60-1.95)	13.43 µg/dl (5.0-12.7)	11.32 pmol/L (3.0-9.0)	33.76 pmol/L (9.0-25.0)	4.01 mU/ml (0.50-4.0)
Oct 4th, 2004	2.15 ng/ml (0.60-1.95)	11.38 µg/dl (5.0-12.7)	8.58 pmol/L (3.0-9.0)	28.07 pmol/L (9.0-25.0)	13.45 mU/ml (0.50-4.0)
Jan 7th, 2005	2.0 ng/ml (0.60-1.95)	9.0 µg/dl (5.0-12.7)	9.28 pmol/L (3.0-9.0)	22.72 pmol/L (9.0-25.0)	24.78 mU/ml (0.50-4.0)
Feb 14th, 2005	2.03 ng/ml (0.60-1.95)	11.49 µg/dl (5.0-12.7)	10.02 pmol/L (3.0-9.0)	30.09 pmol/L (9.0-25.0)	26.67 mU/ml (0.50-4.0)
Mar 15th, 2005	2.34 ng/ml (0.60-1.95)	11.07 µg/dl (5.0-12.7)			20.14 mU/ml (0.50-4.0)

*Values written in bold are the inappropriately high hormone levels.

test, he was diagnosed as GRTH. Considering the inheritance pattern of the syndrome, his first degree relatives were examined and no abnormality was detected. He was fully informed about the nature and the course of the syndrome. The possible risks of a thyroid operation and radioiodine therapy were clearly told. He was prescribed a β-blocker and a blood sample was obtained for genetic analysis.

On the eighth month of cessation of the ATD, the pituitary adenoma was found to disappear at MRI (Figure 2).

A written inform consent was obtained from the patient.

DISCUSSION

Although it has been far too long since the first description of syndrome of RTH, it is often unrecognized by the physicians, but endocrinologists. As it happened to our patient, many cases are offered inappropriate treatment options. No treatment is available to fully correct the defect causing RTH. Ablation of the thyroid gland either with surgery or radioiodine or prescribing long term ATD may result in thyrotropic hyperplasia of the pituitary.[7,9] The principle rule of treatment is primum non nocere. Following the correct diagnosis, patients with predominant symptoms of hypothyroidism are advised being treated with adequate doses of thyroid hormone, while those with thyrotoxic findings can be given β-blockers.[10]

The absence of overlapping between the clinical presentation and laboratory findings is educative in our case. He clinically seemed to have PRTH,

TABLE 2: The results of TRH stimulation test of the patient.

Intravenous TRH (200µg)	Baseline	30. minute	60. minute
TSH (µIU/ml)	1.73	14.05	10.7

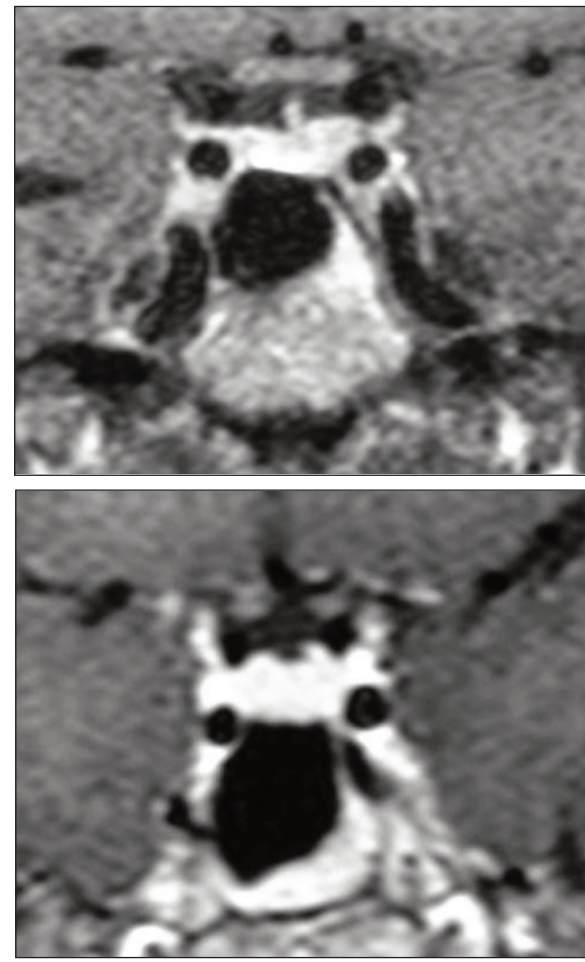

FIGURE 1, 2: Magnetic resonance imaging findings of the case on admission and at the eighth month of cessation of antithyroid drug treatment.

TABLE 3: The results of laboratory analyses performed during L-T3 supression test.

L-T3 administration (oral)	Basal (before the Test)	2x25µg (for 2 days) (At the 3rd day's morning)	2x50µg (for the following 2 days)(At the 5th day's morning)
CPK IU/L (22.0-200.0)	69	54	49
T-chol mg/dl (125-200)	176	167	147
LDL-chol mg/dl (60.0-130)	116	116	102
Tg mg/dl (50-175)	139	105	103
Ferritin ng/ml (15-200)	59.79	105.26	90.12
TSH µuIU/ml (0.30-4.94)	0.97	0.43	0.17
SHBG nmol/L (13.0-71.0)	14.4	14.30	15.8

Abbrv: CPK: Creatinine phoshokinase, T-chol: Total cholesterol, HDL-chol: High density lipoprotein, Tg: Thyroglobuline, SHBG: Sex hormone binding globulin

however, the results of L-T_3 suppression test revealed resistance both at the pituitary and peripheral tissues. Following incremental doses of LT-$_3$, supression in creatinine phosphokinase, cholesterol, triglyceride and thyroglobulin levels, increase in ferritin and sex hormone binding globulin (SHBG) levels underlined the presence of peripheral resistance. Echocardiographic findings that were not presenting a hyper-dynamic heart and stable pulse rates following challenge were also supporting this kind of resistance. Accompanying decline in TSH measurements with increasing L-T_3 doses pointed to the contributing pituitary resistance which enabled us to make the diagnosis of GRTH.

This case can be a good example for understanding the variability of clinical manifestations among RTH cases that may be attributed to different levels of hormonal resistance at various tissue sites. Moreover, we believe that disappearance of the pituitary adenoma following the cessation of ATD makes this case worth reporting.

In conclusion, RTH may present in a wide array of symptoms and correct diagnosis is crucial. The principle rule of treatment is primum non nocere. Although rarely reported, it should be kept in mind that antithyroid drugs or thyroid ablative therapies may result in thyrotroph hyperplasia or even formation of thyrotroph adenoma.

REFERENCES

1. Refetoff S, Weiss RE. Resistance to thyroid hormone. In: Thakker TV, ed. Molecular Genetics of Endocrine Disorders. London: Chapman & Hill Press; 1997. p.85-122.
2. Lafranchi SH, Snyder DB, Sesser DE, Skeels MR, Singh N, Brent GA, et al. Follow-up of newborns with elevated screening T4 concentrations. J Pediatr 2003;143:296-301.
3. Hayashi Y, Weiss RE, Sarne DH, Yen PM, Sunthornthepvarakul T, Marcocci C, et al. Do clinical manifestations of resistance to thyroid hormone correlate with the functional alteration of the corresponding mutant thyroid hormone-beta receptors? J Clin Endocrinol Metab 1995;80:3246-56.
4. Yoh SM, Chatterjee VK, Privalsky ML. Thyroid hormone resistance syndrome manifests as an aberrant interaction between mutant T3 receptors and transcriptional corepressors. Mol Endocrinol 1997;11:470-80.
5. Liu Y, Takeshita A, Misiti S, Chin WW, Yen PM. Lack of coactivator interaction can be a mechanism for dominant negative activity by mutant thyroid hormone receptors. Endocrinology 1998;139:4197-204.
6. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev 1993;14:348-99.
7. Safer JD, Colan SD, Fraser LM, Wondisford FE. A pituitary tumor in a patient with thyroid hormone resistance: a diagnostic dilemma. Thyroid 2001;11:281-91.
8. Studer H. A fresh look at an old thyroid disease: euthyroid and hyperthyroid nodular goiter. J Endocrinol Invest 1982;5:57-68.
9. Gurnell M, Rajanayagam O, Barbar I, Jones MK, Chatterjee VK. Reversible pituitary enlargement in the syndrome of resistance to thyroid hormone. Thyroid 1998;8:679-82.
10. Weiss RE, Refetoff S. Treatment of resistance to thyroid hormone--primum non nocere. J Clin Endocrinol Metab 1999;84:401-4.