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Circulating Antibodies to T4 Causing Discordant Tests of Thyroid Function: A Case Report

Tiroksine Karşı Gelişen Antikorlar Tiroid Fonksiyon Testlerini Etkileyebilir: Bir Olgu

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Abstract

The presence of elevated free thyroxine (fT4) hormone level with non-suppressed thyroid-stimulating hormone (TSH) level is called as "inappropriate secretion of TSH". TSH-secreting adenoma, resistance to thyroid hormone (RTH), iodothyronine deiodinase defect or false elevation of measured free serum T4 as in familial dysalbuminemic hyperthyroxinemia (FDH) and the presence of autoantibodies to T4 may be the cause of this entity. We report a case that presented with high serum fT4 and TSH levels associated with autoantibodies to T4. *Turk Jem 2014; 1: 19-22*
Key words: Anti-T4, anti-T3, discordant thyroid function tests

Özet

Yükselmiş serbest tiroksin (sT4) hormon düzeyiyle birlikte, baskılanmamış tiroid stimule edici hormon (TSH) düzeyi bulunması durumu "uygunsuz TSH sendromu" olarak isimlendirilmektedir. TSH-salgılayan adenom, tiroid hormon direnci, iyodotironin deiyodinaz defekti veya familyal disalbüminemik hipertiroksinemi ve T4 hormonuna karşı oluşan otoantikorlar, ölçülen sT4 düzeyinin yüksek olmasına sebep olabilmektedir. T4 antikorlarına bağlı olarak yanlış ölçülmüş olan sT4 ve TSH değerleri olan bir olguyu sunmaktayız. *Turk Jem 2014; 1: 19-22*
Anahtar kelimeler: Anti-T4, anti-T3, uyumsuz tiroid fonksiyon testleri

Introduction

The presence of elevated free thyroxine (fT4) hormone level with non-suppressed thyroid-stimulating hormone (TSH) level is compatible with TSH-secreting adenoma or resistance to thyroid hormone (RTH) (1,2,3,4). In addition, this may be the result of iodothyronine deiodinase defect or false elevation of measured free serum T4 as in familial dysalbuminemic hyperthyroxinemia (FDH) and the presence of autoantibodies to T4 (5,6,7).

We report a case that presented with high serum fT4 and TSH levels associated with autoantibodies to T4.

Case Report

A 23-year-old, female was admitted to the Endocrinology Department in Turkey for dose adjustment of levothyroxine (L-T4) replacement for hypothyroidism since 9 years of age. Pretreatment thyroid function tests were not available. At the time of admission, she was using 125 µg L-T4 daily. She denied symptoms for hypothyroidism and hyperthyroidism. Her physical examination was unremarkable except for grade 1b goiter.

On admission, serum free fT4 was elevated with normal TSH, Thyroperoxidase (TPO) antibodies (TPOab) were also found to be elevated (Table1). Thyroid ultrasonography showed an enlarged gland with heterogeneous parenchyma, without nodules. L-T4 dosage was reduced to 100 µg/day. Four months later, although TSH levels have increased, fT4 concentration remained high. Therefore, L-T4 treatment was stopped and the patient was followed with thyroid function tests. TSH levels increased further, but fT4 level was still found to be high (Table1). The patient became clinically hypothyroid and thyroid gland progressively enlarged up to grade III in size.

Pituitary MRI revealed a 4 mm microadenoma in the left lateral portion of the gland with lesser contrast enhancement than in the normal pituitary gland. The possibility of RTH and a TSH-secreting adenoma were considered, as these conditions could coexist with autoimmune thyroid disease (8). Therefore, a TSH releasing hormone (TRH) and a T3 suppression tests were performed. An exaggerated TSH response (basal and stimulated TSH level were 26 and 137 µIU/ml, respectively) was obtained after intravenous injection of 200 µg TRH. In addition, TSH levels were readily suppressed following the

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administration of L-T3. However, fT4 levels did not decline (Table 2). TSH α-subunit/TSH molar ratio was lower than 1.

Accordingly, the patient was evaluated for possible antibodies to T4 leading to falsely increased fT4 levels. Antibodies to T4, as well as T3, were identified (Figure 1). The presence of antibodies to T4 was thought to be the cause for increased fT4 levels.

After we have realized the controversy about her thyroid tests, the patient was commenced on L-T4 treatment. At the routine follow-up of the patient, the dose was adjusted according to serum TSH levels. Free thyroid hormone levels were not used anymore. The patient was given appointments to be reviewed every 3, or 6 months for a year.

After obtaining an informed consent, family members were also investigated in terms of their thyroid function tests (Figure 1). Her mother had a history of thyroidectomy and was on L-T4 replacement showing slight overtreatment. Her father and sister had normal thyroid function tests and negative antibodies.

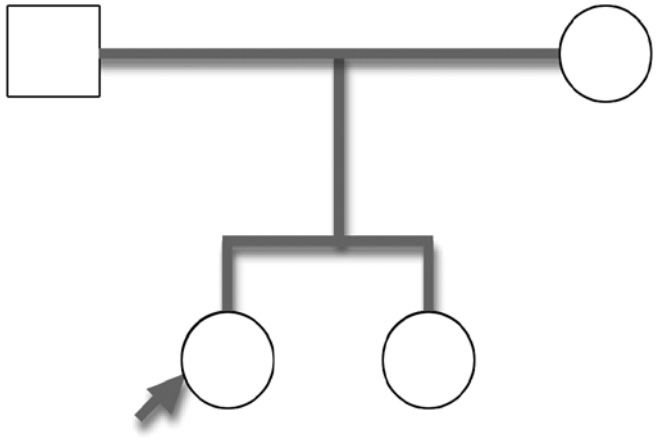

Figure 1. Pedigree of the patient
Pedigrees showing the results of thyroid function tests and presence of iodothyronine antibodies. Results are aligned with each symbol. Ages represent those at the time of blood sampling. For all other abbreviations see methods.
*cannot be measured because of the presence of antibodies to TG
Abnormal values are in bold numbers

					Normal range
age	50	23	19	51	
TT4 (mg/dl)	7.6	**11.2**	10.2	**13.1**	5-11.6
TT3 (ng/dl)	144	**<19**	185	108	80-190
TrT3 (ng/dl)	22.2	**<25**	28.3	**39.7**	15-34
FT4 (ng/dl)	7.8	6	11.8	13.4	6-10.5
TSH (mU/ml)	1	**457**	1.7	**0.08**	0.4-3.6
Tg	17	*	15	2	1-38
TPO ab	<1:10	**1:1000000**	<1:10	**1:80**	<1:10
TG ab	<1:10	**1:8000000**	<1:10	<1:10	<1:10
T4 ab (%)	3.8	**49.6**	2.4	3.2	<4
T3 ab (%)	2.4	**4.5**	1.8	2.8	<3

In Turkey, fT3, fT4 and TSH were measured by chemiluminescence immunometric assays using Elecsys and cobas immunoassay analyzers (Roche Diagnostics GmbH, Mannheim, Germany). Thyroid peroxidase (TPO) antibodies (Ab) were measured by TPO-Ab One Step RIA CT (Biosource, Europe, SA).

In Chicago, total T4, (TT4), total T3 (TT3) and TSH were measured also by chemiluminescence immunometric assays using the Elecsys Automated System (Hitachi Boehringer Mannheim, Germany); 3,3',5'-L-triiodothyronine (reverse T3 (rT3)) was measured by radioimmunoassay (Adaltis Italia S.p.A, Italy) and serum thyroglobulin (TG) by an in-house double-antibody radioimmunoassay with a sensitivity of 1 ng/ml. The serum free T4 index (FT4I) was calculated as the product of the serum TT4 concentration and the T4-resin uptake ratio. TG and TPO antibodies were measured by agglutination (Fujrebio, Tokyo, Japan).

Discussion

Conditions with discordant thyroid function tests characterized by raised fT4 and normal or elevated TSH levels are listed in (Table 3) (1,2,3,7). The patient was referred because of such discordance.

Table 1. Thyroid function tests

	f T3 (2.2-4.7 pg/ml)	f T4 (8-20 pg/ml)	TSH (0.2-3.2 µIU/ml)	Anti-TPO (0-60 U/ml)
L-T4 125 µg/day	4.58	**21.9**	1.85	**5509**
L-T4 100 µg/day	3.35	**22.6**	**9.58**	
2 months after discontinuation of LT4	2.63	**25.91**	**21.67**	**10016**
5 months after discontinuation of LT4	**1.56**	**28.9**	**100.73**	

Table 2. T3 suppression test

	f T3 (2.2-4.7 pg/ml)	f T4 (8-20 pg/ml)	TSH (0.2-3.2 µIU/ml)
Basal	3.28	24.3	31.8
3rd day	3.19	20.8	0.4
7th day	10.22	28	0.09

Table 3. Diseases associated with discordant thyroid test results

Resistance to thyroid hormone (RTH)
Abnormalities of thyroid hormone transport proteins, particularly mutant albumin causing FDH
TSH producing pituitary adenoma
Cystinosis and autosomal dominant petrosis
Thyroid hormone replacement after thyroid gland ablation
Thyroid hormone metabolism defects due to SBP2 gebe mutations.
Circulating antibodies to iodothyronines

Table 4. Differential diagnostic features of conditions associated with discordant serum fT4 and TSH results

	TSH-secreting adenoma	**RTH**	**FDH**	**SBP2 defect**	Iodotyronine antibodies
Clinical findings	Thyrotoxic	Mixed hypo and hyperthyroidism	Eutyroid	Euthyroid	Euthyroid
TSH response to TRH	Non-responsive	Exagerated	Normal	Normal	Responsive*
TSH suppression with L-T3	Non-suppresive	Reduced suppression	Normal suppression	Normal suppression	Normal suppression
α-subunit/TSH molar ratio	>1	<1			<1
Pituitary adenoma	Present	Usually absent **	Usually absent**	Usually absent**	Usually absent**
Goiter	Yes	Yes	No	No	Often
Family history	No	Usually yes	Yes	Often no recessive	No
Antibodies to T4	No	No	No	No	Present
Associated autoimmunity	Usually not	Variable	Usually not	Usually not	Yes
TRβ gene mutation	No	Mostly Yes	No	No	No

* Level of response proportional to baseline TSH

** Rule out incidentaloma when microadenoma is present

Resistance to thyroid hormone is a dominantly inherited disease and primarily caused by mutations to the ligand-binding domain of the thyroid hormone receptor-β (TRβ) gene. This syndrome is characterized by reduced tissue responsiveness to thyroid hormone and its clinical presentation may vary. The common features of RTH include raised fT4 and often fT3 levels, and normal or slightly raised serum TSH concentrations, as in our case. Goiter is commonly seen (1,3,4). Members of the index patient family may show similar features. Definitive diagnosis is confirmed by genetic analysis, but TRH stimulation and T3 suppression tests are helpful in the diagnosis. TRH stimulation test was performed and samples for TSH and free thyroid hormones were obtained. Although normal thyrotrophs do not respond to TRH following administration of supraphysiological L-T3 doses, a persistent TSH response to TRH is seen (1,3). In the present case, after L-T3 administration, although TSH levels decreased markedly, fT4 levels remained high. Laboratory evaluation of our patient was not compatible with RTH syndrome.

One of the rare causes of discordant thyroid function tests is TSH-secreting pituitary adenoma. These patients do not respond to TRH stimulation test or suppress their TSH when given L-T3. Most of them have an α-subunit/TSH molar ratio higher than 1 (Table 4) (5). Because of an exaggerated TSH response to TRH, adequate suppression of TSH following administration of L-T3 and lower α-subunit/TSH molar ratio, the microadenoma in the pituitary was considered as an incidentaloma.

A less rare cause of high fT4 with normal TSH, though relatively common in subjects of Hispanic origin, is FDH. Caused by a gain-of-function mutation in the albumin gene (9), it produces a falsely elevated fT4, when measured by the current automated direct methods, but not by equilibrium dialysis (2,9).

More recently, it has been shown that defects in selenoprotein synthesis caused by mutations in the SBP2 gene reduces the conversion of T4 to T3, resulting in high fT4 but low fT3 values with normal or slightly elevated serum TSH concentration (7).

It has been suggested that non-specific binding of heterophile antibodies or rheumatoid factors, and thyroid hormone autoantibodies may interfere with measurement of thyroid hormones. The prevalence of anti-T3 and anti-T4 antibodies among overall population is estimated to be about 10% and in autoimmune thyroid disease about 40%, but the interference with diagnostic immunoassays is seldom (0.05%-0.5%) (6,10,11). There are some cases that are difficult to diagnose because of the existence of thyroid hormone autoantibodies (12). Autoantibodies to thyroid hormones may lead to abnormal levels of free thyroid hormones (fT3 and fT4) by interference with the one-step assay tests (6,12,13). Thyroid hormone antibody interferences are difficult to predict and can occur even with frequently used and well-characterized methods (14,15). This may result in unnecessary investigations which are expensive and time-consuming.

In conclusion, fT4 levels may be falsely raised due to antibodies to T4. The presence of antibodies to T4 should be kept in mind when discordant results of fT4 and TSH occur in the presence of autoimmune thyroid disease.

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