

NOTE

## Hyperthyroid Graves' Disease and Primary Hypothyroidism Caused by TSH Receptor Antibodies in Monozygotic Twins: Case Reports

JUN-ICHI TANI, KATSUMI YOSHIDA\*, HIROSHI FUKAZAWA, YOSHINORI KISO, NORIYO SAYAMA, KOUKI MORI, YOSHIHIKO AIZAWA, HIRONOBU HORI, NAOKI NAKASATO, AND KEISHI ABE

Second Department of Internal Medicine, and \*Department of Clinical and Laboratory Medicine, Tohoku University School of Medicine, Sendai 980-8574, Japan

**Abstract.** A 33-year-old woman with signs and symptoms of hypothyroidism, including increased thyroid stimulating blocking antibody (TSBAb) activity, was referred for treatment by her local physician. Her monozygote twin was treated for hyperthyroid Graves' disease 10 years earlier. This case of hyperthyroidism and hypothyroidism in identical twins suggests the involvement of environmental factors in the pathogenesis of autoimmune thyroid diseases.

**Key words:** Graves' disease, Hypothyroidism, Monozygote twins, TSH-receptor antibody (TRAb), Thyroid stimulating antibody (TSAb), Thyroid stimulating blocking antibody (TSBAb), Human leukocyte antigen (HLA)

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**THERE** exist at least two types of TSH-receptor antibodies (TRAbs) in the sera of patients with autoimmune thyroid diseases [1]. TRAb usually acts as a TSH agonist causing thyrotoxicosis in Graves' disease (thyroid stimulating antibody: TSAb), but TRAb with TSH antagonist activity has been found in the sera of some patients with primary hypothyroidism. Thyroid stimulating blocking antibody (TSBAb) presumably causes thyroid dysfunction and atrophy [2–4]. TSH-binding inhibitory immunoglobulins (TBII) are positive in most patients with Graves' disease and in primary hypothyroidism caused by TSBAb.

Autoimmune thyroid diseases generally occur when there is a failure of the immune system as a result of a combination of genetic and non-genetic

factors [5, 6]. Both Hashimoto's thyroiditis and Graves' disease have hereditary factors [7]. We report a pair of monozygotic twins, one of whom had hyperthyroid Graves' disease with TBII, while the other had primary atrophic hypothyroidism with TSBAb activity.

### Case Reports

#### Case 1

A 33 year-old woman, having felt fatigue for more than 1 year, her family noting snoring and hoarseness, her body weight increasing, and frequently sleepy, consulted a doctor and was diagnosed as having primary hypothyroidism. She was referred to Tohoku University Hospital for treatment in May, 1996. Laboratory findings were T3 0.3 ng/ml, T4 <1.05 µg/dl and TSH 52.6 µU/ml. Except for her monozygote twin (Case 2), no family member had a history of thyroid disease,

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Correspondence to: Dr. Katsumi YOSHIDA, Department of Clinical and Laboratory Medicine, Tohoku University School of Medicine, 1-1 Seiryochō, Sendai 980-8574, Japan

but we have no evidence except that her mother was euthyroid (T3 1.12 ng/ml, T4 7.6 µg/dl and TSH 0.28 µU/ml).

The laboratory tests done at the time of admission showed normal liver and renal parameters, and normal electrolytes except for lactate dehydrogenase (LDH: 604 IU/dl), triglycerides (TG: 197 mg/dl), total-cholesterol (Tcho: 282 mg/dl), and creatine kinase (CK: 765 IU/dl). A 12-lead electrocardiogram tracing showed 1st grade A-V block. The thyroid function test results are shown in Table 1. On physical examination, she had no goiter, her skin was dry, eyelids were edematous, and Achilles tendon reflex was hypoactive.

She was diagnosed as having primary hypothyroidism, and was started on 12.5 µg/day of levothyroxine sodium (LT4). The dose of LT4 was increased 12.5 µg/day every week. At discharge she was treated with 100 µg/day of LT4 (T4 5.9 µg/dl, T3 0.7 ng/ml, TSH 39.5 µU/ml and CK 91 IU/dl). She had previously suffered from polycystic ovarian syndrome (PCOS) and had undergone wedge resection therapy. She had married at the age of 22, and her husband was 6 years older than she, but she had no history of pregnancy.

### Case 2

Patient 2 noticed palpitation, hyperhidrosis, finger tremors and dyspnea in 1982 at the age of 19. She consulted her family doctor and was diagnosed as having hyperthyroidism. Treatment with 20 mg/day of methimazole (MMI) was started. After treatment she became euthyroid. Two years later when MMI treatment was discontinued, hyperthyroidism recurred, and she was referred to our hospital at the age of 23.

The results of the thyroid function tests done at the time of her first visit are shown in Table 1. Other laboratory studies were normal. On physical examination, she had a large and diffuse goiter, finger tremor, no ophthalmopathy, and hyperactive Achilles tendon and patellar tendon reflexes. She was diagnosed as having hyperthyroid Graves' disease, and was again treated with MMI. She became euthyroid and remained euthyroid without TBII activity after discontinuation of therapy.

She previously also had suffered from PCOS. She had married at the age of 21, and her husband

**Table 1.** Thyroid function tests of Case 1 and Case 2 at the time of their first visit to our hospital and on admission. The normal range is given in parentheses.

	Case 1	Case 2	
Age	34	23	
T <sub>3</sub>	0.2 ng/ml	5.1 ng/ml	(0.7–1.8 ng/ml)
free T <sub>3</sub>	0.3 pg/ml		(2.45–4.65 pg/ml)
T <sub>4</sub>	0 µg/dl	22.1 µg/dl	(4.5–12.0 µg/dl)
free T <sub>4</sub>	0.12 ng/dl		(0.7–2.1 ng/dl)
TSH (IRMA)	91 µU/ml		(0.25–3.5 µU/ml)
TSH (RIA)		0.44 µU/ml	(4.5–12.0 µU/ml)
TGHA	1:400	1:400	(1: <100)
MCHA	1:25600	1:102400<	(1: <100)
TBII	85%	57%	(–15~15%)
TSAb	98%		(<140%)
TSBAb	97%		(<40%)
<sup>131</sup> I uptake	0.4%	79%	(10~40%)
BMR		+24%	(–10~+15%)

IRMA, immunoradiometric assay; RIA, radioimmunoassay; TGHA, thyroglobulin hemagglutination test; MCHA, microsome hemagglutination test; TBII, thyrotropin binding inhibitory immunoglobulin; TSAb, thyroid stimulating antibody; TSBAb, thyroid stimulating blocking antibody; BMR, basal metabolic rate.

**Table 2.** Human leukocyte antigens (HLA) of the cases described.

HLA	Case 1	Case 2
A	A24 (9) A 26 (10)	A24 (9) A26 (10)
B	B48	B48
C	CW3	CW3
DR	DR4	DR4
DQ	DQ4	DQ4

Their HLA loci are assuredly identical because they are monozygote twins.

was 7 years older than she. Unlike her monozygote sister, however, she was treated with hormonal agents and twice became pregnant.

Human leukocyte antigen (HLA) typing is presented in Table 2. The analysis of monozygotism was made by comparing blood groups and serum enzymes (ABO, Rh, MNS, P, Fy, Jk, Gc, aZHS, Hp, C6, Pi, Tf, ESD, ACP, PGM, GPT, PGD, Gm, Km, PYNH24, 3'glb, CSF1PO, FESFPS, THO1 and vWF) and the HLA-system of the twins. The results revealed 99.99% probability of identity.

They had lived in the same house until they were 21. They had no previous history of other diseases and had not been taking any drugs. Their tastes for food were similar and they had been eating iodide-rich foods such as seaweed, similarly to other Japanese.

### Discussion

In Case 1, TBII and TSBAb activities were very high and the goiter was not palpable. We can speculate that hypothyroidism in this patient was not due to classical Hashimoto's thyroiditis, but mainly to TSBAb.

The occurrence of hyperthyroidism and hypothyroidism in monozygotic twins has been described [8]. In previous reports, however, testing for TRAb was done in only a few cases. Ilicki *et al.* [9] recently reported a pair of monozygotic twins with TSAb-positive hyperthyroidism in one and TSBAb-positive hypothyroidism in the other. This is the second report of a pair of monozygotic twins in whom TRAb played a pathogenetic role in the development of hyper- and hypothyroidism. The difference between their cases and ours are as follows: In their cases, the mother and grandmother had suffered from Graves' disease, and thyroid diseases occurred simultaneously at the age of 10 years. In our cases, no other family member had a history of thyroid disease, hyperthyroidism occurred in Case 2 more than 10 years before that in Case 1, and the both cases had PCOS. Our cases suggest that not only genetic factors, but such endogenous and environmental factors as sex hormones, stress and infection also play a role in the occurrence of autoimmune thyroid diseases [5, 10]. They both were housewives, married at almost the same age, and had taken iodide similarly. Because we have no information concerning previous stress or infections, we do not have any direct data supporting the role of endogenous and environmental factors in the occurrence of autoimmune thyroid diseases.

TSBAb is detected in some patients with primary hypothyroidism [2, 3] and is considered responsible for their thyroid hypofunction. In most Japanese patients, however, primary hypothyroidism is due to destruction of the thyroid by chronic thyroiditis, and TSBAb is positive in 14% to 34% of patients with primary atrophic hypothyroidism [2, 3].

Both TSAb and TSBAb exist in some sera from patients with autoimmune thyroid diseases. Some patients with Graves' disease who subsequently developed hypothyroidism, and vice versa, have been described [11–14]. Kasagi *et al.* [15] reported a TRAb-positive patient with initially hyperactive thyroid function who became hypoactive, and reverted to hyperactive as the ratio of TSAb to TSBAb changed. The autoimmune mechanisms underlying Graves' disease and hypothyroidism in these twins therefore appear to be identical.

Inoue *et al.* [16, 17] analyzed HLA types in Japanese patients with primary hypothyroidism and reported that patients with positive TSBAb are genetically similar to those with Graves' disease, whereas patients with idiopathic myxedema without TSBAb are genetically similar to those with Hashimoto's thyroiditis. They proposed a new concept of an autoimmune anti-TSH receptor disease among autoimmune thyroid diseases [6, 16]. Cases reported by Ilicki *et al.* [9] and by our laboratory support their hypothesis. These cases help us speculate as to the pathogenesis of autoimmune thyroid diseases.

Associations between some HLA antigens and autoimmune thyroid diseases have consistently been observed [5, 16, 18–24]. For instance, HLAs that are associated with Japanese Graves' patients include HLA-A2, B8, DR3, DR5, DRw8, DPB1\*0501 and DQB1\*0501 [16, 18–20]. Those associated with Hashimoto's disease include A2, DR2, DR3, DQ7, DRB4\*0101, DQA1\*0102 and DQB1\*0602 [16, 21]. In Japanese patients with high TSBAb activity the HLA antigens include B35, B67, Bw60 and Dw 8 [16, 17]. The HLAs in our cases were not characteristic of Japanese patients with autoimmune thyroid diseases. Recently, however, thyroid disease, especially Graves' disease, has been reported to be related to the HLA-DP locus [17, 20]. Because we did not analyze DQ, D and DP HLA types, we cannot tell whether they have a relationship to thyroid diseases.

Both patients suffered from PCOS, the etiology of which remains debatable [25]. Some reports have demonstrated a link between PCOS status and HLA (DRw6 and DR7) [26], but our cases had no HLA locus associated with PCOS. The coexistence of PCOS and hypothyroidism has been reported [25], but the coexistence of PCOS and hyperthyroidism is uncommon. It is reported that PCOS is accompanied by hyperandrogenism [27].

In our cases, we did not measure serum levels of androgen. However, hyperandrogenism probably did not play a role in the pathogenesis of their thyroid diseases, because the frequency of autoimmune thyroid diseases is much lower in men than in women. Furthermore, the genetic relationship between PCOS and autoimmune thyroid diseases is not known. We think that in the present cases PCOS was associated with the

autoimmune thyroid diseases by chance.

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