

# Transient Hypothyroidism in a Case of Untreated Graves' Disease

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**Abstract.** We report the case of a 41-year-old female with untreated Graves' disease who developed transient hypothyroidism. The hypothyroid state was thought to be caused by silent thyroiditis, based on findings of a non-tender thyroid gland, suppressed thyroidal radioactive iodine uptake, normal white blood cell count and normal erythrocyte sedimentation rate, and ultrasonogram results. Silent thyroiditis may play a role in the development of Graves' hyperthyroidism. Results for TSH-binding inhibitor immunoglobulins (TBII), thyroid-stimulating antibodies (TSAb), anti-thyroglobulin antibodies (TgAb) and anti-thyroid peroxidase antibodies (TPOAb) were positive before the development of hypothyroidism. Their levels were decreased during and after the hypothyroid phase. These results suggest that the same or similar mechanism(s) were involved in the production of these different antibodies during the course of her illness.

**Key words:** Silent thyroiditis, Graves' disease, TSH-binding inhibitor immunoglobulins, Thyroid-stimulating antibodies, Anti-thyroid antibodies

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ANTIBODIES to TSH receptor are functionally divided into two groups: stimulating type (thyroid-stimulating antibodies; TSAb) and blocking type (thyroid stimulation-blocking antibodies; TSBAb). TSAb are considered to play an important role in the pathogenesis of Graves' disease [1] and TSBAb are considered to be one of the factors which cause primary hypothyroidism [2]. Recently, TSAb have been detected in some patients with subacute thyroiditis [3] or silent thyroiditis [4] who developed transient hypothyroidism.

In the present paper, we report the case of a patient with untreated Graves' disease who showed transient hypothyroidism and investigate the changes in thyroid-related antibodies including TSH-binding inhibitor immunoglobulins (TBII) and

TSAb during the course of the disease.

## Methods

Serum samples were stored at  $-20^{\circ}\text{C}$  until assayed. Serum levels of free T3 (FT3), free T4 (FT4) and TSH were measured by radioimmunoassay (RIA) or immunoradiometric assay (IRMA) with commercially available kits (Amerlex-M FT3 & FT4 kits, Amersham International, Tokyo and TSH-RIA-BEAD II kit, Dainabott, Tokyo). The normal ranges of FT3, FT4, and TSH were 3.4–7.7 pmol/l, 11–25 pmol/l, and 0.41–4.10 mU/l, respectively. Anti-thyroglobulin (TgAb) and anti-thyroid peroxidase antibodies (TPOAb) were also tested by RIA (TgAb-Cosmic & TPOAb-Cosmic, Cosmic Corporation, Tokyo) (normal range: <0.3 unit/ml for TgAb and <0.2 unit/ml for TPOAb). The 24-h thyroidal uptake of  $^{123}\text{I}$  (RAIU) was determined by a standard procedure (normal range: 10–40%). TBII were mea-

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sured by the inhibition of  $^{125}\text{I}$ -TSH binding to its receptor (TRAb-Cosmic, Cosmic Corporation, Tokyo) (normal range: <15%). TSAb were measured by using cultured rat thyroid cells (FRTL-5) as previously reported [5] (normal range: <150%). When the serum TSH level was higher than 30 mU/l, TSAb activity was assayed after TSH removal by means of anti-TSH antibodies. FT3, FT4 and TSH were assayed at each visit to determine the patient's thyroidal state, and TgAb, TPOAb, TBII and TSAb were measured in one assay run.

### Case Report

A 41-year-old female was referred to our hospital on June 25, 1992. She had been in good health until early June, 1992 when she noticed finger tremor. She consulted a doctor on June 16, 1992. At that time, serum levels of T3, T4, and TSH were 6.0 nmol/l (normal: 1.1–2.9) (390 ng/dl), 232 nmol/l (normal: 64–167) (18.0  $\mu\text{g}$ /dl) and less than 1 mU/l (normal: <10), respectively. She also noticed weight loss (about 10 kg over one year), but she was not aware of neck pain, fever, excessive sweating, or palpitation. Her mother had thyroidal disease (details unknown).

Physical examination revealed that her height

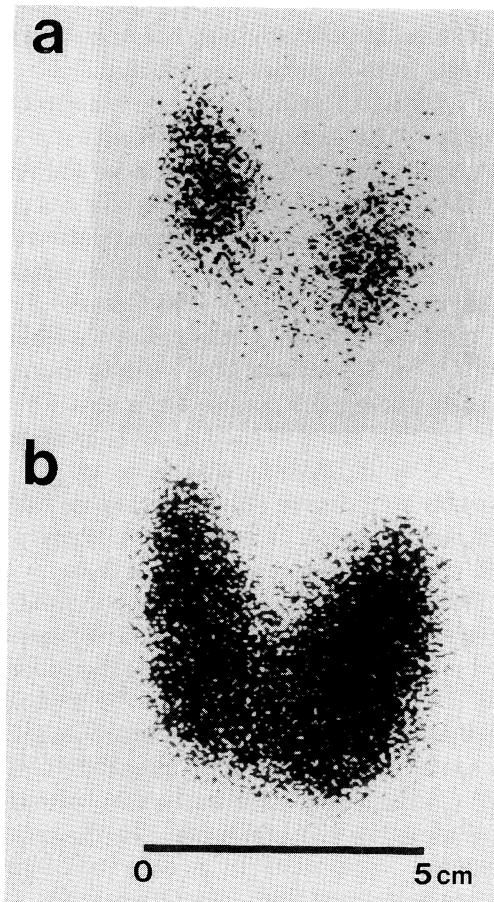
was 154 cm and weight was 53 kg. Blood pressure was 130/66 mmHg and pulse rate was 72 beats per min and regular. The skin was warm and moist. Mild exophthalmos (left eye) was observed, and lid lag (left eye) was present. The thyroid was moderately enlarged and soft. Finger tremor was observed, and reflexes were hyperactive. Other physical findings were non-contributory.

Serum levels of FT3, FT4, and TSH were 9.8 pmol/l, 40 pmol/l, and less than 0.1 mU/l, respectively. Results for TBII, TSAb, TgAb, and TPOAb were positive (see Table 1). The white blood cell (WBC) count was  $5.7 \times 10^9/\text{l}$  and erythrocyte sedimentation rate (ESR) was 14 mm/h. C-reactive protein (CRP) was 0.55 mg/dl (normal <0.30). Serum total cholesterol was 3.3 mmol/l. From the physical findings and the thyroid hormone levels, the patient was tentatively diagnosed as having hyperthyroid Graves' disease, but RAIU measured on July 2 was suppressed to 5.6%. A scintigram with  $^{123}\text{I}$  is shown in Fig. 1a. The transverse width of the thyroid was 5 cm (normal: <4.5). Ultrasonography of the thyroid on the same day showed mixed and reduced echogenicity on both lobes (Fig. 2a). Thickness of the isthmus of the thyroid was 7 mm (normal: <3). No drug was given. In late July, she became clinically euthyroid and no finger tremor was observed. She became hyperthy-

**Table 1.** Changes in thyroid function

	FT3 (pmol/l)	FT4 (pmol/l)	TSH (mU/l)	TBII (%)	TSAb (%)	TgAb (U/ml)	TPOAb (U/ml)	CRP (mg/dl)
92 -06 -25	9.8	40	<0.1	94	493	3.6	>150	0.55
07 -02			RAIU (24 h) 5.6%					
07 -24	3.1	4	<0.1	91	467	3.7	>150	<0.30
08 -21	4.5	3	70.6		567			
09 -18	10.4	13	0.16	90	113	2.1	94.4	<0.30
10 -28	8.1	16	<0.1	85	180	0.9	51.6	<0.30
11 -24	10.1	16	<0.1	78		0.6	26.6	<0.30
12 -25	17.7	50	<0.1	72	160	0.6	12.6	<0.30
93 -02 -19	12.0	36	<0.1					
03 -26	10.0	33	<0.1	58	127	<0.3	5.1	<0.30
03 -28			RAIU (24 h) 45.1%					
04 -23	11.5	32	<0.1					
05 -27	17.5	47	<0.1	51	187	<0.3	6.9	<0.30
normal range	3.4-7.7	11-25	0.41-4.10	<15	<150	<0.3	<0.2	<0.30

Treatment with methimazole was started on May 27, 1993. Goiter size detected by palpation or ultrasonogram (see Fig. 2) did not change significantly during the investigation period.



**Fig. 1.** Thyroid scans with  $^{123}\text{I}$  (a: July 2, 1992, b: March 28, 1993).



**Fig. 2.** Ultrasonograms of a transverse section obtained on July 2, 1992 (a), October 28, 1992 (b), and March 26 (c).

roid again in November. The eye signs did not change during the investigation period.

The changes in thyroid function are shown in Table 1. Assay results for CRP changed from positive to negative within one month after the initial examination at our hospital. The free thyroid hormone level transiently decreased to below normal, and then increased to above the normal range, whereas TSH transiently increased to 70.6 mU/l and then became undetectable again. Ultrasonography on October 28 showed very low echogenicity throughout the entire thyroid (Fig. 2b). The echo level was increased on March 26 (Fig. 2c). The RAIU measured on March 28 was 45.1% and a scintigram disclosed diffuse enlargement of both lobes (Fig. 1b). The patient was diagnosed as having hyperthyroid Graves' disease. Treatment with biso-

prolol fumarate (beta-blocker) was started on April 3, 1993. Additional treatment with methimazole was initiated on May 27 since the thyroid hormone level had remained high. As shown in Table 1, the titers of TBII, TSAb, TgAb and TPOAb were decreased during the investigation period.

### Discussion

The patient manifested the signs and symptoms of thyrotoxicosis followed later by transient hypothyroidism and eventually thyrotoxicosis again. We consider that silent thyroiditis occurred in the patient, since 1) the patient did not complain of neck pain or fever, 2) both the WBC count and ESR were normal, 3) the first RAIU measured was

suppressed to below the normal range, and 4) changes in echo findings were compatible with those reported in patients with silent thyroiditis [6, 7]. It is well known [8–10] that silent thyroiditis occurs before the development of Graves' disease or during the remission of Graves' disease. In the present study, however, silent thyroiditis is thought to have occurred in our patient with untreated Graves' disease, since 1) the T3 (ng/dl)/T4 ( $\mu$ g/dl) ratio based on measurements performed at another clinic was 21.7 [11], 2) Graves' ophthalmopathy was detected at the first visit, 3) the first RAIU measured was not as suppressed (5.6%), as usually seen in silent thyroiditis [4, 7–10, 12–14], probably due to the presence of TSAb, and 4) the euthyroid period after the hypothyroid phase usually observed in silent thyroiditis [4, 8, 12, 13] was not detected. The results of the present study, however, cannot rule out the possibility that the patient had euthyroid Graves' disease before the onset of silent thyroiditis and/or developed Graves' hyperthyroidism during the course of silent thyroiditis. The patient became hypothyroid despite the presence of TSAb. The thyroid gland probably could not respond to TSAb since thyroid tissue was destroyed by the inflammation. Initially, results for CRP were slightly positive in our patient although these results were reported to be negative in patients with silent thyroiditis [12–14]. We cannot explain at the present time why they were positive in our patient.

After the resolution of thyrotoxicosis, patients with silent thyroiditis either develop transient hypothyroidism [4, 8, 12, 13] or become euthyroid without passing through hypothyroidism [4, 8, 13, 14]. Morita *et al.* [4] reported that the incidence of positive results for TBII and TSAb was higher in patients who developed hypothyroidism than in those who did not during the course of their illness. In their report, TBII and/or TSAb activity disappeared or decreased in the majority of the patients during the course of their illness. They suggested that, in view of these results, production of TBII and TSAb is related to thyroid damage which causes transient hypothyroidism during the course of silent thyroiditis. On the other hand, Mitani *et al.* [15] reported the case of a patient with

silent thyroiditis who had been diagnosed as having subclinical hypothyroidism due to Hashimoto's thyroiditis. In their patient, results for TSAb activity were positive 1 year before the onset of silent thyroiditis. TSAb activity increased after the onset of silent thyroiditis and decreased after the resolution of the disease. However, they did not detect TBII or TSAb activity in 17 other patients with silent thyroiditis. They suggested the possibility of silent thyroiditis associated with Graves' disease when TSAb are detected in a patient with silent thyroiditis. In the present study, silent thyroiditis developed during the course of Graves' disease, suggesting that the production and/or degradation of TBII and TSAb is influenced by not only thyroid damage due to silent thyroiditis but also Graves' disease itself. In our patient, titers of TBII and TSAb in 1993 were lower than those in June, 1992. Furthermore, the FT3/FT4 ratio in June, 1992 was clearly lower than those obtained between December, 1992 and May, 1993. It is therefore suggested that the high levels of TBII and TSAb detected at the first visit were induced and/or influenced by the presence of silent thyroiditis. Mitani *et al.* [12] reported decreases in anti-nuclear antibodies, anti-DNA antibodies, TgAb, and anti-microsomal antibodies in a case of Sjögren's syndrome associated with silent thyroiditis. In the present study, titers of TgAb and TPOAb were decreased and their changes were similar to those of TBII and TSAb. The same or similar mechanism(s) might be involved in the production of these different antibodies during the course of the illness. The patient became hyperthyroid again despite the decrease in TBII and TSAb activity. One explanation for this phenomenon is that TSAb were able to stimulate the thyroid gland sufficiently even though their activity was decreased, since inflammation of the thyroid gland subsided and the action of TOPAb on thyroid cells decreased.

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