Antitriiodothyronine Antibody in Patient with Hashimoto's Thyroiditis

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Abstract

We described a 44-year-old female patient with a history of goiter for 2 months. Physical examination revealed a diffusely enlarged thyroid gland weighing 40 g firm to hard in consistency. She was clinically euthyroid and had neither ophthalmopathy nor dermopathy. Serum thyroid hormone levels revealed total T_4 (RIA) of 4.8 μg/dL (normal, 4-11 μg/dL), total T_3 (RIA) of above 600 ng/dL (70-175 ng/dL), and TSH (IRMA) of 54 mU/L (0.3-6 mU/L). Antithyroglobulin and antiperoxidase antibody titers were 1:5,120 and 1:409,260, respectively. Because of the discrepancy between the patient's clinical status and laboratory values, assay for thyroid hormone autoantibodies (THAA) was done and subsequently demonstrated antitriiodothyronine antibody with percentage of precipitation by polyethylene of 98.4 per cent (normal range, 3.06±8.58%). In conclusion, THAA should be suspected in patients whose clinical status is incoherent with the thyroid function test.

Thyroid hormone autoantibodies (THAA) have been found in various conditions including thyroid and nonthyroid-related diseases. Most patients were found because of discrepancy between clinical status and thyroid function test. We reported a patient diagnosed as Hashimoto's thyroiditis with primary hypothyroidism who had abnormally high serum triiodothyronine (T_3) by solid-phase radioimmunoassay due to antitriiodothyronine antibody.

CASE REPORT

A 44-year-old woman was noted to have a goiter for 2 months. During this period she lost 2 kg of body weight and complained of hoarseness of voice. She was first seen at Siriraj Hospital in August 1994 and the physical examination revealed body weight of 55 kg and pulse rate of 80 per minute. The thyroid gland was diffusely enlarged approximately 30 g firm to hard in consistency and mild tenderness at the right lobe.

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There was neither ophthalmopathy nor dermopathy and she was clinically euthyroid. The thyroid function test at that time showed serum total thyroxine (T_4) level of 4.6 μg/dL (normal range 4-11 μg/dl, RIA) and total T_3 of 77.8 ng/dL (normal range 70-175 ng/dL, RIA). Serum thyrotropin (TSH) and thyroid autoantibodies were not performed. The 24-hour ^{131}I thyroid uptake was 58.7 per cent (normal range 15-45%) and was 12.3 per cent after T_3 suppression. The ^{99m}Tc thyroid scan showed good uptake and the ESR was 20 mm/hour. The patient received L-thyroxine 100 μg/day till November 1994 when she discontinued the medication herself. There was some reduction in the gland size during treatment and she did not have any symptoms after stopping L-thyroxine. In January 1995, the patient was seen again at Siriraj Hospital with painful goiter especially on the right lobe. There was no history of preceding upper respiratory tract infection or compressive symptoms. The physical examination revealed body weight of 57.5 kg, pulse rate of 76 per minute. The thyroid gland size was approximately 40 g, firm to hard in consistency, nodular surface and mild tenderness at the right lobe without signs of imflammation. She was clinically euthyroid with no evidence of ophthalmopathy or dermopathy. The serum total T_4 level was 4.8 μg/dL, total T_3 level was >600 ng/dL, and TSH level was 54 mU/L (0.3-6 mU/L). The antithyroglobulin and antiperoxidase antibody titer were 1:5,120 and 1:409,600 respctively. Similar sample of serum was sent to another laboratory for counterchecking the spuriously high total T_3 value. Again, the serum total T_3 level was >600 ng/dL (52-170 ng/dL), total T_4 was 4.4 μg/dL (4.6-12.9) μg/dL) and TSH was 54 μU/mL (0.43-3.8 μU/mL). The patient underwent fine needle aspiration of the right lobe of the thyroid gland and the cytology report was negative for malignancy. She received L-thyroxine 100 μg/day. Repeated thyroid function test 2 weeks after treatment showed serum total T_4 level of 8.7 μg/dL, total T_3 level of 800 ng/dL, TSH level of 11.7 mU/L and free thyroxine index of 6.4 per cent (3.6-11.0%). Her body weight was 59 kg, she was euthyroid and thyroid gland size was 35 g without tenderness. After one month of treatment, the drug was discontinued for one month and the patient was reevaluated. She weighed 57 kg and was still clinically euthyroid with no change in thyroid size. Serum total T_4 level was 4.3 μg/dL, total T_3 was >600 ng/dL and TSH was 55 mU/L. Antithyroglobulin antibody titer was 1:5,120 and antiperoxidase antibody titer was 1:6,553,600. The 24-hour ^{131}I thyroid uptake was 49.1 per cent and ^{99m}Tc thyroid scan revealed single cold nodule at the right lobe.

Because of the discrepancy between the patient's clinical status and laboratory values, assay for thyroid hormone autoantibodies (THAA) was done at the Division of Endocrinology, Rajavithi Hospital, Bangkok. Twenty microliters of the patient's serum and normal control serum were incubated overnight at 4°C with 50 μl of ^{125}I-T_4, 40,000 cpm or ^{125}I-T_3, 25,000 cpm. The reaction took place in the presence of blocking agents which served to liberate labelled T_4 or T_3 from endogenous carrier proteins. After incubation, precipitation with 15 per cent w/v polyethylene glycol

Table 1. Results of thyroid function tests in the patient's family members.

Family members	T_4 (μg/dL)	T_3 (ng/dL)	FT_4I	TSH (μU/mL)	TGHA*	MCHA**	% Precipitation T_3-Ab	% Precipitation T_4-Ab
Patient	3.2	>700	0.09	26.8	1:256,000	>1:1,638,400	98.4%	6.6%
Husband	7.7	121	2.09	1.87	1:10	negative	6.2%	4.3%
First daughter	8.6	172	2.02	1.71	1:1,280	1:1,600	15.6%	4.1%
Second daughter	6.6	86	2.18	1.30	1:80	1:100	6.6%	4.4%
Normal range	4.5-11.5	65-170	1.33-3.67	0.35-5.2	1:10	1:100	3.06±8.58 (mean ± 3SD)	1.80±9.42 (mean ± 3SD)

* TGHA = Antithyroglobulin antibody
** MCHA = Antiperoxidase antibody

(PEG : MW8,000) was then carried out. The radioactivity in the pellets after centrifugation at 4,500 rpm for 30 minutes was expressed as a percentage of the total counts. Antitriiodothyronine antibody was found in the patient's serum as shown in Table 1.

DISCUSSION

Thyroid hormone autoantibodies have been reported in various conditions including autoimmune thyroid diseases and nonthyroidal illness. The first case was described by Robbins et al in a patient with thyroid carcinoma[1]. Afterwards, there were many reports of such antibodies in patients with Hashimoto's thyroiditis with or without primary hypothyroidism, idiopathic primary hypothyroidism, secondary hypothyroidism, Graves' hyperthyroidism treated with antithyroid drugs and/or radioactive iodine, subacute thyroiditis, nodular goiter and other autoimmune diseases including Waldenstrom's macroglobulinemia, Sjogren's syndrome and systemic lupus erythematosus[2]. Interestingly, there have been reported cases of positive thyroid antoantibodies in patients with laryngeal cancer who received radiotherapy and in patients with hepatocellular carcinoma[3,4].

The prevalence of these antibodies is difficult to assess since the method used for detection of antibodies and selection of patients is different. However, they were found more frequently in females than in males (75.9% *vs* 24.1%)[2]. The antibody to triiodothyronine, the antithyroxine antibody and autoantibody to both thyroid hormones were found in 41.7 per cent, 33 per cent and 25.2 per cent respectively[2]. The frequencies of these antibodies in hypothyroid and hyperthyroid patients in study of Vyas and Wilkin were 7 per cent and 1.5 per cent and were 7.5 per cent in non-thyroid autoimumue conditions[5]. Almost all the antibodies were detected in the patient's IgG fraction, although less frequently found in IgE, IgA and IgM classes and usually were polyclonal[2].

In almost all patients, thyroid hormone autoantibodies were found because of the discrepancies between physical findings and result of thyroid function tests. The falsely high or low values of these hormones depend on the methods used. If single-antibody technique was used, the result was lower than actual value, but the double-antibody technique or solid-phase radioimmunoassay would result in spuriously high values[2].

Because free thyroid hormones are not immunogenic and are haptens. They essentially require conjugation with macromolecules such as albumin to initiate antibody formation. There has been considerable interest that thyroglobulin might be the antigen for thyroid hormone autoantibodies production because these antibodies have been found frequently in patients with autoimmune thyroid diseases who have a high incidence of antithyroglobulin antibodies and thyroglobulin molecule also contains considerable amounts of T_3 and T_4. Animal experiments have shown that antithyroid hormone antibodies could be produced by immunization with thyroglobulin whether from bovine, rabbit or human. Although there are some reports of autoantibodies to thyroid hormones in patients who had negative titers for antithyroglobulin antibodies, there is no direct evidence that serum protein other than thyroglobulin might bind to thyroid hormones and initiate antibody production. Interestingly, a component interfering with hemagglutination of thyroglobulin was found but a solid-phase radioimmunoassay using ^{125}I - protein A could detect a high titer of antithyroglobulin antibodies[2]. Therefore, negative titers of antithyroglobulin antibodies by hemagglutination test cannot exclude the possibility that thyroglobulin was not an antigen in these cases.

There has been much interest regarding the effects of the autoantibodies to metabolism of thyroid hormone and to hypothalamo-pituitary-thyroid axis and whether exogenous thyroid hormone will have any effect on these autoantibodies production and detection. Several reports found that the clearance of T_3 was reduced in euthyroid patients with antitriiodothyronine antibody but Geola and co-workers demonstrated normal T_4 clearance in euthyroid patient diagnosed as Hashimoto's thyroiditis with antithyroxine antibody treated with L-thyroxine[6-8]. In contrast, Inada et al reported increased T_3 clearance in hyperthyroid patient with autoantibody to triiodothyronine[9]. Therefore, these results were not consistent. The net effect probably depends on thyroid function status, the concentration and affinity of the antibodies, as well as the degree of antibody saturated by thyroid hormones. Sakata et al showed that in five patients with Hashimoto's thyroiditis

and four patients with Graves' disease with antithyroxine antibody, the FT_4 level measured by analog tracer radioimmunoassays was unusually high. By using equilibrium dialysis/radioimmunoassay method they demonstrated that the FT_4 values were compatible with basal TSH. Interestingly, the FT_4 concentration measured after treatment sera with 12.5 per cent polyethylene glycol correlated well with the values obtained by equilibrium dialysis/radioimmunoassay. They concluded that real FT_4 values in patients with thyroid hormone autoantibodies correlated well with basal TSH concentrations and the autoantibodies did not affect the control mechanism of hypothalamo-pituitary-thyroid axis[10]. Premachandra and Walfish found that prior to thyroxine treatment thyroid hormones autoantibodies bound virtually to all thyroid hormones in their patients diagnosed as having lymphocytic thyroiditis[11]. During treatment with L-thyroxine of 0.2-0.3 mg/day which normalized TSH concentration, there was an apparent decrease in T_3 and T_4 antibodies activity. They also pointed out that the dose of exogenous thyroxine to treat patients with thyroid hormone antibodies was not markedly different from those without, as long as there was sufficient thyroid reserve as in the case of increased TBG in pregnancy which failed to cause hypothyroidism.

Our patient was undoubtedly diagnosed as having Hashimoto's thyroiditis with primary hypothyroidism. The abnormally high level of triiodothyronine by solid - phase radioimmunoassay was subsequently demonstrated to be caused by antitriiodothyronine antibody. She also had high titer of antithyroglobulin and antiperoxidase antibodies. Seven months after treatment with thyroxine she was clinically euthyroid with reduction in goiter size but her T_3 level was still high (839 ng/dl). This high T_3 value may be inconsistent with the result of Premachandra and Walfish who found that exogenous hormone reduced the activity of antibody.

We had an opportunity to evaluate her family members as shown in Table 1. All had normal physical examination. There was no goiter and all of them were clinically and laboratory euthyroid. Her first daughter had high normal level of T_3 with normal T_4, FT_4I and TSH. She also had rather high titer of antithyroglobulin and antiperoxidase antibodies and the percentage of precipitation of antitriiodothyronine antibody was 15.6 per cent which is slightly higher than normal. We proposed that this level of antibody was sufficient only to cause high normal T_3. Based on these findings it is insufficient to propose the inherited process of these autoantibodies.

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แอนติบอดีย์ต่อไตรไอโอโดธัยโรนีนในผู้ป่วยโรคต่อมธัยรอยด์อักเสบฮาชิโมโตะ

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ผู้ป่วยหญิงไทยคู่อายุ 44 ปี มาโรงพยาบาลด้วยอาการคอโตมา 2 เดือน ตรวจร่างกายพบว่าลักษณะทางคลินิกอยู่ในเกณฑ์ยูธัยรอยด์ ต่อมธัยรอยด์โต่ทั่วๆไป ค่อนข้างแข็งขนาดประมาณ 40 กรัม ไม่มีตาโปน การตรวจระดับฮอร์โมน T_4 และ T_3 (เรดิโออิมมูนโนแอสเสย์) ได้ค่า 4.8 ไมโครกรัมต่อเดซิลิตรและมากกว่า 600 นาโนกรัมต่อเดซิลิตรตามลำดับ (ค่าปกติ 4-11 ไมโครกรัมต่อเดซิลิตร และ 70-175 นาโนกรัมต่อเดซิลิตร ตามลำดับ) ระดับฮอร์โมน TSH (อิมมูนโนเรดิโอเมตริกแอสเสย์) ได้ค่า 54 มิลลิยูนิทต่อลิตร (ค่าปกติ 0.3-6 มิลลิยูนิตต่อลิตร) ระดับแอนติบอดีย์ต่อธัยโรโกลบูลินและเพอรอกซิเดสได้ 1:5,120 และ 1:409,260 ตามลำดับ จึงตรวจหาแอนติบอดีย์ต่อฮอร์โมน T_3 ด้วยวิธีตกตะกอนซีรั่มผู้ป่วยด้วยสารโพลีย์เอธิลีนไกลคอลและได้ค่าเปอร์เซ็นต์ของการตกตะกอน 98.4% (ค่าปกติ 3.06±8.58%) ดังนั้นควรคิดถึงและตรวจหาแอนติบอดีย์ต่อธัยรอยด์ฮอร์โมนในผู้ป่วยที่มีอาการทางคลินิกไม่เข้ากับระดับธัยรอยด์ฮอร์โมนในกระแสเลือด

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