NOTE

Thyroid-Stimulating Antibody in a Patient with Euthyroid Graves' Disease

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Abstract. We report an 11-year-old girl with euthyroid Graves' disease. She was referred to our clinic because of left exophthalmos without other symptoms suggestive of hyperthyroidism. Her serum concentration of free thyroxine (FT₄) and free triiodothyronine (FT₃) were normal, but thyroid-stimulating hormone (TSH) was below normal and impaired TSH response to TSH releasing hormone (TRH) was found. Although the sera were positive for anti-TSH receptor antibody (TRAb) and thyroid-stimulating antibody (TSAb), both titers were not as high as usually observed in Graves' disease. Three months later, she developed hyperthyroidism and was treated with propylthiouracil. Within 2 weeks of the initiation of therapy, all symptoms except exophthalmos disappeared, and after 2 months of treatment TRAb was negative though TSAb remained positive. TSAb is therefore a good indicator to use in the diagnosis and follow-up of euthyroid Graves' disease and should be measured in patients with exophthalmos of unknown origin, even in children.

Key words: Euthyroid Graves' disease, Thyroid-stimulating antibody, TSH receptor antibody.

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EUTHYROID Graves' disease has ophthalmological findings as its only manifestation. However, it is often difficult to diagnose this disease because it depends on clinical examination and lacks objective standards. Some patients show no evidence of thyroid abnormality and others show sub-normal thyroid-stimulating hormone (TSH) levels. According to studies of long-term follow-up, some develop hyperthyroidism, some develop hypothyroidism and others remain euthyroid. Recently, this disease has been thought to be related to a thyroid-associated autoimmune mechanism [1], and thyroid-stimulating antibody (TSAb) has been considered to be a useful marker for the diagnosis and follow-up of this disease [2–6]. In this report, we describe a patient with

euthyroid Graves' disease in whom TSAb was thought to be a beneficial marker for diagnosis as well as follow-up.

Case Report

An 11-year-old-girl was referred to National Iwakuni Hospital in December 1997, because of left exophthalmos. In August 1997, an ophthalmologist at another clinic did not detect any organic abnormalities except left myopia though her family complained of her left proptosis. Although the exophthalmos progressed thereafter, she had no symptoms suggestive of hyperthyroidism. She was referred to an otolaryngologist at another clinic in December and was diagnosed with acute sinusitis by a computerized scan. She was treated with antibiotics, and the sinusitis improved, but the exophthalmos did not.

Physical examination revealed that her height

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was 156.5 cm and weight was 52.2 kg. Her blood pressure was 124/58 mmHg, and pulse rate, 100 beats/min with regular rhythm at first visit, but pulse rate had been 80 to 95 beats/min since then. She did not have a history of hyperthyroidism and weight loss was not observed. She did not complain of easy fatigue, excessive sweating or palpitations. Nervousness or hyperkinesia was not noticed by her family. The proptosis was 16 mm for the left eye and 12 mm for the right with a baseline of 92 mm, measured with Hertel's ophthalmometer. There was no Graefe's sign or lid retraction. The thyroid gland was not palpable. No abnormalities of the heart, chest or abdomen were detected and the deep tendon reflexes were normal. Her bone age was equivalent to chronological age (by Greulich & Pyle).

There was swelling of the left medial rectus muscle but no retro-orbital tumor was detected by magnetic resonance imaging (MRI) (Fig. 1). Laboratory studies revealed no abnormality of blood analysis and normal urinalysis values (data not shown). Thyroid function studies revealed the following: free thyroxine (FT₄) value was 1.19 ng/dl (normal range, 0.90 to 1.80 ng/dl), free triiodothyronine (FT₃) value was 3.71 pg/ml (normal range, 2.20 to 4.10 pg/ml), TSH value was 0.05 IU/ml (normal range, 0.35

to 3.73 μ IU/ml), thyroxine-binding globulin value was 18.6 μ g/ml (normal range, 15 to 30 μ g/ml), thyroglobulin value was less than 5.0 ng/ml (normal range, less than 47 ng/ml), anti-thyroxine antibodies combined with the thyroxine at 2.2% and anti-triiodothyronine antibodies combined with the triiodothyronine at 3.5%. There was no TSH response to TSH releasing hormone (TRH). The patient's titer of anti-thyroglobulin antibodies (TgAb) and that of anti-microsomal antibodies (McAb) were measured by a commercial kit of passive agglutination (Fujirebio Inc., Tokyo, Japan) at 1 : 1,600 (normal range, less than 1 : 100) and 1 : 102,400 (normal range, less than 1 : 100), respectively. TSH receptor antibodies (TRAb), also called TSH-binding inhibitor immunoglobulins (TBII) were measured by a commercial kit of radioreceptor assay (Ortho Clinical Diagnostics, Tokyo, Japan) at 21% (normal range, -10 to 10%) and the TSAb was measured by a radioimmunoassay commercial kit using porcine thyroid cells (p-TSAb, Yamasa Corporation, Choshi, Japan) at 198% (normal range, less than 180%). However, the TSAb measured by a sensitive bioassay using rat thyroid cell strain FRTL-5 (r-TSAb) was negative (less than 0.3 IU/ml of bovine TSH, SRL, Tokyo, Japan) [7]. The thyroid-stimulation block-

Fig. 1. MRI scan of the orbits. A: PD-weighted image, B: T1-weighted image.

ing antibody (TSBAb) measured by a sensitive bioassay was negative. Thus, we diagnosed this patient with euthyroid Graves' disease because she was clinically euthyroid, her FT_4 and FT_3 were normal, she had exophthalmos, low TSH, positive TRAb and suppressed TSH response to TRH.

Because the ophthalmopathy was not so severe and the thyroid function was normal, she was followed without medication such as corticosteroid or anti-thyroid drugs. During this time, her FT_4 and FT_3 had been normal. In April 1998, she complained of easy fatigue, shortness of breath, polyphrasia and easy excitability. At that time, her height was 158.9 cm and weight was 57.1 kg, showing no weight loss. Her blood pressure was 132/48 mmHg and pulse rate, 112 beats/min with regular rhythm. The thyroid gland was palpable, diffuse and soft. Each lobe measured about 20 mm in vertical and about 5 mm in horizontal dimension above the isthmus. The FT_4 and FT_3 levels were 1.81 ng/dl and 5.43 pg/ml, respectively, showing thyrotoxicosis.

As a result of these findings, she received propylthiouracil 100 mg every 8 hours initially. In 1 week her thyroid function was normal and in 2 weeks, all symptoms except exophthalmos disappeared. In 6 weeks, TSH level increased to the normal range. As shown in Fig. 2, the titer of TRAb decreased to normal range as the thyroid function was normalized, but the p-TSAb remained positive and the r-TSAb, negative.

Discussion

Euthyroid Graves' disease is defined as ophthalmopathy of Graves' disease in euthyroid subjects without other known ocular disease or history of hyperthyroidism. Although there have been many reports of this disease in adults since it was first reported in 1945 [8], it is very rare in children. Of course, exophthalmos is noticeable in most children with Graves' disease but is usually mild. Although euthyroid Graves' disease is thought to be related to an autoimmune reaction against the retro-orbital tissue, its pathogenesis is still unknown. Recently a 64-kd eye muscle membrane protein was discovered to be expressed by orbital tissue and recognized by autoantibodies in serum of patients with thyroid-associated eye disease [9, 10]. Whether it is significant or not, however, remains controversial, because sera of normal subjects also react with this protein [11, 12] and there is no evidence that this protein is present in a significant proportion of patients with ophthalmopathy [13]. It was also determined that TSH receptors are present on retro-orbital tissue [1, 14–17]. Therefore, it has been suggested that autoantibodies to an antigen cross-reacting with the TSH receptor may be involved in the pathogenesis of ophthalmopathy. The report showing the relationship between TSAb activity and the extent of ophthalmopathy in this disease by Watanabe *et al.* may support this speculation [3]. However, Kashiwai *et al.* reported that the TSAb

Fig. 2. Changes in TSAb, TRAb, FT_4 and TSH after initiation of treatment with propylthiouracil.

value was not related to the severity of the ophthalmopathy in this disease [4].

In our case, thyroid antibody studies were positive for McAb, TRAb, and p-TSAb, and negative for TgAb, TSBAbs, and r-TSAb. Both TRAb and p-TSAb were positive, but the titers were not as high as usually observed in patients with untreated Graves' disease. Thus, the TSH receptor antibodies may not be high enough to cause hyperthyroidism in these patients [6]. It is interesting to note that r-TSAb was negative although p-TSAb was positive. We speculate that this discrepancy is due to species-specificity or sensitivity of the assay. TSAb activity may vary depending on thyroid cell type used. Thus, those with negative TSAb activity using FRTL-5 thyroid cells might have positive activity using porcine thyroid cells. Measurement of TSAb activities using both methods might be best until the significance of these methods is determined. Another interesting point is the lack of correlation between the changes in TRAb and TSAb during therapy. Although the TRAb activity quickly decreased parallel to normalization of thyroid function, the TSAb activity remained high and the left exophthalmos remained unimproved. Both TRAb activities and TSAb activities are positive among over 90% of untreated Graves' disease [2, 4, 6], and both usually decrease as a result of therapy. However, the changes in TRAb and TSAb activities do not always parallel each other

[18], suggesting that there are heterogeneous antibody activities in sera of patients. There are some reports regarding euthyroid Graves' disease in which TSAb is detectable as frequently as in untreated Graves' disease though the positive rate of TRAb is lower [2, 4–6]. This indicates that the presence of TSAb does not necessarily lead to hyperthyroidism [6]. This may be due to differences in sensitivity of the TRAb and TSAb assays or to differences in disease expression represented by the two antibodies. Thus, TSAb appears to be a more sensitive marker for the diagnosis and follow-up of euthyroid Graves' disease.

Our patient developed thyrotoxicosis during follow-up as observed in other reports [4, 5]. Moreover, compared with a previous portrait (approximately 3 years prior), both eyes were proptotic at the first visit to our hospital. This suggests that she had suffered from this disease for more than 1 year before developing thyrotoxicosis. Although her thyroid function normalized after initiation of therapy, left exophthalmos did not change and TSAb activity remained high; therefore, long-term follow-up is important. The measurement of TSAb in euthyroid patients who have ophthalmopathy without other known ocular disease is essential for accurate diagnosis. Furthermore, in euthyroid subjects with subnormal TSH levels in serum, TSAb measurement is useful for detection of subclinical Graves' disease.

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