Euthyroid Graves' Ophthalmopathy with Negative Autoantibodies

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Graves' disease is an autoimmune-based hyperthyroidism in which a number of different antibodies directed against thyroid tissue plays a role. Graves' ophthalmopathy is thought to be a consequence of this autoimmune basis and occurs in some patients with Graves' disease. On occasional cases, the disease may present only with ophthalmopathy without hyperthyroidism. A 32-year-old woman with euthyroid Graves' ophthalmopathy and negative thyroid autoantibodies, including TSH receptor antibody, is presented here.

Key words: Euthyroid Graves' ophthalmopathy ■ thyroid autoantibodies

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INTRODUCTION

Graves' disease is thought to be caused by an autoimmune process in which stimulatory autoantibodies bind to TSH receptor and activate gland function, leading to hyperthyroidism. Graves' ophthalmopathy is seen in 25–50% of patients with Graves' disease, but most of these patients have only mild eye discomfort.[1] A 32-year-old Caucasian woman with euthyroid Graves' ophthalmopathy and negative thyroid autoantibodies is presented here.

CASE REPORT

The patient was admitted with proptosis in her right eye. She had orbital pain, increased tearing and foreign body sensation in her eyes 1.5 years ago. She did not have redness in conjunctiva or swelling of caruncle or eyelids. She was referred to an ophthalmologist, and artificial tears and eye ointments were prescribed for her symptoms. Within six months, her symptoms gradually resolved and an obvious protrusion occurred in her right eye. She did not have diplopia. She was again referred to her ophthalmologist and an orbital CT scan was performed. On CT imaging, proptosis was noted for both eyes. The diagnoses of orbital neoplasm, orbital pseudotumor and cavernous sinus thrombosis (which presents with unilateral proptosis) were ruled out, and she was referred to an internal medicine specialist with a preliminary diagnosis of Graves' ophthalmopathy. Her serum thyroid hormone levels [TT3:95 (70–130) ng/dL, TT4:7.7 (4.5–12.5) μg/dL] were found to be within normal ranges and no treatment was given.

One year after the presenting symptoms, she was admitted to our hospital. On personal history, she had 17 packet years of cigarette smoking and was a current smoker. On ophthalmological examination, lid lag and exophthalmus were noted on her right eye; she had no limitation of eye movements, conjunctival redness or swelling. Hertel exophthalmometer measurements were 23 mm on the right and 19 mm on the left eye. Her serum TSH level was within the normal range [0.855 (0.490–4.670) uIU/mL]. Her antithy-

roglobulin (Brahms, Dynotest, Berlin, Germany), antithyroperoxidase (Brahms, Dynotest, Berlin, Germany) and TSH receptor binding antibodies (TRAK assay, Brahms, Berlin, Germany) were negative. On orbital magnetic resonance imaging, proptosis was noted bilaterally (Figure 1). Bilaterally enlarged lateral rectus (horizontal diameters 6- and 7 mm on the right and left, respectively), left inferior rectus (horizontal diameter 5 mm) and right oblique (horizontal diameter 3 mm) muscles were observed (Figure 2). As she was asymptomatic and the disease was not active, no treatment was given. She was advised to quit smoking and is under follow-up.

DISCUSSION

Graves' disease is the most common form of thyrotoxicosis and may occur at any age, more commonly in females. Major histocompatibility complex (MHC) class-II alleles have been associated with Graves' disease in several populations of distinct ethnic backgrounds, and there is increasing evidence supporting an association between Graves' disease and HLA-DR3 in Caucasian populations.[1] There is only one study from Turkey about Graves' disease and HLA typing that shows that the HLA DR4 antigen may contribute to the predisposition of Graves' disease more strongly than HLA-DR3 in Turkey.[2]

It is currently believed that Graves' ophthalmopathy reflects the underlying autoimmune process and it is not a direct consequence of alterations in thyroid function.[3] Degree of exophthalmos in Graves' ophthalmopathy is measured with Hertel exophthalmometer. Normal readings range from 15–20 mm in Caucasians, and the difference between the eyes usually does not exceed 1 mm.[4] There are racial differences in normal values of proptosis and normal ranges are higher in black subjects, according to previous studies.[5] Regarding relationship of Graves' ophthalmopathy risk with ethnicity, Europeans were found to have a substantially greater risk of developing Graves' ophthalmopathy than were Asians in a study by Tellez et al.[6] The detected thyroid autoantibodies in Graves' disease are: antithyroglobulin (TgAb); antithyroperoxidase (TPOAb) and TSH receptor antibodies (TRAb). Antibodies directed against TSH receptor either exhibit no functional effect on the thyroid or can stimulate or block TSH activation of the thyroid, depending on their types. Some patients may have both stimulatory and blocking TRAbs, and the net biological effect of the serum might be influenced by the relative concentrations of these antibodies. Currently, there are several methods to detect TRAb positivity. These include TSH stimulating antibodies (TSAb); TSH receptor blocking antibodies (TBAb or TSBAb), which are detected by cell bioassays; and TSH binding inhibitory immunoglobulin (TBII) assays, which do not measure biologic activity directly but assess whether the specimen contains immunoglobulins.[7] TBII assays do not distinguish between stimulating and blocking TRAbs.[2]

Figure 1. Horizontal section of orbital MRI showing bilateral proptosis. Note both ocular globes lying nearly totally superior to interzygomatic line.

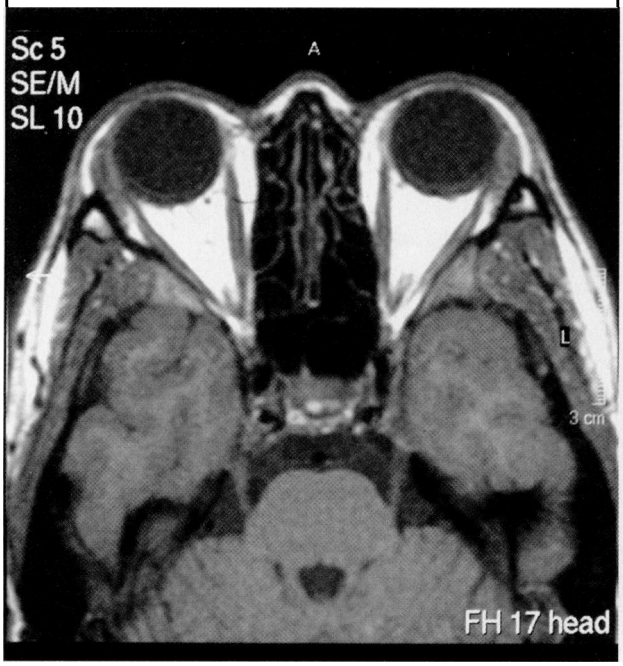
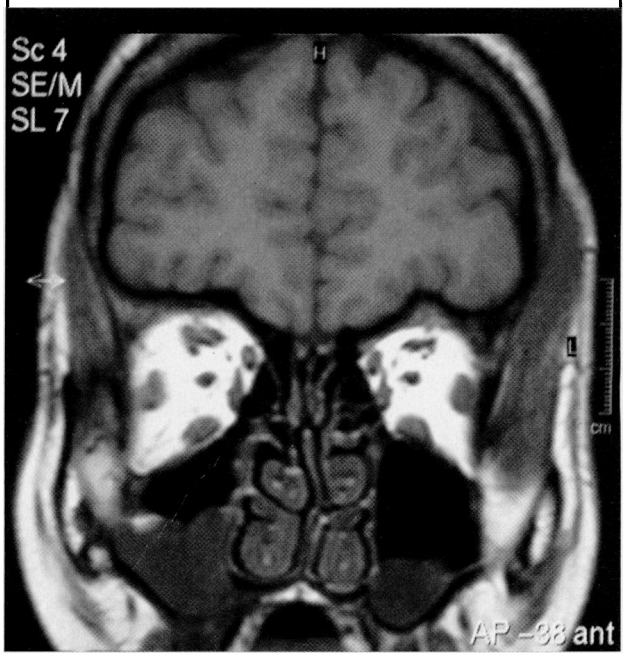


Figure 2. Coronal section of orbital MRI showing enlargement of right and left inferior rectus, left lateral rectus and right oblique muscles.



Several studies have investigated the relationship between different antibody profiles and hyperthyroidism and Graves' ophthalmopathy in Graves' disease. In two previous studies, TSAb positivity correlated with ophthalmopathy and TBII was related to hyperthyroidism.[8,9] In the study by Goh et al., ophthalmic dominant patients also had significantly lower TPOAb and TgAb levels.[9] Regarding the correlation between the presence, type or levels of TRAb and Graves' ophthalmopathy, there are studies that report both TSAb and TBII to be closely correlating with Graves' ophthalmopathy clinical activity score.[10] Weaker but significant correlation was also noted between antibody levels and proptosis. In a study by Khoo et al., in patients with severe ophthalmopathy, an unexpectedly high prevalence of TPOAb and TgAb negativity and high TSAb positivity was reported.[11] Conversely, two studies by Kim et al. demonstrated TSBAb positivity was significantly associated with the presence of Graves' ophthalmopathy.[12,13]

Euthyroid Graves' ophthalmopathy is defined as ophthalmopathy without no present or past history of hyperthyroidism and is reported in 0.7% of patients in a large series of Graves' ophthalmopathy.[14] TSAb positivity has been shown in 10 of 11 patients with euthyroid Graves' ophthalmopathy by Ealey et al. by a cytochemical bioassay.[15] In 1995, two patients with euthyroid Graves' ophthalmopathy showing no thyroid abnormalities except positive TSAb were reported by Watanabe et al.[16]

The case presented here had no defined thyroid dysfunction since her symptoms and signs started and, thus, is a case of euthyroid ophthalmopathy. Interestingly, all her thyroid antibody levels were also negative. The TBII assay, which has been used in this patient, shows high sensitivity (98.8%) and specificity (99.6%) for the detection of TRAbs and measures both TSAb and TSBAb.[17] Thus, this case may represent another interesting exception for the spectrum of antibody profiles in euthyroid Graves' ophthalmopathy. Nevertheless, it must be kept in mind that, in some patients, receptor assays may not detect some TSI types as the nature of TRAbs are very heterogenous. Unfortunately, cell bioassays, which are more sensitive and specific under these circumstances, are not available in our laboratory. Another explanation may be that the antibodies were measured nearly one year after her signs started, and this case may be an inactive Graves' ophthalmopathy having moderate eye disease in which the autoimmune attack has ceased. As a conclusion, even highly specific antibodies, such as TRAb, may not be detected in patients with euthyroid Graves' ophthalmopathy. This case confirms the complicated and controversial nature of the disease.

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