ABSTRACT: We report a 71-year-old woman with concomitant ocular myasthenia gravis and euthyroid Graves' ophthalmopathy. Unilateral ophthalmoplegia, including ptosis, initially was responsive to edrophonium and corticosteroids, except for diplopia on upward gaze, but refractory swelling of the inferior rectus muscle and proptosis followed. Autoantibodies to acetylcholine and thyrotropin receptors were detected. Her ophthalmopathy abated after orbital irradiation in combination with systemic steroids. There may be an immunological basis for the association of ocular myasthenia gravis with euthyroid Graves' ophthalmopathy.

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OCULAR MYASTHENIA GRAVIS ASSOCIATED WITH EUTHYROID OPHTHALMOPATHY

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Myasthenia gravis (MG) sometimes is associated with other autoimmune disorders, including autoimmune thyroid diseases. Thyrotoxicosis occurs in about 5% of myasthenic patients.[1] Ophthalmopathy is one of the triad in Graves' disease, but also occurs alone without hyperthyroidism. Overlapping clinical features may cause diagnostic confusion when ocular MG and euthyroid Graves' ophthalmopathy coexist. Reports of such an association are few, but Marinò et al.[8] found that in 418 patients with Graves' disease, those with MG had a significantly greater prevalence of euthyroid ophthalmopathy than those without it. They speculated that there is immunological cross-reactivity against common autoimmune targets in the eye muscle, or a common genetic background. We report a patient who had ocular myasthenia gravis and euthyroid ophthalmopathy, probably of close onset.

CASE REPORT

A 71-year-old woman who had a 3-month history of double vision and left ptosis was referred. Her medical history was not significant, and there was no family history of neuromuscular or autoimmune disorders. Physical examination showed neither exophthalmos nor goiter. There was left ptosis. Adduction and upward rotation of her left eye were restricted and worsened in the evening. Her cranial nerves were otherwise normal, and there was no weakness in her neck and limb muscles. After intravenous administration of 5 mg edrophonium chloride, the ptosis and restricted movement of the left eye completely disappeared, but diplopia on upward gaze remained. Routine hematological and biochemical screening tests, including thyroid function tests, were normal. Serum acetylcholine receptor (AChR) antibody titer was slightly elevated at 0.7 nmol/L (normal < 0.3). Magnetic resonance imaging (MRI) of the orbit was normal (Fig. 1A). Ocular-type myasthenia gravis was diagnosed, and she underwent two 3-day courses of intravenously administered methylprednisolone (10 mg/kg daily). Thereafter, her symptoms and signs disappeared, except for diplopia on upward gaze which persisted and was refractory to another 3-day course of intravenous methylprednisolone.

One year later, she experienced dull pain in the left orbit that lasted for 2 days and was followed by diplopia in all directions. Physical and ophthalmologic examinations were unremarkable, except for left ocular position and movement. There was no ptosis on either side. Her primary eye position showed hypotropia of the left eye. Both horizontal and vertical movements of the left eye were severely restricted. Movement of the right eye was normal. Intravenous edrophonium chloride (10 mg) had no

Abbreviations: AChR, acetylcholine receptor; MG, myasthenia gravis; MRI, magnetic resonance imaging; TSH, thyrotropin

Key words: autoantibodies; euthyroid ophthalmopathy; Graves' disease; magnetic resonance imaging; myasthenia gravis; ophthalmoplegia

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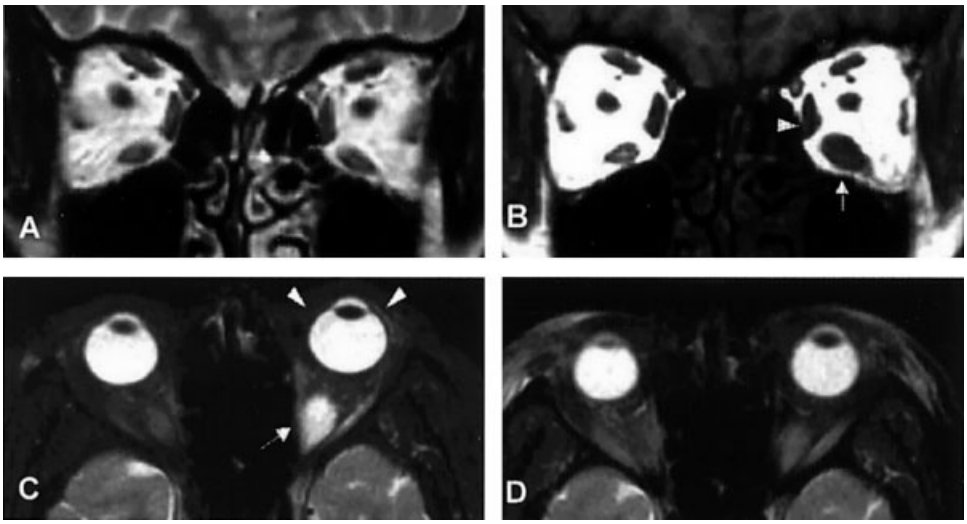

Figure 1. MRI of the orbit at the initial examination **(A),** after 1 year **(B,C),** and at remission after irradiation **(D). (A)** There is no enlargement of the extraocular muscles on either side. **(B)** The left inferior rectus (arrow) is markedly enlarged and the left medial rectus (arrowhead) muscle is mildly thickened. **(C)** The inferior rectus muscle is enhanced by gadolinium (arrow) sparing the muscle tendon, and there is mild proptosis on the left (arrowheads). **(D)** Enhancement of the inferior rectus muscle and proptosis have resolved after irradiation.

effect on the abnormal position and movement of the left eye. There was no weakness in her neck and limb muscles, and repetitive stimulation of the accessory nerve elicited normal responses in the sternocleidomastoid muscle. Her serum AChR antibody titer was weakly positive at 0.6 nmol/L.

Routine blood test results, including the erythrocyte sedimentation rate, were normal. Antinuclear antibody was positive in low titer. The cerebrospinal fluid examination was normal. Thyroid function tests gave the following values: free thyroxine, 1.19 ng/dl (normal, 0.71–1.85); free triiodothyronine, 2.5 pg/ml (normal, 1.9–3.7); and thyrotropin (TSH), 0.95 μU/ml (normal, 0.49–4.67). Autoantibodies to thyroperoxidase and thyroglobulin were negative. Of the antibodies to TSH receptors, thyroid stimulating antibody was negative, and TSH-binding inhibitory immunoglobulins were positive in low titer. An ultrasonographic examination of the thyroid showed no abnormalities, and computerized tomography of the chest found no thymomas. MRI of the orbits now showed marked enlargement of the left inferior rectus muscle (Fig. 1B) with fusiform high signal intensity on the T2-weighted image that was enhanced by the contrast medium (Fig. 1C). The muscle tendon was spared. Mild swelling also was present in the left medial rectus muscle (Fig. 1B), and there was mild proptosis on the left (Fig. 1C).

Because orbital myositis could not be excluded, the patient was given two 3-day courses of intravenous methylprednisolone (20 mg/kg daily), then a 5-day course of intravenous immunoglobulins (0.4 g/kg daily). There was neither clinical improvement nor change in the MRI findings after these treatments. Based on the treatment strategy for intractable Graves' ophthalmopathy,[2] she underwent orbital irradiation in combination with systemic corticosteroid treatment. Betamethasone (12 mg/day) was administered intravenously for 10 days preceding irradiation, then tapered off during irradiation. Radiation therapy was undertaken with laterally opposed beams. The total dose to the central axis was 20 Gy delivered as a daily fraction of 2 Gy three times per week. After treatment, motility of the left eyeball returned, and diplopia on downward gaze disappeared. Hypotropia of the left eye and mild diplopia in upward and lateral gaze remained. Orbital MRI 4 months after irradiation showed that both the left proptosis and contrast enhancement of the left inferior rectus muscle had disappeared (Fig. 1D). Low AChR antibody and TSH-binding inhibitory immunoglobulin titers persisted, and thyroid stimulating antibody was positive 2½ years after the onset of ophthalmopathy.

DISCUSSION

The patient's initial presentation of left ophthalmoplegia that included ptosis was responsive to edrophonium and corticosteroids. In addition to the diurnal fluctuations of symptoms and positive AChR

antibodies, MG was diagnosed and successfully treated with corticosteroids, except for double vision on upward gaze. The recurrence of left ophthalmoplegia after 1 year was accompanied by pain, proptosis, and swelling of the inferior and medial recti muscles. It was refractory to edrophonium. All these features indicate a nonmyasthenic etiology for her ophthalmopathy. Retrospectively, diplopia on upward gaze early in her illness suggests that the inferior rectus muscle may have been involved due to the second etiology concomitant with MG. Although orbital myositis could not be excluded because of unilateral swelling of the ocular muscles,[10] the preferential involvement of the inferior rectus muscle sparing the muscle tendon,[10] a lack of general inflammatory responses, and refractoriness to immunomodulating therapies[11] favored Graves' ophthalmopathy. Moreover, the patient's serum was positive for antibodies against the thyroid TSH receptor.

Approximately 10% of patients with Graves' ophthalmopathy are euthyroid.[4] Almost all of those patients have at least one of the TSH receptor antibodies, thyroglobulin antibodies or thyroperoxidase antibodies.[3] Although TSH receptor antibodies are the autoantibodies responsible for thyroid dysfunction and markers of euthyroid Graves' ophthalmopathy, whether they function in the development of ophthalmopathy is not clear. In euthyroid Graves' ophthalmopathy, TSH receptor antibody titers are low and not associated with the severity of ophthalmopathy.[6] A thyroid and eye-muscle shared protein has been proposed as the primary autoantigen in thyroid-associated ophthalmopathy.[5,7] The primary autoantigens in ocular MG also may differ from those in generalized MG. In ocular MG, AChR antibodies tend to be present in low titer, and were not found in one-third of a patient population studied.[13] Ocular MG patients showed minimal, unstable sensitization of anti-AChR $CD4^+$ T cells.[12] Even in seronegative MG, plasma from generalized seronegative MG showed inhibition of AChR function, whereas that from ocular seronegative MG did not.[9]

Clinically, eyelid ptosis in patients with thyroid ophthalmopathy should be considered evidence of MG, whereas orbital pain and proptosis in patients with ocular MG imply orbital inflammatory disease. It is not necessary to obtain orbital imaging in every case of ocular MG. The case of our patient is evidence that there can be concomitant ocular myasthenia gravis and euthyroid Graves' ophthalmopathy associated with low AChR antibody and TSH receptor antibody titers. The detection of these antibodies should aid in diagnosing such overlapping conditions. The presence of AChR antibodies and TSH receptor antibodies, however, could be an epiphenomenon. The primary autoimmune target is not known, but it may be common to the two disorders.

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