CASE REPORT

Progressive bilateral ophthalmoparesis—a case of simultaneous autoimmunity: balancing Graves' ophthalmoparesis and ocular myasthenia

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SUMMARY

A 44-year-old woman with no medical history presented with a 1-year history of horizontal diplopia, bilateral exophthalmos and progressive asymmetrical ophthalmoparesis, with no pupillary dysfunction or ptosis. Within 3 months of her initial presentation, she noticed paresis of right eye abduction, followed after 1 month with paresis of left eye abduction. Initial investigations revealed positive antiperoxidase antibodies for Graves' disease and positive AChR for myasthenia gravis. MRI of the brain showed increased intensity in bilateral inferior rectus muscles and CT of the chest showed thymic hyperplasia. Treatment with carbimazole and pyridostigmine was started, with complete resolution after 1 month.

BACKGROUND

- This report outlines the clinical differences between two autoimmune conditions—Graves' disease and ocular myasthenia—which can overlap and cause some clinical confusion
- We specify the need for proper clinical and laboratory assessment to exclude concomitant autoimmune diseases

CASE PRESENTATION

A previously healthy 44-year-old woman presented with a 1-year history of progressively worsening horizontal diplopia, which she characterised as worse during the afternoons and evenings. There was no associated headache, dizziness, nausea or vomiting. However, during the latter half of her presentation, she reported mild fatigue without shortness of breath, which got worse by the end of the day.

Seven months before her evaluation in clinic, she had noted a limitation to abduct her right eye. Four months later, she noted that she also had limitation to abduct her left eye. Simultaneously, her fatigue had slightly worsened and she noticed bilateral eye protrusion and lid retraction. These symptoms led to an endocrinologist and a neurologist assessment in clinic.

Following the endocrinology assessment, a clinical diagnosis of Graves' disease with hyperthyroid ophthalmopathy was given and a further positive antiperoxidase antibody result certified the diagnosis. Treatment with carbimazole was started. Subsequently, after neurological assessment, a diagnosis of ocular myasthenia was given based on fatigability and asymmetrical ophthalmoparesis

without pupillary dysfunction. Physical examination was remarkable for bilateral paresis during abduction on forced gaze and limitation of bilateral supraversion; there was no pupillary dysfunction and no bulbar involvement. The lack of ptosis was considered a consequence of lid-retraction secondary to Graves' hyperthyroidism. A positive AChR antibody result confirmed the clinical diagnosis. Treatment with pyridostigmine was started at 60 mg four times a day, which led to some improvement.

A brain MRI (figure 1) revealed increased intensity in both inferior rectus muscles, supporting a diagnosis of hyperthyroid ophthalmopathy. However, a chest CT was performed (figure 2), revealing thymic hyperplasia and supporting the diagnosis of myasthenia.

Based on symptoms, laboratory and imaging results compatible with concomitant Graves' ophthalmopathy and ocular myasthenia, simultaneous treatment with carbimazole and pyridostigmine was continued. After approximately 1 month, the patient continued to have a remarkable improvement of her symptoms.

Finally, the patient underwent thymectomy and the pathological report was positive for a thymoma.

INVESTIGATIONS

Blood results: AChR antibodies positive, antiperoxidase antibodies positive, ANCA-p/c negative, HIV negative, hepatitis B/C negative; anti-Jo1, anti-Mo, anti-La, ANA, antidouble-stranded DNA negative. Complete blood count without abnormalities. No electrolyte disturbances.

Figure 1 MRI of the brain—bilateral increased intensity of inferior rectus muscles.

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Figure 2 CT of the chest—thymic hyperplasia.

DIFFERENTIAL DIAGNOSIS

- ▶ Drug-induced myasthenia-like syndrome
- ▶ Mitochondrial myopathies, with or without external ophthalmoplegia
- ▶ Oculopharyngeal muscular dystrophy

TREATMENT

The patient is currently on carbimazole and pyridostigmine, demonstrating very good results. She has greatly improved: she no longer has diplopia, extraocular palsies and lid retraction. She has undergone thymectomy, which further improved her symptoms.

OUTCOME AND FOLLOW-UP

The patient has recently been seen in neurology and endocrinology clinic; no side effects from either treatment have been referred and she is showing progressive improvement.

DISCUSSION

Both Graves' disease and myasthenia gravis are mediated via autoantibodies to membrane receptors, antithyroid-stimulating hormone and AChR. Graves' disease develops in approximately 5% of patients with myasthenia gravis and, conversely, myasthenia gravis develops in 0.2% of patients with Graves' disease. Graves' disease more commonly occurs in association with the restricted ocular form of myasthenia gravis—this is reflected in the frequency with which thyroid antibodies are found in patients with ocular myasthenia gravis and generalised myasthenia gravis, 40% and 12%, respectively. Furthermore, 50% of patients presenting with ocular myasthenia develop generalised weakness within 6 months and up to 80% will generalise within 2 years.¹

The prevalence of autoimmune thyroid disease is higher in myasthenia gravis patients compared to the general population. The reasons for the co-occurrence of the two conditions have not yet been elucidated. The chemokine CXCL-10 and its receptor, CXCR-3, seem to play an important role in the pathogenesis of systemic-specific and organ-specific autoimmune diseases. High levels of CXCL-10 are found in cases of organ-specific autoimmune disease such as Graves' disease or systemic autoimmune disease, and these seem to be markers of amplified host immune response that perpetuate the autoimmune process and could lead to the association of the two diseases.²

This patient presented with symptoms of both ocular myasthenia and hyperthyroid ophthalmopathy. This was challenging,

especially for determining the 'primary' or 'first' aetiology for her condition. First, bilateral or unilateral ptosis was thought to be absent secondary to Graves'-associated lid retraction. Second, the patient presented positive AChR in serum and, also, positive antiperoxidase antibodies for autoimmune hyperthyroidism. Third, the increased intensity of both inferior rectus muscles seen on the MRI was more suggestive of an underlying hyperthyroid ophthalmopathy; however, the patient also had a CT of the thorax that demonstrated hyperplastic thymus. And finally, since both carbimazole and pyridostigmine were given simultaneously, the true 'treatment' was difficult to ascertain.

Overall, the prognosis of combined myasthenia gravis/Graves' disease comorbidity is variable: in about 40% of cases the myasthenia improves while the hyperthyroidism worsens; in 20% of cases, the hyperthyroidism is clinically controlled but the myasthenia is not. Our patient, however, showed signs of improvement of both her myasthenia as well as her Graves' disease. Unfortunately, because carbimazole and pyridostigmine were given simultaneously, it is difficult to identify which of them contributed most to the improvement. However, as we will see in the next paragraph, the carbimazole may alleviate existing myasthenic symptoms.

A common treatment modality denotes the use of anticholinesterase medications supplemented by immunosuppression, plasmapheresis and/or thymectomy. Also seen is that any deviation from a euthyroid state will adversely affect myasthenia gravis, and the treatment of thyroid dysfunction may alleviate the existing myasthenic symptoms when both disorders are present concomitantly.³

More so, not only can the treatment for one disease contribute to the improvement of the other, but, also, the presence of an enlarged thymus and thymic abnormalities has been seen in both thyrotoxic and myasthenia gravis patients. Therefore, the beneficial effect of thymectomy in the management of

Learning points

- ▶ In the presence of exophthalmos and extra-ocular muscle dysfunction due to Graves' disease, myasthenia symptoms and signs may be particularly difficult to elicit and, therefore, it is important to be aware of this association.
- ▶ Forty per cent of cases of myasthenia improve while the hyperthyroidism worsens; in 20% of cases, the hyperthyroidism is clinically controlled but the myasthenia is not.
- ▶ A deviation from a euthyroid state will adversely affect myasthenia gravis and the treatment of thyroid dysfunction may alleviate the existing myasthenic symptoms when both disorders are present concomitantly.
- ▶ The presence of an enlarged thymus and thymic abnormalities has been seen in both, thyrotoxic and myasthenia gravis patients.
- ▶ The reasons for the association of autoimmune thyroid disease with ocular myasthenia is largely unknown, but several hypotheses can be considered:
 - Ocular myasthenia and generalised myasthenia might actually represent separate diseases with different spectra of underlying conditions.
 - An immunological cross-reactivity against epitopes or auto-antigens shared by the thyroid and the eye muscles might be the basis of this association.
 - A possible genetic background.

myasthenia gravis performed at an earlier stage in the disease course has been documented. Thymectomy not only aids in improving the symptoms of myasthenia, but it also reduces the morbidity in severe cases, and where large doses of anticholinesterases are required on a daily basis.⁴

Competing interests None declared.

Patient consent Obtained.

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