Endocrinology, Diabetes & Metabolism CASE REPORTS

A E S Arcellana and others | Myasthenia gravis, Graves' disease association

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Dual attack: targeting the rare co-occurrence of myasthenia gravis and Graves' disease with radioactive iodine therapy

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Summary

Occasionally, autoimmune disorders can come in twos. This double trouble creates unique challenges. Myasthenia gravis co-existing with autoimmune thyroid disease occurs in only about 0.14–0.2% of cases. The patient is a 27-year-old man with a 2-month history of bilateral ptosis, diplopia, with episodes of easy fatigability, palpitations, and heat intolerance. On physical exam, the patient had an enlarged thyroid gland. Myasthenia gravis was established based on the presence of ptosis with weakness of the intraocular muscles, abnormal fatigability, and a repetitive nerve stimulation study indicated neuromuscular junction disease. Episodes of fluctuating right shoulder weakness were also noted. He was also found to have elevated FT3, FT4, and a suppressed TSH. Thyroid ultrasound revealed thyromegaly with diffused parenchymal disease. Thyroid scintigraphy showed increased uptake function at 72.4% uptake at 24 h. TRAb was positive at 4.1 U/L. Patient was started on pyridostigmine which led to a significant reduction in the frequency of ocular muscle weakness. Methimazole was also initiated. Radioactive iodine at 14.9 mci was instituted for the definitive management of hyperthyroidism. After RAI, there was abatement of the hyperthyroid symptoms, as well as improvement in the status of the myasthenia gravis, with ptosis, diplopia, and right arm weakness hardly occurring thereafter despite the reduction of the pyridostigmine dose based on a symptom diary and medication intake record. Two distinct autoimmune conditions displayed a markedly improved clinical course with the institution of radioactive iodine therapy for Graves' disease.

Learning points:

- The presence of ptosis, diplopia, and fluctuating muscle weakness are atypical in Graves' disease and should prompt an investigation on the existence of concurrent myasthenia gravis. A prompt diagnosis of both conditions will enable the institution of appropriate management that would target both rare and challenging autoimmune diseases.
- Selecting the therapeutic options with minimal risk of morbidity and mortality, which could lead to maximal benefit especially in a resource-limited setting is paramount.
- Targeted non-surgical management can lead to the remission of two autoimmune diseases which can result in patient satisfaction and improved quality of life.

Background

Occasionally, autoimmune disorders can come in twos, leading to the concurrent development of two distinct conditions such as myasthenia gravis and Graves' disease. This double trouble emanates from defects in autoimmunity, leading to unique challenges in management. Myasthenia gravis, an autoimmune

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neuromuscular disease characterized by defects in the nicotinic acetylcholine receptors (AChR) located in neuromuscular junctions, has an incidence of 5.3 per million person-years, and early onset myasthenia gravis is even more rare in males, with about twice as many women afflicted with the disease as men. Among males, myasthenia gravis usually peaks in the sixth decade (1). Hyperthyroidism affects only about 0.2% of men (2). Graves' disease, a cause of hyperthyroidism that stems from the production of autoantibodies, consisting mainly of the thyroid-stimulating receptor antibody (TRAb), can lead to debilitating complications such as ophthalmopathy, thyrotoxic heart, and liver disease, and osteoporosis. Myasthenia gravis existing in association with autoimmune thyroid disease such as Graves' disease occurs in only about 0.2% of cases. Data from an epidemiologic study in Japan showed that the association of the two conditions is very uncommon, at only 0.14% of cases (3). Currently, there are also limited data on the outcomes of both autoimmune diseases when different treatment modalities are employed.

Case presentation

The patient is a 27-year-old man who presented with a 2-month history of ptosis of both eyes, and diplopia occurring mostly at night with associated fluctuating weakness of the right arm. He also had episodes of easy fatigability, palpitations, and heat intolerance. Incidentally, the patient was found to have an anterior neck mass as well. On physical exam, instead of exophthalmos which is the usual finding in patients with Graves' disease, the patient had ptosis, more apparent on the right eye (Fig. 1). The patient had an enlarged thyroid gland with no bruit. He had a regular heart rate with no dermopathy.

Investigation

The diagnosis of myasthenia gravis was established based on the presence of bilateral ptosis with weakness of the intraocular muscles, abnormal fatigability, and a repetitive nerve stimulation study result indicated the presence of a neuromuscular junction disease. Repetitive nerve stimulation at 2 Hz stimulating the facial nerve with recording at the nasalis muscle showed significant compound muscle action potential (CMAP) amplitude decrement at baseline and post-exercise. These findings are sufficient to establish the diagnosis of myasthenia gravis in this case because the clinical features of ocular muscle weakness and limb muscle weakness directly point to the diagnosis of myasthenia gravis, appropriately fitting

Figure 1
Ptosis, which is a key clinical presentation of myasthenia gravis, more pronounced on the right eye.

the criteria set by the Myasthenia Gravis Foundation of America (MGFA) for clinical classification (1). More than half of patients with mainly ocular myasthenia gravis and those with concurrent myasthenia gravis and Graves' disease may have undetectable acetylcholine receptor (AchR) autoantibodies, therefore, the absence of such autoantibodies is not a basis for ruling out the disease especially in patients where in the clinical presentation is compatible with myasthenia gravis (4). No thymic involvement of myasthenia gravis was noted for this patient.

This patient had elevated thyroid function tests, free triiodothyronine (FT3) 11.85 pmol/L (2.89–4.88), free thyroxine (FT4) 26.02 pmol/L (9.01–19.05), with a suppressed thyroid-stimulating hormone (TSH) 0.0068 uIU/mL (0.35–4.94). Thyroid ultrasound revealed thyromegaly with diffused parenchymal disease, with the right lobe measuring 6.04 × 2.19 × 2.25 cm^3 and the left lobe measuring 6.24 × 2.32 × 1.92 cm^3. A thyroid scintigraphy with the radioisotope iodine-131 (I-131) was done which demonstrated an enlarged thyroid gland with increased uptake function, 39.1 % and 72.4% uptake at 2 and 24 h, respectively (Fig. 2). Thyroid receptor antibody (TRAb) was also positive at 4.1 U/L (> 1.5 U/L is considered positive), consistent with the diagnosis of Graves' disease. Anti- thyroid peroxidase (TPO) antibody, which is a marker in autoimmune thyroid disease, was 1900 IU/mL (normal value < 100 IU/mL).

Treatment

Patient was started on pyridostigmine 60 mg thrice a day, which he took with good compliance for the past 1 year

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Figure 2
Thyroid scintigraphy with I-131, which demonstrated an enlarged thyroid gland with increased uptake function, 39.1% and 72.4% uptake at 2 and 24 h respectively, typical of Graves' disease.

and 10 months. There was a decrease in the frequency of the ocular muscle weakness, but there was still persistence of this bothersome symptom. The patient still complained of episodes of right arm weakness, particularly at the end of the day after work. Methimazole was also initiated at 15 mg per day, which was titrated until his maintenance dose of 5 mg per day. Despite taking methimazole for more than a year, the patient still had symptoms of palpitations and heat intolerance. Prior to the radioactive iodine therapy, the thyroid function tests showed the following values: FT3 6.85 pmol/L (2.89–4.88), FT4 18.12 pmol/L (9.01–19.05), TSH 2.196 uIU/mL (0.35–4.94). Methimazole alone did not lead to remission of hyperthyroidism. Radioactive iodine therapy at 14.9 mci was instituted for the definitive management of Graves' disease.

Outcome and follow-up

After radioactive iodine was initiated, as early as within 4 weeks, the patient reported abatement of the symptoms of palpitations and heat intolerance, as well as improvement in the manifestations of myasthenia gravis, with ptosis and diplopia hardly occurring after the administration of radioactive iodine. The patient also reported being free from symptoms of myasthenia gravis for at least 2 weeks, amidst a reduction in the dose and tapering off of pyridostigmine based on a symptom diary and medication intake diary. The right arm weakness also resolved. Monitoring for signs and symptoms of myasthenia gravis is sufficient in assessing disease progression and remission and yields the greatest clinical utility and impact.

The goal of radioactive iodine therapy was also attained – the thyroid gland was ablated and biochemical hypothyroidism was documented through repeat thyroid function tests after radioactive iodine therapy, which revealed the following: FT3 1.00 pg/mL (1.40–4.20), FT4 0.64 ng/dL (0.80–2.24) and TSH 9.98 uIU/mL (0.40–5.50). Though he was started on levothyroxine replacement therapy for the biochemical hypothyroidism, the patient's risk for developing complications of thyrotoxicosis such as thyrotoxic heart and liver disease, osteoporosis has been totally eliminated. More than 1 year after RAI, at currently 17 months after the therapy, the patient also reported a better quality of life and increased functionality because of the favorable therapeutic response to RAI of both hyperthyroidism and myasthenia gravis.

Discussion

This double trouble comes with a unique clinical presentation. In the uncommon association of myasthenia gravis with autoimmune thyroid disease, the manifestations of myasthenia gravis are usually limited to the ocular muscles, and the disease is usually mild with a lower frequency of thymic involvement (4). Ptosis, a prominent clinical manifestation in the patient, is not a feature of Graves' disease, rather, it is pathognomonic of myasthenia gravis, seen in a vast majority of cases. The presence of fluctuating neuromuscular weakness in a hyperthyroid patient suggests the existence of concurrent myasthenia gravis (5), as was seen in our patient. One phenomenon that could account for this rare association is the immunological or cross-reactivity against epitopes or auto-antigens shared by the thyroid and eye muscles. Thyroid disorders may co-exist with myasthenia gravis due to shared autoimmunity, and there is a need to evaluate patients with myasthenia gravis for the presence of thyroid dysfunction. The common genetic lineage of Graves' disease and myasthenia gravis with alterations in the same set of genes leads to susceptibility to both autoimmune conditions (6).

Since the clinical presentation of myasthenia gravis associated with autoimmune thyroid disease is usually mild and predominantly ocular, the use of an acetylcholinesterase inhibitor such as pyridostigmine is a viable option in controlling the symptoms and inducing the remission of myasthenia gravis. Acetylcholinesterase

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inhibitors, which are primarily used in the treatment of myasthenia gravis, lengthen the time that acetylcholine is viable in the neuromuscular junction. Predominantly ocular myasthenia gravis is associated with higher remission rates (1). Our patient was treated with only pyridostigmine for the myasthenia gravis. Thymectomy, which leads to the obliteration of the source of autoantigens, and elimination of the B cell reservoir producing autoantigens, was offered as an option, rather than as an emergent procedure because of the presence of mild symptoms, and the good outcomes associated with medical management alone. It still remains a treatment option for myasthenia gravis but less optimal outcomes with thymectomy have been demonstrated in patients whose disease onset was before 50 years old such as that of our patient (1).

Radioactive iodine therapy, which involves the use of ^{131}I beta-radiation to destroy functioning thyroid tissue to halt the overproduction of thyroid hormones, is the standard of care for the cure of Graves' disease. The goal of radioactive iodine is to administer an optimal dose of I-131 to render the patient euthyroid or hypothyroid to prevent the occurrence of complications of Graves' disease such as thyrotoxic heart disease, arrhythmias, liver disease, and osteoporosis. A high activity at 14.9 mci, the dose given to our patient, is recommended for a thyroid gland weight of between 40 and 80 g (7). Definitive treatment of hyperthyroidism is necessary especially for males in which hyperthyroidism is unlikely to respond solely to the use of anti-thyroid drugs such as methimazole. Males have poorer outcomes in Graves' disease as demonstrated in a retrospective study, in which medical treatment alone resulted in a remission rate of only 19.6% in males, compared to 40% for females (8). Spontaneous remission of Graves' disease in males is also unlikely, and hyperthyroidism in males usually follows a progressive clinical course without definitive treatment such as radioactive iodine. This strongly suggests that the improvement in the symptoms of Graves' disease in our patient was brought about by the radioactive iodine therapy and was not simply a result of a spontaneous remission. Radioactive iodine enabled control of the autoimmune process, which had a ripple effect in terms of controlling the progression of his myasthenia gravis as well.

Though thyroidectomy is also a therapeutic option that could lead to the remission of Graves' disease, thyroid surgery is also associated with risks such as recurrent laryngeal nerve injury and post-operative hypoparathyroidism. There is also a risk of myasthenic crisis during total thyroidectomy. For patients with both Graves' disease and myasthenia gravis, there is a paucity of data suggesting that total thyroidectomy as definitive management would result in better clinical outcomes (5). Radioactive iodine, on the other hand, is a non-invasive therapeutic option with a good success rate. It is relatively inexpensive and has a good safety profile.

Because of the rarity of the co-existence of both diseases, there has been variation in the outcome of myasthenia gravis documented after radioactive iodine therapy for Graves' disease. There is one documented case of transient worsening of the symptoms of myasthenia gravis after radioactive iodine therapy for Graves' disease was initiated; likely due to the persistence of high levels of AchRAb and TRAb. This phenomenon was also seen in a patient with thymic involvement in myasthenia gravis, which was not seen in our patient's case. When the myasthenia gravis was treated with pyridostigmine and thymectomy and the titers of AchRAb and TRAb substantially decreased, remission was achieved for both diseases, indicating that the aggravation of the symptoms of the myasthenia gravis is only temporary and should not be a contraindication to radioactive iodine therapy (3). On the other hand, in one case report that featured a 53-year-old man with both myasthenia gravis and Graves' disease, the administration of radioactive iodine resulted in the decrease in the clinical symptoms of myasthenia gravis in that patient (9). We opted to employ the optimal first-line treatment of Graves' disease for this patient to achieve effective control of this disease; which helps in improving the condition of his myasthenia gravis as well.

Two distinct autoimmune conditions experienced a markedly improved clinical course with the institution of definitive treatment for Graves' disease, which is radioactive iodine therapy in this patient's case. The long follow-up at 17 months done for this patient adequately demonstrates that the favorable response to radioactive iodine therapy of the patient is durable. Both diseases reflected sustainable benefits from the non-invasive, relatively low-cost therapy given in this case. Radioactive iodine treatment leads to a significant reduction of thyroid tissue; thereby halting the production of thyroid antigens that fuel autoimmunity. The lymphocytes and B cells are irradiated in the thyroid gland, causing destruction of antigen. This phenomenon also leads to a decreased production of auto-antibodies by the peripheral immune cells (10). Since cross-reactivity between auto-antigens of the thyroid and eye muscles has been demonstrated, the attenuation of thyroid autoimmunity can have a beneficial spill-over effect on the eye muscles.

With the right treatment armamentarium, double trouble can actually lead to a double victory.

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Patient's perspective

I felt markedly better after the radioactive iodine therapy. I had no more palpitations and I already seldom experience having drooping eyelids and double vision. I do not have episodes of weakness of the right arm anymore. My symptoms were addressed without surgery and I am able to function well as a driver and provide for my family. I am able to take care of my children as well.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

A written informed consent has been obtained from the patient featured in this research work.

Author contribution statement

All authors contributed to the management and documentation of this case. A E A is the primary physician of the patient and initiated the writing of this report. M B S is the consultant adviser of this case and took an active role in the preparation and revision of this manuscript. K J A is the neurologist who co-managed this case, who shared her valuable inputs for this report.

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