CASO CLÍNICO/CASE REPORT

Simultaneous Diagnosis of Ocular Myasthenia *Gravis* and Graves' Disease in an Adolescent Female: The Need for Thyroid Evaluation in Myasthenia *Gravis*

Diagnóstico Simultâneo de Miastenia *Gravis* Ocular e Doença de Graves numa Adolescente: A Necessidade de Avaliação da Função Tiroideia na Miastenia *Gravis*

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Abstract

The association of ocular myasthenia *gravis* and Graves' disease is an uncommon occurrence, but well recognized. It is best described in adults, with only a few reports being described in children. We report the case of a 13-year-old girl who presented a history of general fatigue, binocular diplopia, and bilateral ptosis accentuated on the right side that affected her predominantly in the evening, with about a month and a half of evolution. The symptoms were worsening and ocular myasthenia gravis was confirmed by the detection of high titers of anti-acethylcholine receptor antibodies in serum. Graves' disease was diagnosed at the same time by the detection of thyrotoxicosis biochemistry, elevated anti-thyrotropin receptor antibodies in serum and homogenous uptake of radioactive iodine in the thyroid scintigraphy. Treatment with pyridostigmine and methimazole resulted in clinical improvement. Simultaneous diagnosis of myasthenia *gravis* and Graves disease is uncommon in children and adolescents and its pathophysiological significance remains unclear. Nevertheless, our case highlights the importance of early diagnosis of these disorders, since, if left untreated, both may have negative functional repercussions.

Resumo

A associação de miastenia *gravis* ocular e doença de Graves é uma ocorrência incomum, mas bem reconhecida. Encontra-se descrita essencialmente em adultos, existindo apenas alguns relatos em crianças. Descrevemos o caso de uma menina de 13 anos que apresentava história de fadiga generalizada, diplopia binocular e ptose palpebral bilateral, mais acentuada à direita e de agravamento vespertino, com cerca de um mês e meio de evolução. Os sintomas foram piorando e a miastenia *gravis* ocular foi confirmada pela deteção de um elevado título de anticorpos anti-recetor de acetilcolina no soro. A doença de Graves foi diagnosticada em simultâneo, por estudo analítico a revelar tirotoxicose, com elevação do título de anticorpos anti-recetor da tirotropina no soro e captação homogénea de iodo radioativo na cintigrafia da tiróide. O tratamento com piridostigmina e metimazol resultou em melhoria clínica. O diagnóstico simultâneo de miastenia *gravis* e doença de Graves é incomum em crianças e adolescentes e o seu significado fisiopatológico permanece incerto. No entanto, o nosso caso reforça a importância do diagnóstico precoce desses distúrbios, pois, se não tratados, ambos podem ter repercussões funcionais negativas.

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Introduction

Graves' disease (GD) is an autoimmune disorder (AD) in which thyrotropin hormone (TSH) receptor antibodies (TRAbs) activate TSH receptors, causing hyperthyroidism, goiter ophthalmopathy, and, less commonly, pretibial myxedema. It is uncommon in children, with an overall incidence of 0.1–3 per 100 000 individuals. It accounts for 10% - 15% of thyroid disorders in patients under 18 years of age, being the main cause of hyperthyroidism. Although it may occur at any age during childhood, it is more likely to occur between the ages of 10-15 years, being females more affected than males (female to male preponderance is about 4:1 through adolescence, being slightly lower during childhood).[1-4]

Myasthenia *gravis* (MG) is a rare acquired chronic autoimmune disorder with an estimated incidence of 1 to 5 cases per million person-years, in paediatric ages.[5] It is caused by an antibody-mediated attack that targets acetylcholine receptors in the postsynaptic membrane of the neuromuscular junction, resulting in decreased available acethylcholine receptors (AChRs).[6] When present before the age of 19 years old, it is designated juvenile MG, being 10% - 15% of the ocular MG (OMG) subtype, with a few patients progressing to a generalized form of the disease (GMG) over time.[5]

Autoimmune thyroid disorders (ATD) frequently occur in MG, with a frequency of about 10%, whereas MG is reported in only 0.2% of patients with ATD, the most common being GD.[7] Here, we present the case of a 13-year-old girl who was found to have OMG with concomitant evidence of GD. To date, the association of these two disorders in childhood has been described in only a few cases.

Case Report

A 13-year-old Caucasian girl was admitted at the emergency department complaining of progressive bilateral ptosis (of right predominance) and generalized fatigue, getting worse at the end of the day, with about one and a half months of evolution. She also presented complaints of binocular diplopia and a feeling of fatigue during moderate-intensity physical activities in the last few weeks. A recent worsening of the symptoms was reported. She had her menarche at the age of 10 and has having regular menses. Her medical history was remarkable for myopia, astigmatism, attention-deficit/hyperactivity disorder and allergic rhinitis. Current medications included methylphenidate and ebastine. Family history was unremarkable.

On the examination, she was afebrile, the blood pressure was 118/71 mmHg and the heart rate was 103 beats/min. She weighted 56.9 kg (standard deviation score [SDS] -1.47), had a height of 152 cm (SDS 0.53) and the body mass index was 24.6 kg/m^2 (+1.31). Chest, heart and abdomen evaluations were normal. Thyroid examination revealed a diffuse non-tender goiter. She presented clear and fluent speech during neurological examination. Bilateral ptosis (with right predominance) was observed and, additionally, the ocular movements examination revealed an incomplete elevation and adduction of the right eye, but both direct and consensual pupillary reflexes were present (Fig.1). The following maneuvers were performed, to evoke fatigability of ocular deficits: sustained upgaze during 60 seconds, sustained lateral upgaze during 60 seconds and manual elevation of the more ptotic lid, leading to worsening of contralateral ptosis. No clear facial asymmetry was noticed, and the examination of the last cranial nerves was normal. Counting aloud (1 to 50) did not result in dyspnoea or dysarthria. No upper or lower extremities weakness was observed when patient was asked to sustain elevation of arms and legs during 60 seconds. Deep

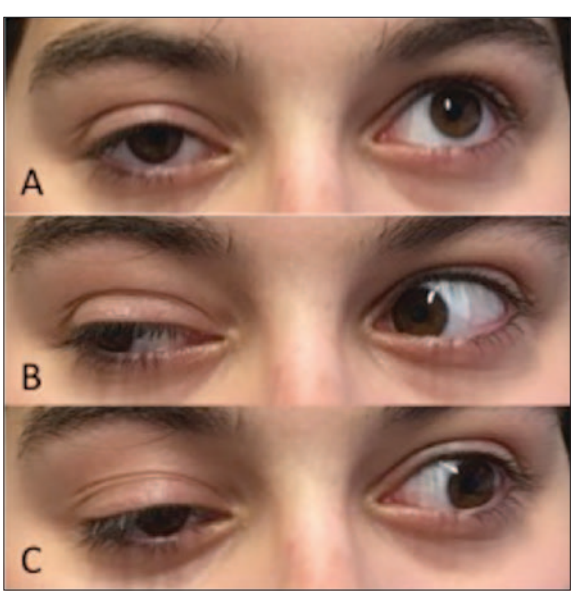

Figure 1. Clinically relevant changes in eye movements. A: evident right palpebral ptosis (which is maintained in all positions of the gaze) and right superior rectus muscle paresis, contributing to a vertical diplopia referred by the patient; B: no abnormalities involving the right lateral rectus muscle seemed to be identified; C: evident limitation in the adduction of the right eye (medial rectus muscle), also conditioning a horizontal binocular diplopia.

tendon reflexes were normal. The patient did not present any change in the kinetic coordination tests. The ice pack test was inconclusive.

She was then evaluated by an Ophthalmologist, who documented that she did not present conjunctiva hyperaemia or proptosis, but exophoria was observed and compensated in binocularity. The visual acuity was 20/20 in both eyes. There was no evidence of papilledema in the funduscopic exam. The visual axes were not obstructed by the ptosis.

Haematological and other biochemical investigations were all normal. Anti-AChR antibodies (Ab) levels were raised at 1.5 nmol/L (< 0.25). Thyroid function tests were consistent with a hyperfunctioning thyroid state: thyrotropin (TSH) < 0.004 mU/L (0.7-4.17), free thyroxine 2.3 ng/dL (0.89-1.37), free triiodothyronine 8.6 pg/mL (2.5-3.95); anti-thyroid autoantibodies were positive: thyroid peroxidase antibodies (anti-TPO) 372 UI/mL (< 35), thyroglobulin antibodies (anti-Tg) 190.8 UI/mL (<60 UI/mL), and TRAbs 3.3 U/L (< 1).

No lesions were detected in brain computed tomography (CT), also in magnetic resonance imaging and the electromyography was normal (it included nerve conduction velocities and repetitive nerve stimulation; despite being tried, the patient did not tolerate the single fibre test, which was then described as inconclusive). Thyroid ultrasonography showed a diffuse enlargement of the thyroid gland, with heterogeneous echo pattern and no visible nodules. A thyroid nuclear scan revealed a diffuse homogenous uptake of radioactive iodine, suggestive of GD. Based on the previous findings, namely the clinical presentation, positive anti-AChR Ab and TRAbs, a diagnosis of simultaneous OMG and GD was made. She was given pyridostigmine bromide (120 mg per day) and methimazole (10 mg per day), starting afterwards on Pneumology surveillance. A CT scan of the thorax revealed the absence of thymoma and pulmonary function tests were normal. By the eighth month of follow-up, her pyridostigmine dose was increased to 240 mg/daily, due to the persistence of generalized fatigue, although there was a progressive improvement of the ptosis and of the pattern of ocular movements, comparing with the initial evaluation (Fig. 1). Despite fatigue complaints (eminently subjective), with no additional motor deficits identified, it was decided to maintain symptomatic therapy alone, at this initial stage, without proceeding with immunosuppression or immunomodulation. An euthyroid state was reached under methimazole (10 mg/day). At the present

Table 1. Summary of cases of co-existing myasthenia *gravis* and Graves' disease in children reported in literature.

Case	Sex	1st disease identified	Age at 1st diagnosis	Clinical features	Treatment	Comments
Cohen JS, 1973[9]	M	GD	14 y/o	Hot flashes, palpitations, diplopia, proptosis, ptosis, generalized weakness	Methimazole RAI Pyridostigmine Prednisone	MG diagnosis: 20 y/o
Kobayashi T *et al*, 1997[10]	F	MG	14 y/o	Ptosis, diplopia dysphagia, palpitations, headache, hand tremor	Ambenonium Thymectomy Methimazole	GD diagnosed at 20 y/o OAD: polymyositis
Koves H *et al*, 2009[11]	M	Concurrent diagnosis	10 y/o	Xerophthalmia, ptosis, ocular fatigability, diplopia, heat intolerance, tremor	Pyridostigmine Carbimazole	
Sarkhy *et al*, 2009[12]	F	GD	13 y/o	Proptosis, jaudince. thyrotoxicosis, dysarthria, PMW, slurred speech	RAI Corticotherapy IVIg Azathioprine	OAD: Autoimmune hepatitis
Kubiszewska J *et al*, 2014[13]	F	GD	14 y/o	Generalized fatigue, weight loss, facial weakness, ophthalmoplegia, diplopia, dysphagia	Methimazol Pyridostygmine IVIg Prednisone Thymectomy	
Lindsay M *et al*, 2018[14]	M	MG	17 y/o	Ptosis, proptosis	Pyridostigmine Methimazole	Seronegative MG
Cruz MC *et al*, 2018[15]	F	GD	12 y/o	Weight loss, PMW, bulbar symptoms, thymoma	RAI Prednisone Thymectomy	MG diagnosed at 19 y/o OAD: dermatomyositis

GD, Graves' disease; MG, myasthenia *gravis*; OAD: other autoimmune disease; PMW, proximal muscle weakness; RAI, radioactive iodine; IVIg, intravenous immunoglobulin; y/o, years old; M, male; F, female

moment, she remains being monitored by Pneumology, Neurology and Endocrinology.

Discussion

ATD are seen in both OMG and GMG, the most common being GD.[7] The association of GD with MG was firstly described in 1908.[8] Since then, some reports have been published in the literature, mostly as single case reports. We found seven cases of co-existing MG and GD during childhood, in medical literature written in English and Portuguese (Table 1).[9-15] In two cases, the diagnosis of one of the autoimmune diseases was made in adolescence, while the other was only identified in adulthood.

In the presence of ATD, MG is associated with a younger age of onset, mild clinical expression with preferential ocular involvement, lower/absent levels of anti-AChRs and lower incidence of thymic disorders.[7,16] However, Kubiszewska et al did not find a significant relationship between GD and OMG.[16] The association of these two disorders is consistent with a previous report revealing a higher frequency of thyroid autoantibodies among patients with MG: approximately 40% in OMG, and a lower frequency in generalized MG, of approximately 12%.[17]

Extraocular muscles involvement can be observed in both diseases. Graves's ophthalmopathy (GO) typically presents itself with persistent symptoms of exophthalmos, eyelid retraction, chemosis, periorbital oedema and ophthalmoplegia.[18] Otherwise, in respect to OMG, the symptoms are fluctuant and lead to ptosis, fatigability and ophthalmoparesis.[6] There seems to be a higher prevalence of OMG in patients with GD, which can be easily missed and for that reason it requires a careful diagnostic evaluation.[7] Diplopia may be present in both diseases and the presence of exophthalmos may complicate the detection of ptosis.[18] Our patient's ocular symptoms were much more likely to be caused by OMG than by GD, since there was a clear notion of fatigability and fluctuation of deficits.

In the majority of patients, clinical signs of hyperthyroidism appear previously or during the onset of MG symptoms.[16,19] In this case, with the exception of fatigue, which may also occur in MG, there were no obvious clinical signs of hyperthyroidism, which, combined with the lack of research for thyroid disorder, could have resulted in the patient not being diagnosed or being misdiagnosed. Additionally, the clinical picture, characterized by the fluctuation of neurological symptoms and an elevated anti-AChR antibodies titres led to the diagnosis of OMG. Regarding OMG, the sensitivity of ice pack test seems to be high in the presence of ptosis, however it was inconclusive in our patient.[20]

The presence of anti-AChR antibodies gives the laboratory confirmation of MG, being highly specific. They are present in approximately 55% of those with OMG, with a lower sensitivity, when compared to GMG.[6,19,21] Electrophysiological tests allow the confirmation of the diagnosis. They are not specific for MG, but for disorders of neuromuscular transmission, in general. Single-fibre electromyography (SFEMG) has a higher sensitivity for those with OMG, comparing to repetitive nerve stimulation (RNS).[6,21] In our patient, RNS was negative and SFEMG inconclusive. At paediatric age, results of this type are often observed, despite clinical manifestations and serological confirmation of the diagnosis. The technical conditions in which the neurophysiological study is performed are crucial for the sensitivity of the method and children/adolescents may find it difficult to collaborate in its execution, especially due to the painful nature associated with the stimulus (which makes even more difficult the repetition of an inconclusive essay). Moreover, in this particular case, a very restricted involvement of some orbital muscles was observed, which would necessarily make it difficult to perform a study directed to their contractile function (and would naturally reduce the sensitivity of the neurophysiological approach).

The exact pathophysiology of GD and MG is complex and it is not yet fully understood. The autoimmune overlap between them reflects similar pathogenic mechanisms. The existence of an immunological cross-reaction against common autoimmune targets in the eye muscles was hypothesized in patients with OMG and GD. Both disorders have a higher frequency of human leukocyte antigens B8 and DR3. Cytotoxic T-lymphocyte antigen-4 (CTLA4) and protein tyrosine phosphatase non-receptor 22 (*PTPN22*) genes polymorphisms are associated with both MG and ATD. Interferon-1-based therapies can trigger the development of MG and ATD. T-lymphocyte-mediated cytokine production seems to have a pathogenic role in both diseases.[5,7,19] Understanding these mechanisms could open new opportunities for the development of immunosuppressive agents that act on both diseases.

Rituximab is a chimeric murine/human anti-CD20 monoclonal antibody that targets B lymphocytes and has been used "off-label" for various auto-immune diseases (AID), namely GD and MG. Thus, it may be a pharmacological hypothesis to consider when these two clinical entities coexist. However, randomized, controlled clinical studies are needed to evaluate its efficacy and safety.[22,3] There are two Phase 2 clinical trials registered at ClinicalTrials.gov for MG and GD, with CFZ533, a novel anti-CD40 monoclonal antibody that is being developed for AID, which may have a role when a clinical picture such as described above is present.[24] A positive relationship between the clinical activities of these two disorders has been previously reported. Thus, an improvement in MG is observed when GD gets better.[16]

In conclusion, when both clinical entities are present, their diagnosis is difficult. This clinical case highlights the importance of recognizing a possible coexistence of both GD and MG and thereby avoiding possible comorbidities/complications. For this reason, we believe that thyroid function/autoimmunity should be evaluated on a regular basis, when MG is diagnosed. Moreover, the possibility of sharing the same pathogenic mechanisms points new trends in the future research of more useful therapies. ■

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