Arq Neuropsiquiatr 2008;66(2-A):251-253

# MYASTHENIA GRAVIS AND MULTIPLE SCLEROSIS

## An uncommon presentation

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Myasthenia gravis (MG) is an autoimmune disease that compromises neuromuscular transmission and is mediated by autoantibodies against acetylcholine receptors on the postsynaptic membrane[1]. In its usual form it leads to symptoms of decreased muscle strength and fatigue[1]. Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system that shows a wide range of clinical features and a variable natural history[2]. There is some evidence that patients with MG or MS have a higher risk of developing autoantibodies and other neuroimmune disorders than normal controls[3,4].

An autoimmune pathogenesis is implicated in both MG and MS, but the coexistence of the two disorders has rarely been documented, and for this reason we report this case[4].

**CASE**

A 28-year-old woman presented with diplopia, dysphagia and mild limitation of ocular movements, with progressive palpebral ptosis and weakness, which changed in intensity from day to day and during the day according to the patient's physical activity.

Physical examination did not reveal any abnormalities. On neurological examination she was found to have asymmetrical palpebral ptosis (left>right); symmetrical muscle weakness (grade 4 on the MRC scale) in the proximal upper and lower limbs; and deep tendon reflexes. Gait and all sensory examinations were normal.

The investigation yielded the following results: (1) positive anti-acetylcholine receptor antibody test (14.91 nmol/L; normal < 0.20 nmol/L); (2) normal needle electromyography and nerve conduction studies; (3) repetitive stimulation of the facial, spinal accessory and ulnar nerves at 3 Hz with a decrement of more than 10% in compound muscle action potential amplitude (Fig 1); and (4) improvement of symptoms after treatment with pyridostigmine (180 mg daily). Chest computed tomography scan was normal.

A diagnosis of MG was made, and the patient showed an improvement in symptoms after she started to receive prednisone and pyridostigmine. Prednisone was discontinued after one year and was followed by oral administration of azathioprine (100 mg/day), with an improvement in palpebral ptosis and muscle strength (grade 5 on the MRC scale).

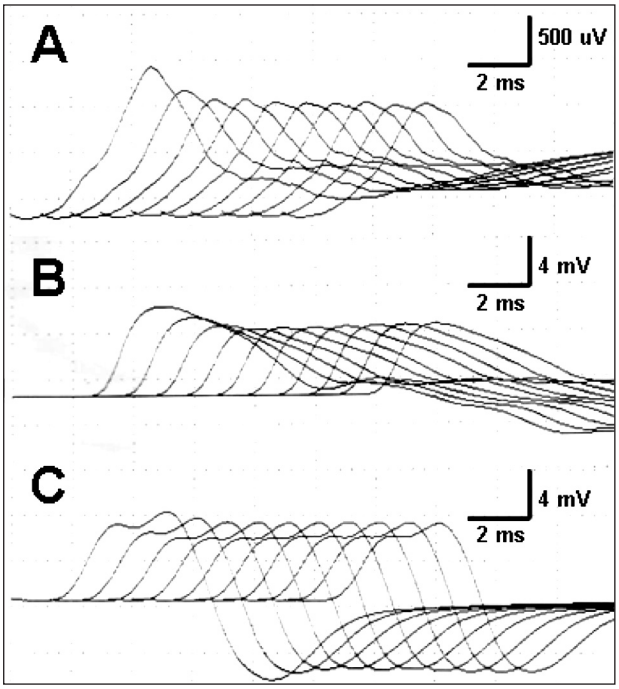


*Fig 1. Repetitive stimulation at 3 Hz showing a 26.3% amplitude decrement in compound muscle action potential in the facial nerve recorded from the orbicularis oculi muscle (A), a 24.4% decrement in the spinal accessory nerve recorded from the trapezius muscle (B), and a 12.3% decrement in the ulnar nerve recorded from the abductor digiti quinti muscle (C).*

When she was 32 years old and still on azathioprine treatment, the patient developed a sudden weakness in her left lower limb and was treated with prednisone (60 mg/day). After this new neurological manifestation suggestive of MS, the patient was submitted to brain magnetic resonance imaging (MRI), which revealed multiple areas of high signal on FLAIR and T2-weighted images in the periventricular and subcortical white matter of the brain hemispheres (Fig 2A).

**MIASTENIA GRAVIS E ESCLEROSE MÚLTIPLA: UMA APRESENTAÇÃO INCOMUM**

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Received 6 September 2007, received in final form 2 January 2008. Accepted 16 February 2008.

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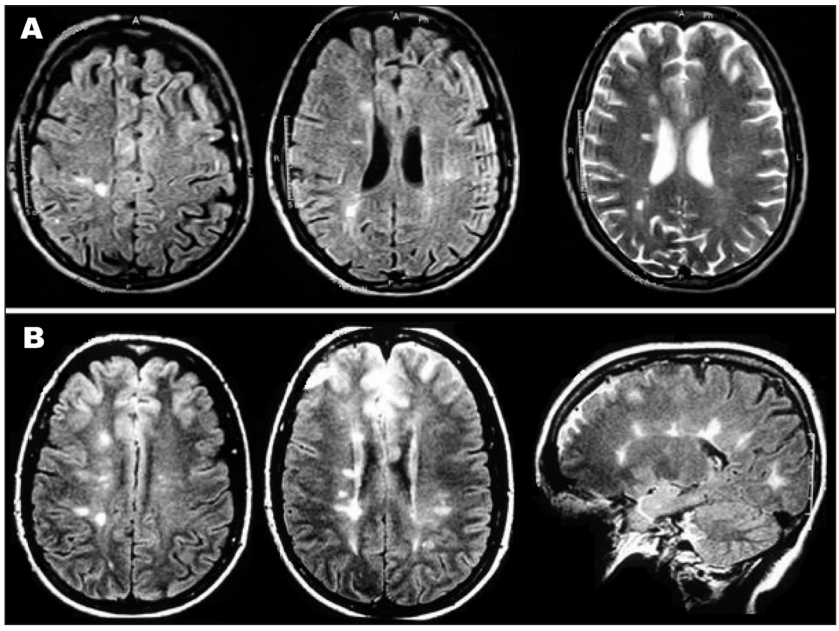


*Fig 2. (A) First relapse (2003): multiple areas of high signal on axial FLAIR and T2-weighted images in the periventricular and subcortical white matter of the brain hemispheres. (B) Second relapse (2006): high signal on axial and sagittal FLAIR images in some periventricular and subcortical areas of white matter of the brain hemispheres.*

Three years later, she presented with a sudden episode of deafness, paresthesia and weakness in her left lower limb. Neurological examination showed nystagmus; left facial paresis; bilateral hearing loss; muscle strength grade 4 (MRC scale) in the left lower limb; bilateral increased deep tendon reflexes in the lower limbs; left Babinski sign; gait ataxia; and impaired pain, temperature, pinprick and light touch sensory examinations in the left lower limb. Vibration sensibility and joint position sense also revealed impairment in the left lower limb.

MRI showed new areas of high signal on FLAIR and low signal on T1-weighted images in the periventricular and subcortical white matter of the brain hemispheres as well as in the cerebellum (Fig 2B).

Hematological tests, biochemistry screening and thyroid function were normal, and serological tests for HIV and HTLV were negative. Anti-nuclear antibody test (1:640 with diffuse pattern; normal <1:40) and anti-SSB/La (13.8 U/mL; normal <10 U/mL) were positive, but the other serum antibody tests (anti-RNP, Sm and SSA/Ro) were negative. Cerebrospinal fluid analysis was normal with a normal electrophoretic protein pattern.

The patient was diagnosed as having had another MS relapse (her disability EDSS score was 5.5) combined with MG. Intravenous methylprednisolone pulse therapy was started, with substantial improvement in muscle strength in the left lower limb. Currently the patient is receiving azathioprine, and her disability EDSS score is 4.5 after five years of follow-up.

All studies were carried out following informed consent.

## DISCUSSION

MG is a rare disease with a prevalence ranging between 0.5 and 15.0 cases per 100000 inhabitants and an incidence of 0.4 to 1.1 cases per 100000 inhabitants[1,5]. In Brazil there are probably 15500 persons affected by MG[6]. In a number of studies of MS, a variation in prevalence and clinical pattern with geographical location was observed, probably related to ethnic and environmental factors[2,7]. With 15.0 cases of MS per 100000 inhabitants, Brazil is considered to have a low prevalence, particularly compared with other countries at similar latitudes[7]. The probability of the same patient developing both of these disorders is extremely low, although it should be remembered that these patients are more likely to develop other autoimmune diseases than patients without immune-mediated disorders[8].

However, the combination of these two diseases occurs at rates higher than those expected by random association and appears to be more common than estimated. An epidemiological survey in Finland found that two persons in a population of 1.5 million had combined MG and MS. As the expected combined prevalence was 3.6 cases per 100 million people, the prevalence identified in the study was 37 times greater than that expected[3]. A similar study in Canada found a significantly higher prevalence than that predicted by estimates of the prevalence of this combination of disorders[4].

This nonrandom association of MG and MS in patients could support the hypothesis of an immunological mechanism of pathogenesis common to both disorders[4,9]. The Finnish study referred to above speculated that a similar immunogenetic background predisposes to susceptibility to these two disorders but that unknown genetic factors and different triggering factors result in two different clinical diseases[3,9]. The same might be said of the increased occurrence of other autoimmune disorders such as systemic lupus erythematosus in patients with MG[8].

The clinical onset of MS can be observed before or after the development of MG, and the time to onset of this association can vary from 1 to 28 years[3,9]. The patients were young and predominantly female and appear to fit the typical demographic characteristics for both MS and the younger peak of the bimodal age distribution in MG, as in our case[4]. According to case reports, the clinical course of both MG and MS is mild in most patients with this combination of neuroimmunological disorders, but the onset of MG could cause an exacerbation of MS, whereas MG can be relatively unaffected by fluctuations in the clinical course of MS[3,4]. Neurologists must bear in mind that patients with MG who present with atypical clinical characteristics or evolution can have other associated autoimmune disorders, such as MS, and, as in our case, these patients should be submitted to others tests, such as brain imaging, for differential diagnosis.

Antinuclear antibodies (ANAs) occur more frequently in patients with MS or MG than in the general population, and their presence often causes uncertainty in the diagnosis of these two diseases[10-12]. ANAs usually occur in 20 to 30% of MS patients and can be observed in almost 40% of MG patients[11-13]. The high frequency of ANAs in MS and MG probably reflects ongoing systemic immune dysregulation[11-13].

The most recent descriptions of this association refer to the onset of MG in MS patients during immunomodulatory drug treatment[4,14,15]. The development of MG during interferon-β or glatiramer acetate treatment has two possible explanations: first, it may be a coincidental autoimmune disorder, as sporadically described in the literature; or, second, it may be triggered by the treatment with these drugs as a result of deviation of the immune response towards enhanced Th2 cell reactions[14,15].

The patients reported in the international literature in whom MG occurred before MS were not on immunosuppressive therapy at the onset of MS[4]. Azathioprine is often considered for the treatment of patients with MG and can be used for the management of MS. The development of central nervous system demyelinating diseases, such as acute myelitis or disseminated encephalomyelitis, after the start of MG treatment with azathioprine has been reported previously, supporting the possibility that immune modulating treatments may play a role in the immunological mechanism of pathogenesis of this combination[10]. However, the development of MS in a patient with MG during treatment with azathioprine has not been reported to date.

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