

Coexistence of myasthenia gravis and neuromyelitis optica spectrum disorder: case report in Colombia and literature review

Abstract

Myasthenia Gravis (MG) and Neuromyelitis Optica Spectrum Disorder (NMOSD) are antibody-mediated channelopathies caused by complex immunological mechanisms, which are thus associated with multiple autoimmune diseases. This paper describes the case of a Colombian male patient with a history of seropositive MG that required thymectomy. After four years, he had an Optic Neuritis event and 30 years later, due to suspected autoimmune comorbidities, further investigations were performed, confirming the coexistence of NMOSD with presence of Anti-Aquaporin 4 (AQP4) antibodies (Abs).

Several reports in the literature show that the coexistence of these two pathologies is more common than expected by chance. Few cases have been reported in Latin America, which makes this report meaningful. In contrast to our case, the literature shows a higher incidence among women, but, on the other hand, it is consistent with an onset with mild or moderate MG symptoms at the clinical presentation, most of which led to thymectomy, followed by manifestations of NMOSD. Timely diagnosis and the consequent therapeutic adjustment may have a significant impact on the disability of these patients. There is a need for more reports in order to extend the statistical information and to improve the characterization of these patients, primarily in our Latin American region.

Keywords: myasthenia gravis, neuromyelitis optica spectrum disorder, autoimmune diseases, antibody-mediated disease, case report

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Abbreviations: MG, myasthenia gravis; NMOSD, neuromyelitis optica spectrum disorder; CNS, central nervous system; AQP4, aquaporin 4; AChR, acetylcholine receptor; MUSK, muscle-specific kinase; Abs, antibodies; MRI, magnetic resonance image

Introduction

MG is an antibody-mediated autoimmune disease involving different components of the postsynaptic membrane of the neuromuscular junction, such as muscle-specific kinase (MUSK) and the acetylcholine receptor (AChR), the latter being present in 70-80% of the cases, with clinical manifestations of weakness and fluctuating muscle fatigue.¹

Its incidence and prevalence ranges from 0.8 to 1 and from 15 to 25 cases per 100,000 individuals, respectively, with a bimodal presentation of 20 to 40 years with female predominance, and 60 to 80 years, balanced between men and women.^{1,2} Patients with MG are associated with other autoimmune diseases between 5-30%, with predominance of thyroid diseases such as Graves' disease and exhibit a higher incidence of demyelinating diseases compared to the general population.^{3,4}

Neuromyelitis Optica (NMO) is a demyelinating disease of the Central Nervous System (CNS), mainly involving the optic nerve and spinal cord, mediated by antibodies targeted against the most abundant water channel protein in astrocytes, Aquaporin-4 (AQP4). These anti-AQP4 Abs, also called NMO IgG Abs, are used as a specific test for Neuromyelitis Optica Spectrum Disorders (NMOSD), with a specificity of 99-100% and a sensitivity of 58-91%, though detection rates vary among different laboratory tests, with patients within the NMOSD group being seronegative.^{5,6}

The prevalence of NMOSD ranges around 3.9 to 10 with an incidence of 0.07 to 0.73 per 100,000 individuals respectively; the difference between women and men is 8-9:1 (1). Higher associations with autoimmune diseases have been reported in seropositive NMOSD patients in up to 25-50% of cases (4), including Systemic Lupus Erythematosus (SLE), Sjögren's syndrome (SS), autoimmune thyroid diseases, and MG (5).

In this paper the case of a patient with a history of seropositive MG, coexistence of NMOSD and presence of anti-AQP4 Abs is reported. Additionally, the relevant literature is reviewed.

Case report

Male patient, born in Bogotá, Colombia, with no personal or family history of autoimmunity or any other clinically meaningful pathology. At 16 years of age, the patient presented with diplopia and fluctuating weakness in 4 limbs. Myasthenia Gravis is diagnosed by electrodiagnostic tests and positive anti-AChR Abs. Three years after diagnosis, he underwent thymectomy (no pathology report available). The patient exhibits adequate adherence and response to treatment with pyridostigmine, achieving recovery of prior performance status and physical activity.

At 20 years of age, the patient presents with an event of blurred vision and pain in the right eye, he is assessed in the emergency room where optic neuritis is diagnosed and managed with pulses of methylprednisolone. Thirty years later, he attended our Neurology service for a control visit with symptoms of MG controlled with pyridostigmine. The following positive findings on physical examination were collected: a 20/30 visual acuity score (left eye), seeing shadows (right eye), ipsilateral afferent pupillary defect, with normal Intraocular pressure measured by Ophthalmology and

evidence of disc pallor in the fundus of the right eye. There were no alterations in other cranial nerves, no alterations in strength or reflexes, normal sensitivity, with no evidence of fatigability or gait impairment. Additionally, there is evidence of changes in skin and skin appendages due to alopecia and madarosis. This, in association with the visual deficit derived from the optic neuritis event, makes the presence of autoimmune comorbidities suspicious, so further

investigations are undertaken (Table 1) and CNS MRI was performed without abnormal findings. Anti-AChR Abs and anti-AQP4 Abs are positive, thus confirming the coexistence of MG and NMOSD in this patient. Considering the above, it was decided to add azathioprine to medical management, which showed adequate response and so far, no new relapses have emerged.

Table 1 Serum paraclinical studies

Test	Result	Test	Result
HIV ELISA Test	Negative	Anti-dsDNA Antibodies	Negative
Glucose	Normal	Anti-Sm Antibodies	Negative
Potassium	Normal	Anti-RNP Antibodies	Negative
VDRL	Nonreactive	Rheumatoid factor	Negative
TSH	Normal	Anti-TPO Antibodies	Negative
Vitamin B12 levels	Normal	Anticardiolipin Antibodies	Negative
Folic Acid	Normal	Anti-Acetylcholine Receptor Antibodies	Positive
Complete Blood count	Normal	Creatinine	Negative
AQP4-IgG	Positive	PTH	Negative
Antiphospholipid Antibodies	Negative	Iron	Negative
Anti-nuclear Antibodies	Negative	Serum Protein	Negative
Anti-SSA	Negative	Peripheral Smear	Negative
Anti-SSB	Negative	Erythrocyte Sedimentation Rate	Negative

HIV, human immunodeficiency viruses; ELISA, enzyme-linked immuno sorbent assay; VDRL, venereal disease research laboratory; TSH, thyroid stimulating hormone; AQP4, Aquaporin 4; SSA, Anti-Sjögren's-syndrome-related antigen A; SSB, Anti-Sjögren's-syndrome-related antigen B; dsDNA double stranded deoxyribonucleic acid; Sm, Smith; RNP, ribonucleo protein; TPO, thyroid peroxidase; PTH, Parathyroid hormone

Literature review and discussion

The first case of NMO associated with autoimmune diseases was a woman with SLE in 1976. Since then, there have been reports

regarding various pathologies sharing such antibody-mediated pathogenesis, where MG has been described (Figure 1).⁵ Studies state that the number of cases of NMOSD and MG are 70 times higher than expected by chance.⁴

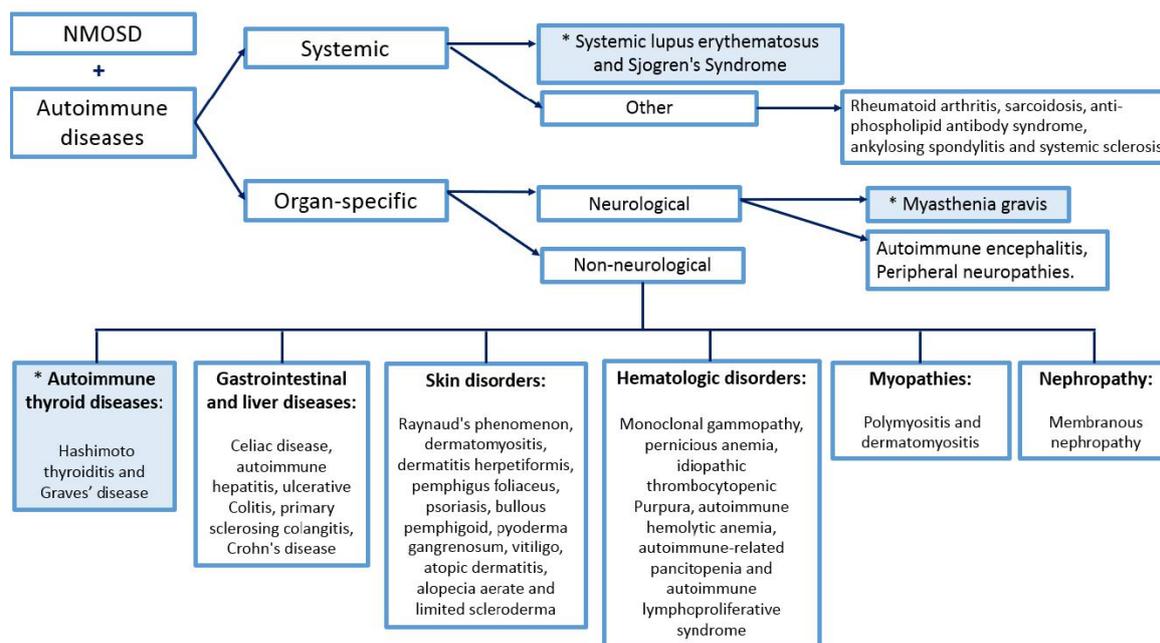


Figure 1 Coexistence of autoimmune diseases and NMOSD (* the most frequently reported diseases in each group). (Based on (5)).

Both diseases are channelopathies caused by complex immunological mechanisms, mediated by the presence of Th1, Th17 and Thf lymphocytes. These end up promoting the production and maturation of B cells, which in turn produce self-reactive antibodies, causing complement activation and tissue damage.¹

Most of the reports found in the literature describe Caucasian and Asian patients, with few reports in Latin America, mainly in Argentina and Brazil. Unlike the reported case, the literature describes female predominance. This has a biological rationale, apparently explained by inherent factors of gonadal hormones. Estrogens are believed to promote the presence of self-reactive B cells by acting on follicular T cell formation and contributing to antibody maturation and selection.¹

Our case was in line with the predominant pattern reported in the literature, where most patients had presented MG manifestations prior to NMOSD. This could be caused by a deviation of immunity towards the predominant T helper 2 cell pathways, secondary to immunomodulatory therapy, thus increasing susceptibility to antibody-mediated disorders. The above is evidenced not only in patients with MG on pharmacological therapy and who subsequently presented with NMO,⁷ (7), but also in cases of NMO managed with low-dose interferon-beta 1b or azathioprine who subsequently present MG.^{4,8}

Consistent with the literature, our patient had a history of thymectomy prior to developing NMOSD. A rationale for this pattern, is based on the suppressor T cells contained in the thymus, which are responsible for inhibiting the spontaneous reaction of B cells, thus preventing autoimmune diseases. After thymectomy, patients have been shown to have increasing numbers in circulating CD4+ and CD8+ T cells, serum IgG and IgM, increased anti-DNA Abs, ANA Abs, anti-cardiolipin Abs and a decrease in regulatory T cells, with reports not only from NMOSD but also from other pathologies such as SLE.⁹⁻¹¹

In addition, antibodies in NMO have been proposed to be a paraneoplastic response in MG patients with thymoma.⁷ Studies have proven that thymoma cells from patients with and without MG, express AQP4 in their cell membrane. Anti-AQP4 antibodies taken from the serum of patients with diagnosis of NMOSD bind to this site (12). In our case, there was no report from the Pathology Department available.

However, the coexistence of these two pathologies is evident in some cases where patients never underwent thymectomy.^{4-8,10,13,14} or presented NMO before having such surgical procedure done,⁴ suggesting that the thymus is not the only responsible factor.

Seropositive patients for both pathologies have an increased association (up to 38-75%) with other autoantibodies, mainly, but not limited to, antiphospholipid, anticardiolipin, antinuclear (ANA), anti SSA and SSB, single and double stranded DNA antibodies, and rheumatoid factor.⁵ This association is evidenced in many reviewed reports.^{4,14-18} However, our patient showed negative results for the other immunological profile tests.

In most reports, cases of MG were mild or moderate, like our patient, with adequate response to immunomodulatory therapy. However, there are case reports of severe MG with fatal outcomes. One of these cases was associated with complications of NMO⁴ and another was associated with complications of SLE as the immune-related pathology.¹⁸

There are reports of several patients with major neurological sequelae. In a multicenter study of 16 cases, 10 of them presented blindness or severe gait impairment, associated with the duration of disease and its late diagnosis.⁴. Our patient also presented with a major visual sequela at the time anti-AQP4 Abs were detected. This event had not been initially attributed to NMOSD, but upon diagnosis, immunomodulatory therapy was optimized, which is expected to decrease the relapse rate and long-term disability.

Conclusion

Publications in patients with coexistence of MG and NMOSD in Latin America are limited, which makes the description of this case meaningful, considering that its association is high and greater than expected by chance.

It is important for us to be familiar with its presentations, as well as with the increased risk of new autoimmune diseases. Suspected diagnosis, timely testing for antibodies and a complete immunological profile can change the treatment options and the long-term functional prognosis. There is a need for more reports in order to extend the statistical information and to improve the characterization of these patients, primarily in our Latin American region.

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Conflicts of interest

The authors declare no conflict of interests.

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