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CLINICAL CASES

Coexistence of neuromyelitis optica AQP4+, myasthenia gravis, and ulcerative colitis: a case report

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Abstract

Neuromyelitis optica (NMO), myasthenia gravis (MG), and ulcerative colitis (UC) are disorders in which various autoimmune pathophysiological mechanisms are involved, some of them being shared. According to the literature, these diseases are associated with other autoimmune disorders. However, there are no published cases about the coexistence of these three entities as a continuum of autoimmune manifestations. Here, we present the case of a patient who presented UC posteriorly, MG treated with thymectomy, and finally, met the criteria for NMO, treated with rituximab.

Keywords: *Neuromyelitis optica spectrum disorder. Myasthenia gravis. Ulcerative colitis. Thymectomy. Rituximab.*

Introduction

Neuromyelitis optica spectrum disorder (NMOSD), formerly known as Devic disease, is a rare demyelinating disease characterized mainly by optic neuritis and longitudinally extensive transverse myelitis, which has a clear association (about 90% of patients) with immunoglobulin (Ig) G type autoantibodies against the transmembrane channel aquaporin 4 (AQP4-IgG) of astrocytes[1]. Myasthenia gravis (MG) is a neuromuscular junction disorder clinically characterized by fatigue weakness, particularly of the eye muscles, eyelids, and limbs. There have been identified autoantibodies against the acetylcholine receptor (anti-AChR), autoantibodies against the muscle-specific tyrosine kinase receptor, or autoantibodies against the receptor of low-density lipoprotein-related protein 4[2]. MG may be associated with thymomas, a therapeutic target. Ulcerative colitis (UC), one of the two main types of inflammatory bowel disease (IBD), presents inflammation and ulcerations of the colonic mucosa starting in the rectum, with proximal extension, and manifested clinically with bloody diarrhea; its pathophysiology is multifactorial and mainly involves immunity due to neutrophils, T cells, and interleukins, without specific diagnostic antibodies, resulting in the need for biopsy[3].

Recognizing these diseases in an association is important for proper management and appropriate treatment since these may differ and even be contraindicated due to the coexistence of these disorders. In this case report, we present a patient who developed multiple autoimmune syndromes, defined as at least 3 autoimmune diseases, looking for a potential pathophysiological association with therapeutic implications to prevent long-term neurological and systemic disability.

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Case report

A 43-year-old hispanic man with no known medical history debuted in 2010 with a clinical presentation of 4 months of evolution characterized by hematochezia associated with high-intensity colicky abdominal pain and changes in intestinal habits, presenting mucous-bloody diarrhea, which became very frequent. In 2012, he underwent a colonoscopy where a biopsy was taken, demonstrating the presence of multiple ulcerative lesions consistent with UC. Treatment was started with mesalazine 500 mg every 24 h, with no relapses.

In 2017, he presented with neurological symptoms manifested by vertical binocular diplopia and left eyelid ptosis, so the diagnosis of MG with ocular muscle involvement was suspected, and a therapeutic trial with neostigmine was initiated, with a favorable response. One month later, he presented weakness in all four extremities, predominantly proximal, with exacerbation of weakness during physical exertion, preponderantly in the evening. Anti-AChR positivity was documented, and the repetitive stimulation test showed an electrodecrement > 10%. The patient was categorized in Group IIIb of the Osserman classification, and a quantitative myasthenia score of 24 points was calculated, for which treatment with steroids and oral immunosuppressants was initiated. Despite multiple relapses, a thymectomy and five sessions of therapeutic plasma exchange (PLEX) were performed, with clinical improvement in muscle strength and binocular vision.

In February 2023, the patient presented new neurological symptoms, characterized by paresthesias in the lower extremities, managing to identify a supraumbilical sensory level. Later, paraparesis was added, with difficulty climbing stairs progressing until ambulation was limited, requiring bilateral support and sphincter involvement. The neurological examination revealed a transverse myelopathy syndrome with a sensory level in the T6 dermatome and the anatomical lesion being located in the T8 segment. He was hospitalized for diagnostic and therapeutic treatment. A lumbar puncture was performed, showing inflammatory characteristics (leukocytes 3 cells/μL and microproteins 59 mg/dL), and viral serology (including herpes simplex viruses 1 and 2 [HSV-1, HSV-2], cytomegalovirus [CMV], Epstein–Barr virus [EBV], and human immunodeficiency virus) with negative results, amplifying with polymerase chain reaction (PCR) determination, also negative, for HSV 1, HSV 2, CMV, EBV, human herpesvirus type 7 and 8, varicella-zoster virus (VZV), enterovirus, *Toxoplasma gondii*, human parvovirus B19, hepatitis C virus, lymphocytic choriomeningitis virus, and rubella virus. AQP4-IgG was determined by indirect immunofluorescence technique in a cell-based study and reported positive. Magnetic resonance imaging of the spinal cord was performed with T2-weighted images with fat suppression showing a hyperintense lesion with irregular edges in the T7 and T8 segments, which reinforced after applying gadolinium-based contrast medium, being compatible with longitudinal transverse myelitis of the short segment (Fig. 1).

The diagnosis of NMOSD was established. The patient received three pulses of methylprednisolone with improvement in symptoms and subsequently received disease-modifying treatment with rituximab, with no relapses until January 2024.

Discussion

The association between NMOSD, MG, and UC has not been identified in the literature so far. However, it has been reported that a potential association between NMOSD and other autoimmune diseases in an isolated manner since 20-30% of patients with NMOSD may present immunological disorders isolated to one organ, such as thyroid disease, MG, thrombotic thrombocytopenic purpura, pernicious anemia, IBD, or systemic, such as systemic lupus erythematosus and Sjögren syndrome[4].

NMOSD and MG

In general, both diseases can be considered as autoimmune channelopathies whose pathophysiology is based on processes mediated by B cells, with the production of autoantibodies and mediation by Th-2 lymphocyted[5,6]. A prevalence of 2-3% of both diseases has been reported[7] and an association of 50 cases since 1995[5]. It has been postulated that, in addition to being expressed in astrocytes, AQP[4] can be found in the neuromuscular junction so that it could be a common target in case of autoimmunity and that it can even be expressed in the thymocytes of patients with MG and thymoma[8] or thymomas without MG[9]. Likewise, defects in autoimmune regulation or induction of tolerance and survival of autoreactive T cells have been documented. MG usually precedes NMOSD, with an early onset, appearing before age 50[10] with an unusually mild clinical course[11].

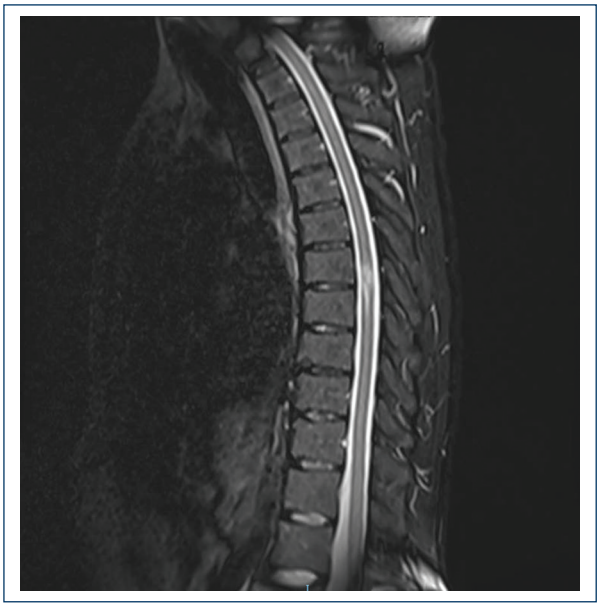

Figure 1. Magnetic resonance imaging in T2-weighted sagittal projection with fat suppression with evidence of central medullary hyperintensity of irregular borders in T7 and T8 segments compatible with short-segment longitudinal myelitis secondary to aquaporin 4+neuromyelitis optica spectrum disorder.

Thymectomy as part of the treatment of MG is one of the factors that promote the development of NMOSD since its symptoms appear after the surgical procedure[5], and this may be due to depletion of regulatory cells and self-tolerance, which is also considered a risk factor for the appearance of other autoimmune diseases[12]. The persistence of pathological peripheral T cells has been demonstrated many years after thymectomy[10]. However, in patients with thymomas, the organ predisposes to producing specific autoantibodies against targets in the central nervous system (CNS), such as AQP4 channels[8]. Hence, the coexistence of both disorders is viable before thymectomy, as has been reported in the literature[13,14]. Likewise, anti-AChR can occur in patients with NMOSD without developing neuromuscular symptoms[4]. Associations between MG and other CNS autoimmune disorders have been documented elsewhere[10].

NMOSD and UC

NMOSD and UC are rare by themselves, and the prevalence of their association is 2.6%[15]. Isolated optic neuritis can be an extraintestinal manifestation of UC and has even been described as a complication of therapy with monoclonal antibodies against tumor necrosis factor alfa (anti-TNFa)[16]. An association between UC and other demyelinating diseases of the CNS, such as multiple sclerosis or acute disseminated encephalomyelitis, has also been documented[17]. Aquaporins are ubiquitous, and their location in the colon is vital for the homeostasis of water and the pathophysiology of UC since the involvement of these channels during the inflammatory process explains the diarrhea in these patients. 15 Interestingly, it has been shown that the disruption of the gut mucosal barrier and dysbiosis could be involved in the appearance of NMOSD[18].

The Gram-negative bacillus *Enterocloster bolteae* (previously within the genus *Clostridium*) is implicated in the dysbiosis of IBD, although mainly involved in Crohn's disease[19]. It is noteworthy that *E. bolteae* has been identified in stool samples from patients with NMOSD, there being a correlation between this bacteria and the levels of inflammatory genes useful for the differentiation of plasma cells, B cell chemotaxis, among other functions[20].

The use of anti-TNFa for the treatment of IBD can unmask underlying aberrant autoimmune responses, with subsequent appearance of inflammatory events in the CNS, and its use is contraindicated in patients with an overt demyelinating disorder[17].

MG and UC

As described above, the pathophysiological basis of both disorders is immunological. Although inflammation is mediated mainly by cells and interleukins in UC, and there are autoantibodies, these are not as specific as in MG. However, it has been shown that they play a role in the onset and duration of the disease, inducing colon inflammation and cytotoxicity[21]. Thymectomy produces good outcomes in the treatment of both disorders[22,23], as stated by Sanghi and Bremner in the case of a woman with UC, MG, and other symptoms associated with a thymoma[24].

Treatment

The treatment of these coexisting conditions is complex. In the NMOSD-MG association, methylprednisolone has been used in acute attacks, PLEX, and intravenous IgG. In these cases, azathioprine is considered first-line therapy as a long-term immunosuppressive treatment combined with steroids in the first 6 months. Methotrexate and mycophenolate mofetil should be considered as second-line treatments[6].

In UC, tacrolimus, a calcineurin inhibitor, has been used as an immunosuppressive treatment[3]. This drug has been proposed for the treatment of NMOSD, initially by Tanaka et al. in 2015[25]. In a retrospective study with 25 patients with NMOSD with positivity for AQP4-IgG made in 2017, where tacrolimus was compared with azathioprine, a significant reduction in the relapse rate was demonstrated (72% vs. 48% p = 0.1 respectively), as well as in the Expanded Disability Status Scale (EDSS) (96% vs. 62%, p = 0.003, respectively). Tacrolimus was well tolerated. However, the study had limitations due to its small sample size, as well as its short follow-up period, which was 5 years[26]. The drug was evaluated again in 2019 in patients with NMOSD with and without positivity for AQP4-IgG (n = 42 vs. 8, respectively) in another retrospective study, using tacrolimus for at least 1 year, where a reduction in the relapse rate of 92% ($p < 0.001$) was documented for the seropositive group and 86% ($p < 0.05$) for the seronegative group. The EDSS also decreased significantly for both groups, although with a greater impact in seropositive patients[27]. These findings theoretically support the use of tacrolimus in the coexistence of NMOSD and UC; however, no randomized controlled trials could justify its use in clinical practice.

Treatment of the coexistence of MG and UC is similar to their isolated forms. It may require surgical treatment in severe cases of UC, and immunosuppressants, such as azathioprine, have been used in case report[22]. As mentioned in the previous section, thymectomy is useful in treating the association of MG and UC. Biological therapies targeting B cells are widely used to treat multiple autoimmune diseases, including the three presented in this paper. In a 2019 systematic review and meta-analysis, Kaegi et al. demonstrated the safety and efficacy of rituximab in treating CNS demyelinating disorders, MG, and IBD[28]. Rituximab was used in the patient presented in this case report. This drug was chosen based on its effectiveness in treating these three conditions in their isolated presentations.

Conclusions

No reported cases in the literature on the presence of these three diseases cojoined, although the coexistence of NMOSD, MG, and UC in isolation is not negligible. Different pathophysiological mechanisms have been proposed, including the hypothesis of intestinal dysbiosis. However, they remain unknown. These immunological associations can be a therapeutic challenge. Inflammatory mediation by B cells is vital for using anti-CD20 monoclonal antibodies for the long-term control of these autoimmune disorders. We considered that rituximab and other anti-CD20 could be an alternative for immunosuppressive treatment in isolated or grouped coexistence of these diseases. However, their justification through randomized controlled trials will be difficult due to the rarity of this finding. Therefore, it will be important to monitor this group of patients closely. The feasibility of the coexistence of three autoimmune disorders, two of them being neurological, clearly justifies long-term follow-up and surveillance to avoid relapses and accumulated disability.

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