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Co-occurrence of Myasthenia Gravis and Multiple Sclerosis: A Case Report

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Summary. Myasthenia gravis (MG) and multiple sclerosis (MS) are thought to have a common autoimmune mechanism as the number of reported co-occurrences of both diseases is increasing. The involvement of both T cells and B cells in the pathogenesis of these two diseases is suspected. As the symptoms and clinical course of MS and MG can be similar in some cases, this makes it difficult to consider the possibility of the coexistence of these disorders. However, laboratory and imagining findings are helpful in distinguishing both diseases and differentiating them from other neurological conditions. Additionally, there can be obstacles in effective treatment selection for patients with MS and MG coexistence. This article presents a clinical case of a woman with previously diagnosed MG who was admitted to hospital 12 years later with new-onset symptoms and was additionally diagnosed with relapsing-remitting multiple sclerosis (RRMS). Remission of MG was achieved with medications and thymectomy, but treatment of MS had its challenges, as first-line immunomodulating drugs interferon beta-1a and dimethyl fumarate were not effective, and second line treatment with monoclonal antibody medication rituximab and ocrelizumab showed efficacy for both diseases, MG and MS. The presented case highlights the importance of considering a manifestation of another disease when treating an already diagnosed disorder. It also emphasizes the importance of further research into the relationship between MG and MS.

Keywords: multiple sclerosis, myasthenia gravis, autoimmune disease, demyelinating disease.

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating disease of the central nervous system (CNS). MS is pathologically characterized by multifocal areas of demyelination with loss of oligodendrocytes and astroglial damage [1]. Myasthenia gravis (MG) is a chronic autoimmune disease in which antibodies specific to the acetylcholine receptor destroy the neuromuscular junction [2]. The co-occurrence of MS and MG is rare, but this combination of diseases has been reported more frequently than would be expected by chance. This has led to the suspicion that autoimmune mechanisms are involved in both MG and MS [3]. In this article, we present the case of a female patient with a previous diagnosis of MG who was admitted to hospital 12 years later with symptoms of MS.

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CASE REPORT

A 29-year-old female patient was admitted to Vilnius University Hospital Santaros Klinikos in January 2005 due to diplopia, severe pain in the upper arms, and weakness in the arms and legs. These symptoms appeared after an infection of unknown etiology. Magnetic resonance imaging (MRI) revealed demyelinating foci. Postinfectious demyelinating encephalitis was diagnosed. The patient was treated with intravenous (IV) infusion of methylprednisolone 1000 mg once daily for two consecutive days.

In April 2005, the patient was hospitalized due to recurrent diplopia (mainly in the right eye), bilateral ptosis, and bilateral arm weakness. These symptoms worsened in the evening and during emotional events. Anti-striated muscle antibodies were found at 2.8 nmol/L (negative value is

<0.4 nmol/L). Electroneuromyography (ENMG) findings were typical of the postsynaptic type of conduction disorder with a positive myasthenic response. The patient was diagnosed with generalized myasthenia gravis, Class IIa in the Osserman classification. The patient improved after a course of plasmapheresis and was prescribed pyridostigmine 60 mg two or three times per day (60 mg/8 h) until thymectomy. After surgery which was performed in 2005, the same amount of pyridostigmine was continued.

In May 2017, the patient was admitted to hospital with right leg weakness and a feeling of tightness from the waist down the entire leg. Weakness in the leg started a year ago, progressed during that time, and became uncomfortable for the patient about 6 months ago. 2-3 weeks before admission the leg weakness worsened. The patient could not walk a longer distance or climb and descend stairs. Neurologic examination upon admission: muscle strength of the arms was graded 5 and muscle strength of both legs was graded 4. In addition, there was hyperreflexia of the right arm and right leg with a unilateral positive Babinski sign. On examination, pyramidal hypertonia and clonus of the right leg were found. The finger-to-nose test was bilaterally normal. The heel-to-shin test of the right leg was asymmetric. The Expanded Disability Status Scale (EDSS) score on admission was 3.0.

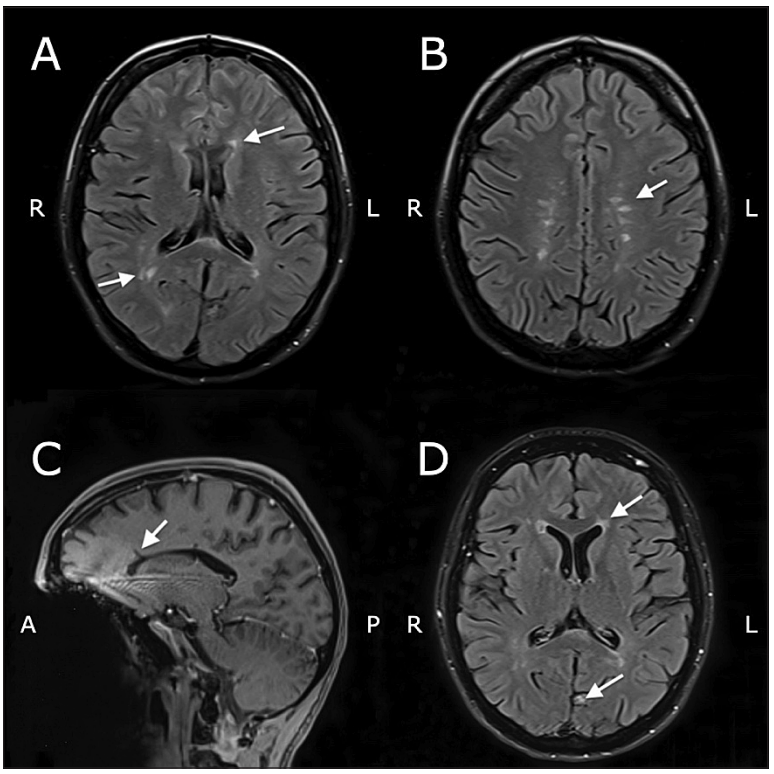

Fig. 1. **Brain MRI (performed in 2017 and 2018).**
(A) T2-hyperintense periventricular lesions on axial fluid-attenuated inversion recovery (FLAIR) image (2017).
(B) T2-hyperintense lesions in the subcortical region on axial FLAIR image (2017).
(C) T1-hypointense lesions adjacent to the lateral ventricle on the sagittal image (Dawson's fingers) (2017).
(D) T2-hyperintense periventricular and occipital lesions on axial FLAIR image (2018).

Cerebrospinal fluid (CSF) analysis revealed the presence of oligoclonal bands with intrathecal synthesis of immunoglobulin G. MRI showed multiple hyperintense lesions (11/8 mm) on T2-weighted images in the subcortical, periventricular, corpus callosum, infratentorial (cerebellum, brain stem) regions. T1-weighted images showed isointense and hypointense demyelinating lesions. There was no contrast enhancement (Fig. 1 A, B, C).

Evoked potentials were not extracted, the patient was unable to relax to perform the test. Anti-Aquaporin 4 antibody (AQP4) test was negative. A diagnosis of the first documented episode of multiple sclerosis was made. The patient received intravenous methylprednisolone 1000 mg daily for 3 consecutive days. Neurological examination before discharge from hospital: muscle strength of arms and legs improved to a score of 5.0, although hyperreflexia of the right arm and right leg with unilateral positive Babinski sign remained. Coordination tests were normal. EDSS score decreased to 1.0. One month later, on return to the clinic for follow-up, the patient was diagnosed with relapsing-remitting multiple sclerosis (RRMS).

Five months later, the patient returned to the hospital with similar symptoms and a new relapse of RRMS was diagnosed. The patient was prescribed subcutaneous injections of immunomodulator interferon beta-1a 44 mcg three times a week as a first-line medication for RRMS. However, this treatment caused side effects such as chills, generalized weakness, and localized reaction around the injection site, and relapse of RRMS occurred while the patient was taking this medication. In January 2018, treatment with interferon beta-1a was changed to dimethyl fumarate. The dose of dimethyl fumarate was initially 120 mg per day and was gradually increased to 240 mg twice a day. After three months of treatment, new symptoms appeared, such as limping and diplopia. However, no changes were observed in the MRI scan compared to the previous one in 2017 (Fig. 1 D and Fig. 2 A). It was decided to discontinue treatment with dimethyl fumarate due to repeated relapses and progression of the EDSS score to 5.5 (Fig. 3). In June 2018, the patient was prescribed the first dose of rituximab 1000 mg IV infusion, and a month later received the second dose of rituximab 1000 mg IV.

In March 2019, the patient was hospitalized to receive the third dose of rituximab; after two doses, there was a positive response (no new relapses) for 6 months. However, for the last two months the patient felt weakness in both legs. During this hospitalization, the patient was premedicated with an IV infusion of methylprednisolone

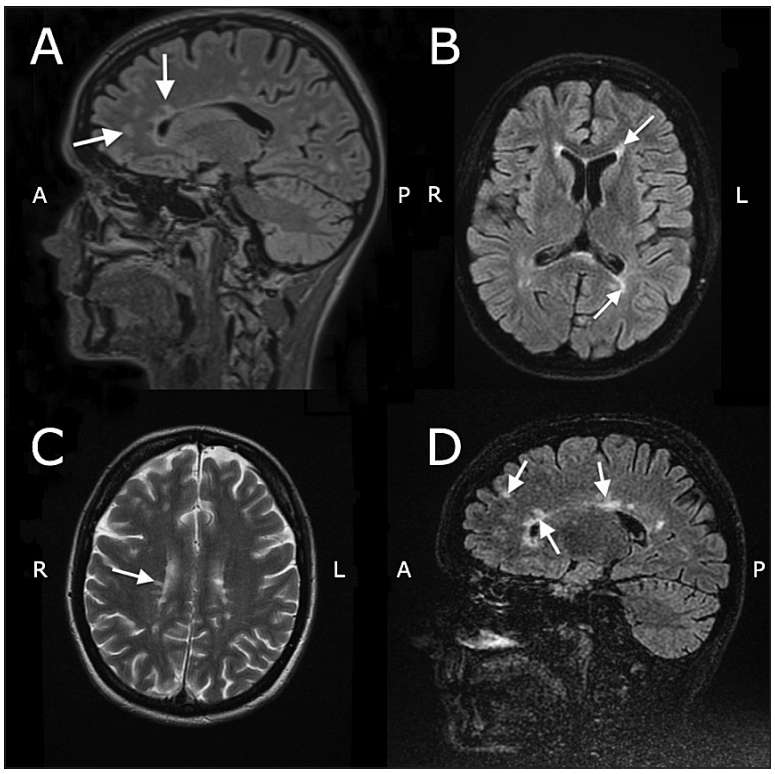

Fig. 2. **Brain MRI (performed in 2018 and 2019).**
(A) T2-hyperintense multiple periventricular and juxtacortical demyelinating lesions on sagittal FLAIR image (2018).
(B) White matter T2-hyperintensities in the periventricular region (2019) on axial FLAIR image.
(C) T2-weighted hyperintense corpus callosum lesions on the axial image (2019).
(D) T2-hyperintense corpus callosum and subcortical lesions on sagittal FLAIR image (2019).

250 mg and administered with rituximab 1000 mg IV infusion.

In October 2019, the patient presented with diplopia and weakness in the legs, and the EDSS score increased to 6.0. RRMS relapse was suspected and treatment with rituximab was changed to ocrelizumab IV infusion 600 mg every 6 months. After one year, the patient was admitted to hospital for the third dose of ocrelizumab. At that time, leg weakness remained with a significantly weaker right leg, ataxia, and rapid fatigue with episodic right eye ptosis. Neurological examination: muscle strength of the arms was graded as 5, muscle strength of the left leg as 4, right leg as 3. Hyperreflexia of the right arm and right leg with a unilateral positive Babinski sign. During the examination, pyramidal hypertonia, clonus of the right leg, and ataxic, paraparetic spastic gait were observed. The finger-to-nose test was bilaterally normal. The heel-to-shin test of the right leg was asymmetric. The patient was able to walk 100 meters without help. The EDSS score was 5.5.

The patient was premedicated with an IV infusion of methylprednisolone 1000 mg, clemastine 1 mg, and received a 600 mg dose of ocrelizumab. At discharge, the patient was also prescribed fampridine 10 mg once daily to improve her walking, in addition to pyridostigmine which she was taking constantly.

In April 2022, the patient came for her seventh dose of ocrelizumab. Her general condition was stable with no new symptoms and no new relapses of MS for 2.5 years. The patient's diagnosis was reconfirmed during this hospitalization: acute RRMS, EDSS score 5.5, and generalized myasthenia gravis Class IIa in Osserman classification. The patient continues to take daily pyridostigmine, fampridine, and baclofen for myorelaxation and receives ocrelizumab 600 mg IV infusion every 6 months.

DIFFERENTIAL DIAGNOSIS

Understanding the differential diagnosis of MS and MG is important in determining the correct diagnosis for the patient. First, it is important to differentiate MS from one of the most common neurological infections, such as Lyme disease. The central nervous system may be involved if the first stage of the disease has not been treated. Neurological symptoms and signs of diffuse demyelination on cranial MRI can sometimes confuse the clinician and lead to an incorrect diagnosis. Detection of antibodies against *B. burgdorferi* can confirm the diagnosis of Lyme disease [4].

Another disease to consider in patients with symptoms of CNS demyelination is Devic's syndrome, also called neuromyelitis optica. Recurrent attacks of optic neuritis and transverse myelitis are typical of Devic's syndrome [5]. Sometimes relapses of neuromyelitis optica can be confused with RRMS. Typically, MRI in Devic's syndrome does not reveal brain lesions which are common in MS patients. It usually shows longitudinal transverse lesions of more than three vertebral segments and involvement of the optic chiasm or optic nerve [4]. Also, in differential diagnosis, it is useful to test antibodies that bind AQP4; they are highly specific for patients with neuromyelitis optica [6].

According to studies, primary Sjögren's syndrome may involve the CNS in 20-25% of patients, and these symptoms can mimic MS [4, 7]. Diagnosis may also be challenging in patients with Sjögren's syndrome with focal neurological manifestations, since 80% of these cases show hyperintense lesions on MRI [4]. In the differential diagnosis, the determination of autoantibodies (anti-SS-A and anti-SS-B) may be useful, as oligoclonal bands on CSF examination are usually absent in patients with Sjögren's syndrome [4, 7]. Other important diseases to consider when differentiating MS include acute disseminated encephalomyelitis, Schilder's disease, Behet's disease, systemic lupus erythematosus, sarcoidosis, progressive multifocal leukoencephalopathy, adrenoleukodystrophy, and many others.

MG must be differentiated from another neuromuscular junction disorder called Lambert-Eaton myasthenic syndrome (LEMS), which may present as a primary autoimmune disorder or as a paraneoplastic syndrome [8]. LEMS is characterized by decreased tendon reflexes or areflexia, autonomic dysfunction, and fluctuating weakness that improves with movement. A retrospective study in the Netherlands found that weakness of muscles in LEMS tends to develop in lower limbs and progress to other parts of the body, whereas in myasthenia gravis it typically starts with ocular and arm muscles [9].

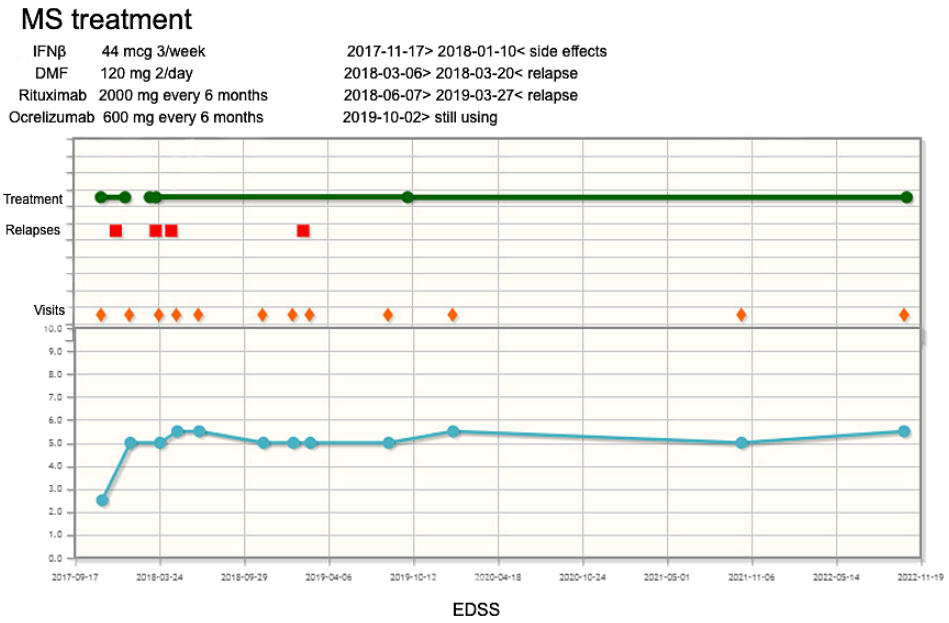

Fig. 3. **Scheme showing the patient's five years of treatment for multiple sclerosis**

Patients with botulism often present with ptosis, double vision, pupillary abnormalities, and progressive weakness. Some of these symptoms are characteristic of MG. However, rapid onset of symptoms, autonomic manifestation, and patient history can help exclude MG [10, 11]. In addition, symptoms such as impaired consciousness, aphasia, epilepsy, and lack of response to intravenous corticosteroids are not characteristic of MG, and the diagnosis of MG must be reconsidered [12]. Differential diagnosis of previously discussed diseases is briefly presented in the Table.

DISCUSSION

The coexistence of autoimmune diseases is not uncommon, but the combination of MS and MG is rare [1]. However, there have been reported cases of the co-occurrence of these two diseases [3]. Various studies have shown that there are immunological similarities and dysfunction of T cells as well as B cells involved in the pathogenesis of both disorders [3, 13].

Both MS and MG are thought to be primarily caused by T cells [13]. T regulatory cells (Tregs) are thought to function by suppressing the effector CD4+ T cell subsets that mediate autoimmune responses. Autoimmune events may be influenced not only by abnormal Treg numbers or defective Treg function, but also by resistance of T effectors (Teff) to suppression. In addition, increased levels of proinflammatory cytokines such as IL-6, IL-17, and IFN- secreted by Teffs have been reported in patients with MS and MG [14].

Earlier studies have proven that rituximab, a B cell-depleting anti-CD20 antibody, is beneficial in both diseases, indicating the importance of B cell in each [14]. Based on the research, our patient was prescribed rituximab for almost 1.5 years, which was effective at the beginning of the treatment. However, MS relapses repeated, and treatment

Table. **Differential diagnosis of MS and MG**

Disease	**Similarities to multiple sclerosis**	**Differences from multiple sclerosis**
Lyme disease	CNS involvement in late stages: paresis, blurred or double vision; Rarely diffuse CNS demyelination found on MRI	Present antibodies against *B. burgdorferi*
Devic's syndrome	Recurrent attacks of optic neuritis	No brain lesions on MRI, present antibodies to AQP4
Sjögren's syndrome	Focal or diffuse CNS involvement, myelitis or optic neuropathy attacks, MRI findings can mimic MS	Present autoantibodies (anti-SS-A and anti-SS-B), positive Schirmer's test for dry eyes
Disease	**Similarities to Myasthenia gravis**	**Differences from Myasthenia gravis**
Lambert-Eaton myasthenic syndrome	Muscle weakness	Autonomic disfunction, decreased tendon reflexes
Botulism	Ptosis, double vision, progressive weakness	Rapid onset, autonomic manifestation

with rituximab was ultimately not successful in our case and was changed to ocrelizumab, which also targets CD20. Moreover, research investigating the modulation of B cell regulatory molecules CD22 and CD72 in MG and MS suggests that CD72 may be involved in the pathogenesis of both diseases. CD72 has been demonstrated to act as a B cell inhibitory receptor in many autoimmune diseases [15].

In our case, treatment with ocrelizumab showed a relatively good effect, there was only one MS relapse in three years and the EDSS remained stable at 5.5. According to a randomized trial comparing the effectiveness of RRMS treatment with ocrelizumab and interferon beta-1a, ocrelizumab was associated with a lower annual relapse rate. This was supported by MRI scans, which showed suppression of the development of new areas of inflammation and new enlarged plaque formation [16].

Studies suggest, that thymectomy may trigger the development of another autoimmune disease in patients with MG [17]. T cell imbalance after thymectomy may provoke an autoimmune response [18]. A Canadian study also found that patients with MS and MG developed the first clinical manifestation of MS about 6-8 years after the onset of MG [17]. Sometimes MG and MS can mimic each other, and new onset of symptoms can be confused with an already diagnosed disease rather than suspecting a new one. Clinical manifestations such as vision disturbance, speech impairment, swallowing problems, difficulty walking, and weakness in the arms and legs are characteristic of both diseases. Due to the clinical similarities of both diseases, diagnosis and treatment of the new condition may be delayed [1, 19].

The literature indicates that the clinical course of both MG and MS is mild in most patients with this co-occurrence of diseases, but the onset of MG may cause a worsening of MS whereas MG may be relatively unaffected by fluctuations in disease activity of MS [20]. In the clinical case we presented, MG appeared to be under control after thymectomy and continuous treatment with pyridostigmine, while MS relapses occurred repeatedly during different therapies.

CONCLUSION

As immune mechanisms of MS and MG are related and the co-occurrence of these diseases is increasingly recognized, it is necessary to study and explore this co-occurrence in order to find the most appropriate management for patients with both diseases.

Clinically, the relationship between MS and MG may go unnoticed due to possible overlap of pathology, especially bulbar and ocular symptoms. Both diseases can mimic each other, which can be confusing for the clinician. For this reason, it is important to consider the possibility of other autoimmune diseases when treatment of MS or MG is not effective or if new symptoms occur.

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MIASTENIJOS IR IŠSĖTINĖS SKLEROZĖS KOMORBIDIŠKUMAS: KLINIKINIS ATVEJIS

Santrauka

Daugėjant aprašomų generalizuotos miastenijos (GM) ir išsėtinės sklerozės (IS) bendrų pasireiškimų atvejų skaičiui ir atliekant imunologinius tyrimus, daroma prielaida, kad abi šios ligos turi bendrą autoimuninį mechanizmą. Įtariama, kad tiek T ląstelės, tiek B ląstelės dalyvauja šių dviejų ligų patogenezėje. Kadangi IS ir GM simptomai bei klinikinė eiga kai kuriais atvejais gali būti panašūs, tai apsunkina šių susirgimų komorbidiškumo įvertinimo galimybę. Greta neurologinio paciento būklės įvertinimo, laboratoriniai ir vaizdiniai tyrimai yra naudingi diferencijuojant abi šias ligas tarpusavyje ir nuo kitų neurologinių būklių. Taip pat pastebėta, kad gali kilti sunkumų, parenkant veiksmingą gydymą pacientams, sergantiems IS ir GM vienu metu. Pateiktame straipsnyje aprašomas klinikinis atvejis apie pacientę, sergančią generalizuota miastenija, kuri po 12 metų kreipėsi dėl naujai atsiradusių neurologinių simptomų. Remiantis atliktais tyrimais ir klinika, pacientei papildomai buvo diagnozuota recidyvuojanti remituojanti išsėtinė sklerozė (RRIS). GM remisija buvo pasiekta paskyrus vaistus ir atlikus timektomiją, tačiau IS gydymas šiuo atveju turėjo tam tikrų iššūkių. Pirmos eilės imunomoduliuojantis vaistas interferonas beta-1a, dimetilfumaratas nebuvo veiksmingi, tuo tarpu monokloninių antikūnų vaistas rituksimabas ir okrelizumabas turėjo teigiamą efektą ir stabdant IS paūmėjimus, ir stabilizuojant GM. Pristatytas atvejis pabrėžia, kaip svarbu atsižvelgti į galimą kitos ligos atsiradimą, gydant jau esantį anksčiau diagnozuotą autoimuninį sutrikimą. Taip pat pateiktas straipsnis pažymi tolimesnio GM ir IS ryšio ištyrimo, efektyvaus gydymo nustatymo ir parinkimo svarbą.

Raktažodžiai: miastenija, išsėtinė sklerozė, autoimuninė liga, demielinizuojanti liga.

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