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Case report

Co-occurrence of multiple sclerosis and myasthenia gravis: A case report and review of immunological theories

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ABSTRACT

Autoimmune mechanisms are implicated in both myasthenia gravis (MG) and multiple sclerosis (MS), and hypothesis of a common immunological mechanism of pathogenesis is supported by the fact that this rare combination of the two diseases occurs more frequently than expected by random association. Although MS is primarily mediated by T lymphocytes and MG primarily involves the destruction of the neuromuscular junction by antibodies, there are evidences that support both cell-mediated and humoral immunity are involved in the pathogenesis of both diseases. Different studies have shown dysfunction of T cells as well as B cells involved in the pathogenesis of both disorders. Previous case reports, mainly present female patients who had a mild presentation of MG, either prior or after diagnosis of MS. In this article, in addition to presenting a unique male patient with a previous diagnosis of MS, who presented with MG crisis, we aimed to review the literature to find the common immunological mechanisms involved in the pathogenesis of MG and MS.

1. Case report

A 54-year-old male with a past medical history of Hyperlipidemia, Hypothyroidism, osteoarthritis and relapsing-remitting multiple sclerosis (MS), diagnosed in 1996 (at age 35) following initial presentation with internuclear ophthalmoplegia (INO), was started on Glatiramer acetate (Copaxone) in 1999, with good control of symptoms. Patient was taking Copaxone for 15 years, until he self-discontinued the medication due to reported side effects, 3 years before presentation to our hospital. In subsequent clinic visits, patient refused to re-start Copaxone, due to not having any MS exacerbation, until a few months prior to presentation, when he complained of right eye blurry vision, diplopia, left leg weakness, which then progressed to generalized weakness. He also developed difficulty chewing and swallowing.

Patient was last seen in clinic 2 months prior to hospital admission. MRI brain and Cervical/Thoracic/Lumbar (C/T/L) spine were done, which showed stable T2/Flare lesions compared to MRIs done in 2015; with no active lesions on T1 with contrast sequence. Copaxone was resumed, however patient continued to be symptomatic despite taking it and eventually presented to emergency room with generalized weakness, dysphagia, and shortness of breath.

Chest X-ray showed pneumonia. Antibiotics were started. Patient soon developed respiratory failure and was intubated.

With a presumed diagnosis of MS exacerbation, IV methylprednisolone (MP), was started.

MRI brain and C/T/L spine were repeated, which didn't show any new active lesions.

Patient didn't have any improvement with IV MP. Negative Inspiratory Force (NIF) and Forced Vital Capacity (FVC) continued to be persistently low, and extubation was not possible. Lumbar puncture was done to rule out possible AIDP, which was unremarkable. NCS/EMG was done to search for other possible etiologies, which didn't show any neurogenic changes in favor of AIDP. In fact, some myopathic changes were noted, however, repetitive nerve stimulation was not performed at that point.

Extensive labs including CK, TSH, Serum NMO antibodies, Acetylcholine binding, blocking, modulating antibodies, Anti-Musk antibody, paraneoplastic and autoimmune panels were sent.

Abbreviations: MG, myasthenia gravis; MS, multiple sclerosis; INO, internuclear ophthalmoplegia; AIDP, Acute Inflammatory Demyelinating Polyneuropathy; NCS/EMG, Nerve Conduction Study/Electromyography; CK, creatine Kinase; TSH, thyroid-stimulating hormone; NMO, neuromyelitis optica; Musk, muscle-specific tyrosine kinase; PPMS, primary progressive multiple sclerosis; Tregs, T regulatory cells; Teff, Effector CD4+ T cells; OMG, Ocular Myasthenia Gravis; GMG, Generalized Myasthenia Gravis; AchR, Acetylcholine Receptor

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Considering the possibility of the diagnosis of myasthenia gravis at this point, plasmapheresis was started after the course of IV methylprednisolone.

Patient started to improve after plasmapheresis started.

Acetylcholine binding antibody (36.3 n mol/L), and blocking Antibody (62 n mol/L) returned positive (Negative values are < 0.40 n mol/L). Anti-Musk antibody was negative.

Patient improved significantly after the course of plasmapheresis and was extubated. Thoracic CT scan ruled out the presence of any mediastinal mass, however considering that thymectomy is recommended for patients younger than 60 years with generalized AchR antibody-associted MG, patient was scheduled for thymectomy. Patient was started on Pyridostigmine 60 mg/8 h, prednisone 60 mg daily (which was later tapered down), Cellcept 500 mg/12 h; and Copaxone was also re-started. On return for follow-up in clinic 1 month later, the patient had full recovery, and was able to perform his activities of daily living without assistance.

2. Discussion

Even though polyautoimmunity exists between different autoimmune diseases, the co-occurrence of MS and MG is rare; however, this rare combination occurs more frequently, as repeatedly reported, than expected by random association.

Previous studies suggest that a similar immunogenetic background predisposes to susceptibility to these two disorders but that different triggering and unknown genetic factors result in two different clinical diseases (Lorenzoni et al., 2008).

In this article, we mainly aim to review and find a similar immunological background and theories for the co-occurrence of these two diseases.

MG can present before or after the diagnosis of MS, and the time to onset of this association may vary from 1 to 28 years. After literature review (review of related articles published since 1980), we found 29 patients reported who had co-occurrence of these two diseases (cases with a diagnosis of ADEM, NMO, relapsing myelitis and relapsing optic neuritis are excluded in our literature review). Most patients were females (26) with a mild clinical course of MG and MS, however rare cases of PPMS or MG crisis (Gharagozli et al., 2011) were reported. Few case reports also described the development of MG after treatment of MS with IFN-B (three patients), Glatiramer acetate (one patient) and alemtuzumab (one patient). Whether these immunomodulatory drugs are triggering factors in an already predisposed patient, or directly causing MG, is unknown.

Different immunological mechanisms and theories for loss of self-tolerance have been implicated in MG and MS, one of which is defects or dysfunction of T regulatory cells (Tregs), which function by suppressing the effector CD4+ T (Teff) cells that mediate autoimmune responses (Danikowski et al., 2017).

As Danikowski et al., described in detail, it is well documented that Tregs' dysfunction and inability to suppress Teff cells, to maintain self-tolerance, is responsible in multiple autoimmune diseases including GBS and type 1 diabetes. Lower suppressive capabilities of Tregs have been reported in both MS and MG patients as well.

The Treg augmentation therapies, by enhancing Treg suppressive activity and/or numbers, enhancing Treg-dependent B cell destruction or suppression (especially in MG), increasing Treg migration, or enforcing tolerogenic signals from Tregs have been implicated as therapeutic modalities by this group, and needs further studies and clinical trials for clinical use.

Also, Oksenberg et al. (1989), very well describe the role of T-cells and genetic susceptibility in both MS and MG, as they suggest that since the antigen-specific T-cell receptor (TcR) plays a major role in the immune recognition, variations in the gene encoding this receptor could potentially contribute to the development and inheritance of these autoimmune diseases. In their study they show that the Pss I TcR alpha-chain polymorphisms are strongly associated with susceptibility to MS and MG, and raise the possibility of designing haplotype-specific immunotherapeutic monoclonal antibodies, which could be used to block the autoimmune T-cell response, if they can identify a TcR gene that contributes to susceptibility to autoimmune diseases.

On the other hand, Lu et al. (2013), raise the theory and discuss the importance of B cells, plasma cells, and self-reactive antibodies in the pathogenesis of MG and MS. The rationale for this theory in MS is 1. The oligoclonal antibody response in the CSF, which is the hallmark diagnostic finding, 2. Presence of clonally expanded B cells in the MS plaques, and 3. The fact that Rituximab, an anti-cluster of differentiation 20 (CD20) monoclonal antibody that specifically depletes B cells, is a potent immunomodulatory therapy for MS patients. These evidence suggest the existence of humoral immune-mediated pathogenesis in MS.

CD72, another B cell regulatory molecule, regulates BCR-mediated signals both positively and negatively. Altered expression of CD72 might result in hyperactivity of B cells and thus play a role in B cell-related autoimmune diseases.

Study (Lu et al., 2013) has shown significantly lower expression of CD72 protein and CD72 mRNA in MG patients, and negative correlation between mRNA and protein levels of CD72 and anti-ACHR antibody levels. This finding suggested that CD72 acts as an inhibitory co-receptor of B cells in MG. Significantly decreased CD72 in MS patients compared to healthy controls, was also found in this study, supporting the hypothesis of B cell activation in the antibody-mediated process of MS, although decreased CD72 did not correlate with Expanded Disability status scale (EDSS) score in these patients.

Interestingly, no obviously abnormal expression of CD22 was found in MG, OMG, GMG, or MS patients, despite previous studies report low CD22 expression in RA patients, which indicate that different autoimmune diseases have different pathogenesis (Lu et al., 2013).

3. Conclusion

Co-occurrence of MG and MS occur more frequently than expected by random association and the association may be underdiagnosed because of the possibleoverlap of symptoms especially bulbar and ocular manifestations in which either MG or MS can mimic each other, leading to underestimating the incidence of the combination.

Although MG is caused by autoantibodies to Ach receptors in neuromuscular junction, the mechanism underlying the autoimmune response, appears to be initiated by activation of T lymphocytes. Alternatively, although MS is primarily mediated by T lymphocytes, there are some evidence that B cells and self-reactive antibodies play a role in the pathogenesis of MS as well.

The enhanced understanding of T cell and B cell surface receptors and genes that are involved in the pathogenesis of MG and MS, needs further studies and clinical trials for developing more effective treatment options.

Conflict of interest and financial disclosure

All 3 authors report no financial disclosures and no conflict of interest to declare.

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