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The relative frequency of Myasthenia Gravis in patients with Multiple Sclerosis and Neuromyelitis Optica

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Abstract

Background: Co-occurrence of autoimmune diseases have always been an area of interest due to common underlying immunopathologic mechanisms. In this study, we assess the relative frequency of myasthenia gravis (MG) in patients with multiple sclerosis (MS) and neuromyelitis optica (NMO).

Methods: Records of patients with MS and NMO who visited the Isfahan MS center were screened. The data of patients with comorbid MG was used to calculate relative frequency.

Results: The relative frequency of MG in our sample MS and NMO population was 0.34% and 5%, respectively, which is higher than the reported prevalence of MG alone in the general population (0.0005-0.024%).

Conclusion: The higher frequency of MG in MS and NMO populations compared to the general frequency of the disease may be due to common immunopathologic mechanisms that underly the diseases. Regulatory T cells, the complement pathway, matrix metalloproteinases, and B cells play critical roles in each disease and share common features in MS and MG. The complement system also plays a central role in NMO and MG. The relative frequency of MG in patients with MS and NMO is higher than of that reported in the general population (0.34% and 5%, respectively).

Background

Neurologic diseases with underlying immunologic mechanisms have been studied for years and many aspects still remain obscure. (1) Myasthenia gravis (MG), multiple sclerosis (MS), and neuromyelitis optica (NMO) comprise the three main neurologic diseases that autoantibodies form their main pathology. Antibodies in myasthenia gravis are formed against postsynaptic neuromuscular junction (NMJ) proteins, namely acetylcholine receptors, leading to a unique set of clinical manifestations; fluctuating muscle fatigue, respiratory complications, and ptosis towards the end of the day. In MS, dysfunction of regulatory T cells (T_{reg}) ultimately leads to unsuppressed effector T cells ($CD4^+$ T cells) and an unregulated T cell response against central nervous system (CNS) myelin structures. (1) NMO spectrum disorders are inflammatory diseases of the CNS which mainly involve the spinal cord and the optic nerves. Anti-aquaporin-4 antibodies (anti-AQP4) are formed against CNS astrocytes causing NMOSD. Antibodies against myelin oligodendrocyte glycoprotein (MOG) can lead to another subset of NMOSD with distinct clinical features. (2)

Patients with NMOSD can present with concurrent autoimmune disorders such as systemic lupus erythematous (SLE), Sjogren's disease, autoimmune thyroid disease, and MG.(3)(4)(5) Concurrent presentation of MS and MG has also been observed, underlining the common immunological pathways that may be involved in the two diseases.(1)

In this study we will present several cases with concurrent presentation of MS and MG or NMO and MG and then discuss common pathways that may be involved, and the features of the patients with

coexisting diseases.

Methods

This is a descriptive cross-sectional study. The data of the study have been extracted by reviewing the registry and medical records of patients who have visited the Isfahan MS Center from March 2017 through March 2020. All patients with the definitive diagnosis of MS and NMO based on the revised McDonald's criteria(6) and the international consensus NMO diagnostic criteria(7), respectively, were included in the study. Patients whose diagnosis were pending or more than 20% of their data based on the study's variables were missing were not included in the study. Patients who had myasthenia gravis concurrently with MS or NMO were contacted by phone or visited in the office and their data for the study was completed and updated. The diagnosis of MG was based on clinical presentation, laboratory evaluation, and electrodiagnostic testing. A total of 3857 patients with either NMO or MS were included in the study. For the descriptive analysis of quantitative data, we used mean and standard deviation which were calculated using IBM SPSS statistics software version 26. Comparison of frequencies was done using the one-sample proportion z-test ($p<0.05$) using an online calculator.(8) The study is approved by the ethics committee of the Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.294) and all methods were performed in accordance with the relevant guidelines and regulations.

Results

Of the total 3857 unique patients, 3777 had MS and 80 were diagnosed with NMO. Patients' demographics are summarized in table 1. Out of the 3777 patients with MS, 13 had comorbid MG (relative frequency = 0.34%). This is higher than the reported frequency of MG in the general population of 5-24/100000 based on different studies(9–11) ($p<0.05$, 95% CI= 0.1%-0.5%). Of the 13 patients with concurrent MS and MG, 3 (0.07%) were male and 10 (0.2%) were female. In nine patients (69.2%), diagnosis of MS preceded MG. Six (46.15%) patients were positive for the acetylcholine receptor (AChR) antibody. Seven (53.8%) had undergone thymectomy. Two patients had hyperthyroidism, and one had hypothyroidism as autoimmune comorbid conditions. Family history of autoimmune diseases was considerable for MS in a patient's sibling. The presenting signs of MS were mainly limb paresthesia (61.5%), facial paresthesia (15.3%), and optic neuritis (23.1%). Ocular and bulbar symptoms were the main presenting features of MG (ptosis – 69.2%, dysphonia – 23.1%, and diplopia - 30.8%). Twelve patients had relapsing-remitting MS and only one had primary progressive MS (PPMS) disease. Except for the one patient with PPMS (EDSS=7) which was disabled, all other patients had their disease well under control and could perform normal daily activities (overall mean EDSS=1.5). Pyridostigmine was the principal drug used for the treatment of MG and disease modifying therapies such as azathioprine, fingolimod, and interferon beta were the primary drugs used for MS.

Table 1: Summary of patients' demographic data				
Characteristics	Patients with MS only	Patients with NMOSD only	Patients with concurrent MS and MG	Patients with concurrent NMOSD and MG
Age				
Mean ± SD	32.01±9.08	35.74±11.52	39.46±11.31	42.75±7.8
Distribution – Number (%)				
£ 18 years	159 (4.1%)	3 (0.07%)	0 (0%)	0 (0%)
19-55 years	3563 (92.3%)	69 (1.7%)	11 (0.2%)	4 (0.1%)
³ 56 years	42 (1.08%)	4 (0.1%)	2 (0.05%)	0 (0%)
Sex – Number (%)				
Male	787 (20.4%)	16 (0.4%)	3 (0.07%)	2 (0.05%)
Female	2977 (77.1%)	60 (1.5%)	10 (0.2%)	2 (0.05%)

Eighty of the patients were diagnosed with NMOSD, four (two males and two females) of which had concurrent MG. The relative frequency of NMO and MG in our sample population is 5%, which is also higher than the prevalence of MG in the general population ($p<0.05$, CI 95%=1.38%-12.31%). All patients were positive for AChR and AQP4 antibodies for MG and NMO, respectively. Two patients had undergone thymectomy, and NMO presented after thymectomy in both. One patient had a history of Hashimoto's thyroiditis. All patients had ptosis and optic neuritis as their presenting sign of MG and NMOSD, respectively. A case-by-case overview of the patients' data is provided in table 2.

Discussion

Concurrence of autoimmune diseases has always been a field of interest in medicine. The discovery of a common pathway in the pathogenesis of related autoimmune diseases can guide future therapies and assist in disease mitigation. The frequency of MG along with MS and NMO is higher than the prevalence of MG in the general population based on the results of this paper and another report(12). It seems that this is not a mere coincidence, and strengthens the hypothesis that common immunopathologic mechanisms may exist.

Although there are different pathological mechanisms in MS and MG, immunologic similarities exist. Studies suggest that regulatory T cells (T_{reg}) may have a lower suppressive function which on the one hand leads to increased pro-inflammatory cytokines such as IL-6, IL-17, IFN-g, and proliferation of antibody producing B cells, on the other. Although antibody damage to neuromuscular junction is evident,

the presence of specific antibodies in the pathogenesis of MS has not been unveiled, still. However, the role of rituximab in the treatment of MS implies the role of B cells in MS.(13) In a study, decreased expression of CD72, a B cell regulatory molecule, further highlighting the importance of B cells in the pathogenesis of the two diseases. (14)

The thymus, which is the origin of T cells, is a key organ in the pathogenesis of MG. Thymectomy is a notable treatment option in patients with MG but is not a typical therapy for MS patients. However, in our population, MS attacks were either none or very few after thymectomy of patients with MG and MS. Unlike patients with concurrent MS and MG, thymectomy is proposed to be a trigger of NMO in MG patients.(15)

Matrix metalloproteinases (MMPs) also have pathogenic roles in the central nervous system diseases. MMPs 3 and 9 are common MMPs that are elevated in MG and MS relapses.

On the other hand, granulocyte-macrophage colony-stimulating-factor (GM-CSF) are pathogenic in the context of MS, whereas they have protective effects in patients with MG.(16)

Midaglia et al.(17) reported an interesting case of a 24-year-old female with MS who was being treated with alemtuzumab and subsequently developed MG. Gharagozli et al.(18) also reported a case of an interferon-beta 1b treated MS patient who developed MG later on. There is also a report of a patient with PPMS who subsequently developed MG. Similar to one of our cases with PPMS and MG, the clinical course was unfavorable with an EDSS score of 7.0. (19)

Several cases of concurrent NMO and MG have been reported suggesting a common immunopathological mechanism in the two diseases. However, the altered immune response caused by thymectomy or immunosuppressive drugs used in MG have also been put forward as triggers of NMO in MG patients. (20)

The complement system is remarkably involved in the pathogenesis of NMOSD and MG, which may be the underlying mechanism for their concurrent presentation.(21) Both MG and NMOSD are mediated by IgG1 antibodies against distinct proteins, therefore, common immunological pathways may be involved in the two diseases considering the fact that the concurrence of NMOSD and MG is relatively higher in the general population than each of the diseases alone.(22) In AChR positive MG, similar to NMO, IgG1 and IgG3 antibodies are the main pathogenic antibodies that can lead to complement activation and ultimately, complement dependent cytotoxicity. (23) In a unique study Mizrachi et al.(24) injected NMO immunoglobulins and AQP4 peptide into mice with experimental autoimmune MG (EAMG) which caused increased muscle weakness and exacerbation of EAMG.

Castro-Suarez et al.(22) reported two cases of MG who developed NMOSD later on. A 57-year-old woman developed bilateral vision loss while being treated for MG, and a 26-year-old female with tingling sensations in her upper extremities, but was not being treated for MG, although diagnosed. The latter patient underwent thymectomy at age 30 with resolution of myasthenia symptoms, and without any

NMO exacerbations. Both patients were able to carry out their daily tasks independently on follow up. Akiyuki et al.(20) reported two cases of MG followed by NMO, both of which had undergone thymectomy prior to NMO diagnosis. Bates et al. (25) reported a case of a 54 year old male who was diagnosed with AQP4 and anti-MOG + NMOSD 15 years after the diagnosis of AChR positive MG and 5 years after thymectomy. This is consistent with the study that retrospectively showed that in almost 80 % of patients with concurrent NMO and MG, thymectomy preceded the diagnosis of NMO. (15) However, there is also a report of concurrent MG and NMO without thymectomy. (26)

When a patient is diagnosed with a primary CNS disease, the diagnosis of the second disease may become difficult. Based on previous studies, MG can present in patients with either NMO or MS, however, diagnosis of MG usually precedes MS, unlike NMOSD which is mainly diagnosed after MG or thymectomy.(27,28) In our study two patients with NMOSD and MG had undergone thymectomy, both of which NMOSD presented after thymectomy.

Conclusion

The relative frequency of concurrent MS and MG is moderately higher than the MG prevalence in the general population (0.34% compared to 0.005-0.024%). The relative frequency of concurrent NMO and MG (5%) is also higher than the prevalence of MG in the general population. The higher frequency may point to common immunopathologic mechanisms.

Declarations

Ethics and Consent to Participate

The study is approved by the ethics committee of the Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.294) and all methods were performed in accordance with the relevant guidelines and regulations.

Appropriate written consent was take from all the patients whose data are used in this article.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funding was received for this study.

Authors contributions

ME, AAS provided the study design and collected data from patients' files. AAS, MS, and NS wrote the primary draft of the manuscript and conducted data analysis of patients. AAS, NS, MS, and ME edited the primary draft and finalized the paper. All authors have read the final manuscript and approve it for submission.

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Abbreviations

MG: Myasthenia Gravis

MS: Multiple Sclerosis

NMOSD: Neuromyelitis Optica Spectrum Disorders

EAMG: Experimental Autoimmune Myasthenia Gravis

AQP4: Aquaporin 4

MOG: Myelin Oligodendrocyte Glycoprotein

AChR: Acetylcholine Receptor

MMP: Matrix Metalloproteinase

GM-CSF: Granulocyte-macrophage colony-stimulating factor

CNS: Central Nervous System

NMJ: Neuromuscular Junction

EDSS: Expanded Disability Status Scale

PPMS: Primary Progressive Multiple Sclerosis

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Table 2

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