



*Original Contribution*

## MYASTHENIA GRAVIS DEVELOPMENT AND CRISIS SUBSEQUENT TO MULTIPLE SCLEROSIS

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### ABSTRACT

During last decade sporadic combination of multiple sclerosis (MS) and myasthenia gravis (MG) has been reported repeatedly. Although they seem anecdotal, they are importance enough to rise concerning about co-occurrence of MG and MS. Here we presented two cases of MS who developed MG during their disease period. Both of them have been received interferon with diagnosis of relapsing remitting MS. Interestingly, one of them developed MG crisis 4 years after diagnosis of MS. MS and MG have relatively same distribution for age, the younger peak of the bimodal age distribution in MG and HLA typing. Furthermore, some evidences support the role of systemic immune dysregulation due to a genetic susceptibility that are common to this group of diseases. The association may be underdiagnosed because of the possible overlap of symptoms specially cranial manifestations in which either MG or MS can mimic each other manifestations leading to underestimating incidence of new ones. The evident warrant physician specially neurologist to always consider presumably occurrence of another disease when encounter with such a patients either with MS or MG.

**Key word:** multiple sclerosis, myasthenia gravis, neuroimmunological disorders

### INTRODUCTION

Anecdotal and sporadic reports of combination of multiple sclerosis (MS) and myasthenia gravis (MG) rise concerning about co-occurrence of them. Here we presented two cases of MS who developed MG during their disease period. Interestingly, one of them developed MG crisis 4 years after diagnosis of MS.

#### *Case 1:*

A 44 year old woman had been diagnosed 4 years ago with MS with presentation of ataxia and left side hemiparesis. According to McDonald criteria with including positive MRI findings and positive CSF for oligoclonal bands definite MS was confirmed and she was treated by 1gram daily methylprednisolone intravenously for 5 days followed by interferon beta-1b two times per week. She had a history of hyperthyroidism which underwent

Levothyroxine sodium since 6 years ago. Forty three months after first attack she presented by regurgitation and dysphagia complaints that was long-standing from 2 months ago and was considered as new attack of MS initially. After history taking and neurological examination other signs including easy fatigability (on examination), nasal speech and ptosis have been detected. The new signs suspected neurologist to myasthenia gravis (MG). The diagnosis of MG was confirmed by positive edrophonium test. Repetitive nerve stimulation in electrophysiological examination showed about 23% decrement in his muscles. However, serum acetylcholine receptor antibodies (ACh-R Ab) were negative. CT of the thorax revealed no thymic enlargement. She has been received 60 mg Pyridostigmine Bromide three times per day and interferon beta-1b was discontinued because of probable adverse effect of interferon on MG and also because patient was symptom free of MS. The signs and symptoms of MG were relieved relatively but not completely after few days. She was discharged with mild orofacial weakness and followed. After two weeks she presented with severe bilateral ptosis,

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intermittent double vision, choking during swallowing and dyspnea. With diagnosis of MG crisis the patients admitted to intensive care unit and was underwent tracheal intubation and plasmapheresis 4 sessions containing plasma exchanging with albumin 2 liters in each day. In addition prednisolones 25 mg per day was prescribed. After extubation Pyridostigmine Bromide each 4 hours were administered via nasogastric tube. After plasmapheresis patients still was suffered from diplopia and ptosis and mild dyspnea and the gag reflex was impaired. Intravenous immunoglobulin was administered 20g daily for six days and produced a dramatic improvement in her clinical condition. After day 8 patients showed alleviation and after day 14 patients discharged with only mild ptosis and few limitations in vertical eye movement. She did not developed new attack of MS after 3 months.

#### **Case 2:**

A 27 years old female who was known case of MS from 3 years ago was admitted to our hospital as new attack of MS due to fluctuating symptoms of ptosis and generalized weakness during last week. Her MS had been presented by diplopia, vertigo and ataxia at first. She developed 3 attacks of hemiparesis and diplopia during 3 year ago and was received Interferon Beta-1a weekly (AVONEX). She had limitation in vertical eye movement. Her ptosis and diplopia showed worsening by Simpson's Test. She also had increased spasticity in lower extremities and Hoffman sign was positive. Brain MRI T2 showed generalized brain atrophy and increasing in demyelinating plaque number in periventricular comparing to 2 years ago. Her ptosis improved dramatically after injection of 2 mg Edrophonium Chloride. But repetitive nerve stimulation and ACh-R Ab were not in consistent with diagnosis of MG. CT of the thorax was normal and for thymic enlargement and thyroid function tests were normal.

With suspicious to MG we prescribed a trial of 60 mg Pyridostigmine Bromide three times per day and Interferon Beta-1a was discontinued. All sign and symptoms were resolved after few days.

#### **DISCUSSION**

We presented two cases that developed MG 4 years and 3 years after diagnosis of MS. Both of them have been received interferon with

diagnosis of relapsing remitting MS. Interestingly we described for the first time crisis of MG in a 44 years old female just two months after presentation of MG symptoms.

In previous years coexistence of MS and MG was reported rarely (1). However during more recent years occurrence of MS and MG subsequent to each other has been reported several times but combination of two diseases has not even been discussed seriously. Supporting evidences comes from an increased incidence of reported CNS demyelinating disease including MS in patients with MG (2). Gotkine et al in 2006 reported five of 214 reviewed patients with MG (2.3%) who had CNS demyelinating disease. However, only completely 1 patient and possibly another one had dissemination in time and space and neither had typical MS. In this series the occurrence of CNS demyelinating disease always occurred subsequent to the initiation of MG treatment, supporting the possibility that immunomodulating treatments including thymectomy and immunosuppression may have a role (3). It has been suggested that thymectomy might have induced immune dysregulation and considerable number of patients showed different autoantibodies in their serum years after thymectomy when compared with non-thymectomized patients and healthy ones (4).

It has been reported that the clinical course of both MG and MS is mild in most patients with this combination of neuroimmunological disorders, but the onset of MG could cause an exacerbation of MS, whereas MG can be relatively unaffected by fluctuations in the clinical course of MS (1,5). However we encountered a case of MS who developed MG crisis. It seems any clinical course could be expected by these two autoimmune diseases.

In largest study by British Columbia on patients with well-documented diagnoses of both MS and MG, 8 patients with co-occurring MS and MG were reported. The value was significantly higher than predicted by prevalence estimates. MS occurred before MG in six patients, after MG in seven patients and within one year in two patients. According to an epidemiological survey 15 patients was reported in the literature with definite diagnoses of both MS and MG (1). In a case series on 1718 patients with definite MS in Isfahan, Iran, five MG were detected

(291/100,000; 0.29%) (6). None of the six patients was positive for ACh-R Abs. Our two cases also had negative for acetylcholine receptor antibodies but other series reported more positive results. In addition three Brazilian patients with MG that presented distinct demyelinating diseases including two monophasic and one recurrent neuromyelitis optica, 6-18 years after the diagnosis of MG was reported. In our study like previous, ocular and bulbar manifestation of MG were most common findings (5, 6).

Some rational mechanisms have been hypothesized for this phenomenon. First, it is a random finding that could happen by the chance. Also it has been considered as a coincidence of two autoimmune disorder (5) or MG may be triggered by interferon treatment via deviation of immune response towards a predominantly Th2 reaction (7). Furthermore two diseases have relatively same distribution for age, the younger peak of the bimodal age distribution in MG and HLA typing (A1, A2, DR3, B8) (8). Antinuclear antibodies (ANAs) usually occur in approximately 20 to 30% of MS and 40% of MG patients. The high frequency of ANAs in MS and MG can support the role of systemic immune dysregulation (9). Both of them are related with some autoimmune disorder. It has been suggested that there may be genetic susceptibility that are common to this group of diseases (10). An accidental coincidence of two diseases was excluded by high significant estimation of British Colombia study as largest series in this setting. Also the incidence of demyelinating diseases in patients with MG is much higher than expected in the general population (7). Also presentation of MS subsequent to MG is against the triggering effect of interferon on presentation of new case of MG as sole etiology. Furthermore, there were some patients who developed MG in MS course without treatment with interferon. So it is too simplistic to pay no heed to important combination between MS and MG.

The association may be underdiagnosed because of the possible overlap of symptoms specially cranial manifestations in which either MG or MS can mimic each other manifestations leading to underestimating incidence of new ones. The evident warrant physician specially neurologist to always

consider presumably occurrence of another disease when encounter with such a patients either with MS or MG. This critical question should always be considered that whether new symptom could be the first presentation of another disease or not i.e, MG versus MS.

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