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Myasthenia Gravis during the Course of Neuromyelitis Optica

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Key Words
Neuromyelitis optica · Devic's syndrome · Myasthenia gravis · Multiple sclerosis · Aquaporin-4 · Interferon · Thymectomy

Abstract
Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder of the central nervous system that has been thought to be a severe subtype of multiple sclerosis for a long time. The discovery of aquaporin-4 (AQP4) antibody as a highly specific marker responsible for the pathogenesis of NMO, not only has made a revolutionary pace in establishing a serologic distinction between the two diseases, but it has also classified NMO as an antibody-mediated disorder. Similarly, myasthenia gravis (MG) is a well-known antibody-mediated disorder. In this report, we describe the case of a middle-aged female patient who experienced definite MG with an unclear clinical picture of chronic demyelinating disease that initially reflected the diagnosis of MS, but further imaging and paraclinical workup (e.g. positive AQP4 antibody test) revealed NMO. The coexistence of NMO and MG is previously described. However, this is the first case with NMO symptoms preceding the onset of MG. Of note, the development of MG occurred after a 2-year period of interferon β-1b (IFN β-1b) administration. This calls the question to mind of whether in our case MG is induced by the administration of interferon, instead of an original pathogenic link between MG and NMO. In other words, immunomodulatory treatments can slip the immunity towards T-helper II predominant pathways that can trigger MG. However, if we assume that such an explanation (i.e. increased susceptibility to autoantibody-mediated disorders) is true, our case can be considered the first case of NMO who developed MG following IFN β-1b treatment.

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Introduction

Neuromyelitis optica (NMO or Devic's syndrome) is an inflammatory demyelinating disorder of the central nervous system (CNS) that has been thought to be a severe subtype of multiple sclerosis (MS) for a long time. However, evidences emerging from clinical status, neuroimaging, and, laboratory findings would aid in distinguishing these two immune-mediated conditions at their developed stages [1–4]. NMO predominantly affects optic nerve(s) and spinal cord; although, involvement of other parts of the CNS, for example, brain is possible. Indeed, NMO-related brain lesions are sometimes undistinguishable from those pertaining to MS and, in some instances, this makes the diagnosis very difficult [4, 5]. During the recent decade, the discovery of aquaporin-4 (AQP4) antibody as a highly specific marker responsible for the pathogenesis of NMO, not only has made a revolutionary pace in establishing serologic distinction between the two diseases, but it has also classified NMO as an antibody-mediated disorder [6, 7]. Moreover, since this discovery, the concurrence of NMO with other types of B-cell autoimmunities has been focused by many authors [8, 9]. On the other hand, myasthenia gravis (MG) is a well-known antibody-mediated disorder that specifically affects nicotinic acetylcholine receptors (AChR) of the muscle tissue. The clinical picture of MG mostly reflects muscular fatigability caused by the disruption of AChR functions and motor-end-plate transmissions [10]. Notwithstanding the fact that the pathophysiology of NMO and MG are both immune and antibody mediated, the concomitancy of these two disorders is uncommon whereby, to date, approximately 16 cases of this condition are reported. In all of such reported cases, MG preceded the development of NMO and, in the majority of them, NMO onset was induced by the procedure of thymectomy which is a routine therapy for MG [11, 12]. As far as we are aware, to date, there are no reports describing the development of MG after initial symptoms of the chronic course of NMO. The purpose of this report was to illustrate the clinical and paraclinical features of a patient who manifested the above-mentioned condition and discuss on possible pathogenic mechanisms.

Case Report

A 40-year-old Persian woman was admitted to our department in October 2005. Her initial neurologic symptoms occurred at age 33, when she was diagnosed with optic neuritis (ON) of the right eye and paraparesia. Over the ensuing 7 years since her first symptoms, she experienced another relapse of ON in the left eye and also several episodes of paresthesia and paraparesia. Neurologic examination revealed mild spastic paraplegia and bilateral optic atrophy. Her 48-year-old sister has definite NMO since 8 years (several ON and myelitis episodes, spinal lesion extending from C3 to C6, and normal brain MRI) with a negative AQP4 antibody test. She is currently taking immunosuppressant drugs. Furthermore, her nephew, a 26-year-old male, was diagnosed with definite MS since 3 years. He is taking interferon β-1b (IFN β-1b). No other significant disorders were present in these relatives.

Our patient's first brain and spinal MRI in 1998 revealed four to six periventricular and only one small cervical plaque(s). In 2005, the second MRI series showed several periventricular plaques with several new T2 lesions (**fig. 1**), and also, the presence of the former single plaque in the cervical spine. At that time, with the diagnosis of clinically definite MS, she was started on IFN β-1b every other day. Except for another relapse of bilateral ON (in early 2006), her neurologic status reached a stable level and the interferon was continued for approximately 2 years until December 2007, when she exhibited bilateral ptosis, diplopia, weakness of masticatory muscles, and, generalized fatigability involving four limbs. Repetitive nerve stimulation (Jolly's test) was employed with a Medelec Synergy system and a significant decremented response was observed.

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Also, Edrophonium (Tensilon) test was performed and consequent objective improvement of signs was prominent. Moreover, serum titers of antibody to AChR were detected at high levels using immunoprecipitation methods. In this respect, the diagnosis of MG was confirmed and pyridostigmine (180 mg/day) and azathioprine (100 mg/day) were commenced. The patient was recommended to undergo thymectomy, but she did not consent to the procedure due to her psychological status.

Over the ensuing 3 years, she was free of any demyelinating relapse until she obstinately discontinued the entire medications for 4 months. In late June 2010, she encountered a severe paraplegic attack with urinary incontinence. We performed the third series of MRI workup that showed a large lesion in the upper cervical spine extending longitudinally in more than three vertebral segments (**fig. 2**). AQP4 antibody was tested qualitatively, using commercially available indirect immunofluorescence kits (Euroimmun, Luebeck, Germany) that showed positive results. In July 2010, our case fulfilled the revised clinical and imaging criteria for NMO [13]. Consequently, she was immediately started on plasmaphresis. Afterwards, mitoxantron was administered with five doses at the first, second, third, fifth, and eighth months (with overall dosage of 80 mg). Then, azathioprine (100 mg/day) and low-dose prednisolone (10 mg/day) were prescribed.

Discussion

We described a patient who experienced definite MG during an unclear clinical picture of chronic demyelinating disease that firstly reflected the diagnosis of MS, but more paraclinical workup (e.g. AQP4 test) in later stages revealed NMO. In sum, six points are worth noting about this case: (1) this is the first case with NMO symptoms preceding the onset of MG. (2) No thymectomy was performed after the diagnosis of MG, although after it, NMO symptoms continued with more severity. (3) MG symptoms occurred in a patient receiving interferon for 2 years. (4) After a relatively long relapse-free period, withdrawal of immunosuppressant drugs aggravated the NMO symptoms with great severity. (5) Although, initial symptoms of NMO preceded the onset of MG, longitudinally extensive spinal cord lesion (LESCL) occurred after MG symptoms. This fact is in line with previous similar reports, and (6) the first and second series of MRI showed periventricular plaques that could simply meet diagnostic criteria for MS.

Regarding the first and second points, as mentioned above, all of the previous studies concerning the concurrence of these two disorders reported the precedence of MG, and the majority of them acknowledged the thymectomy as the main etiologic factor that could alter the balance of the self-tolerance system leading to the development of another autoantibody-mediated disorder [11, 12]. In other words, it is generally postulated that adult thymus contains suppressor T cells that are mandatory to maintain the inhibition of self-reactive cells, and, perform a key preventive role against autoimmune diseases [11, 14, 15]. Of note, this pathomechanism is well supported by several clinical and laboratory lines of evidence [12, 15]. On the contrary, Kay et al. [16] and Furukawa et al. [17] reported the occurrence of NMO after MG without thymectomy. These exceptional instances raise two possible explanations: (1) since the majority of cases developed NMO after thymectomy, the concurrency in these two exceptions might have accidentally occurred. (2) If we assume that in these two instances – instead of a mere incidence – there was an underlying pathomechanism, this suggests that thymectomy might not be the essential preceding factor for the development of NMO. In our case, the ongoing course of NMO does not seem to correlate with the absence of a thymectomy procedure.

According to the third point, to date, patients with MS or hepatitis C are reported to develop MG during the IFN β-1b treatment [18]. The role of incidence in such sparse reports cannot be ruled out because, to date, IFN has been administered to many patients

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with MS who did not present such an adverse condition. However, some authors tried to explain these conditions by adhering to the well-documented increase of autoantibodies in individuals treated with IFN β-1b [19, 20]. Indeed, they postulated that interferon treatment can slip the immunity towards T-helper II predominant pathways and thus raise the susceptibility to autoantibody-mediated disorders [18, 19]. If we consider such explanations, then the question of whether the cause of MG in our case is also related to interferon comes to mind, instead of an original pathogenic link between MG and NMO. However, if we assume that such an explanation is true, our case can be regarded as the first case of NMO who developed MG induced by the administration of interferon. The report of this condition, if repeated in the future, can provide further evidence for the preference of immunosuppressive versus immunomodulatory drugs in NMO patients [21]. Of most importance, we remind that NMO patients are reported to be at higher risks of other autoantibody-mediated disorders. About one third of them represent with either a variety of autoimmune-mediated disorders or seropositivity for different self-reactive antibodies [4, 8, 9]. Hence, neurologists should be cautious that immunomodulation might expose NMO cases to excessive risk of other autoimmunities. In this respect and regarding the fourth mentioned point, our case responded well to the immunosuppressive drugs that were prescribed to control MG before the establishment of the NMO diagnosis. But unfortunately, the discontinuance of treatment deprived her from potential benefits of immunosuppression in controlling the course of NMO that was not still confirmed at that stage. Moreover, due to the fact that the AQP4 antibody test is a brand new method that was not ordinarily available from 2004 to 2009 in our country, she could not receive benefit from this method at early stages. Aside from these therapeutic benefits, to indicate the uniqueness of our case, it seems to be important to report the AQP4 antibody titers before the onset of MG. However, our patient developed MG in 2007 when the test was not available.

According to the fifth point, in sum, all of the studies on concomitancy of NMO and MG including our case reported the occurrence of LESCL after MG. This might be suggestive of a pathogenic nature of MG that is not related to all clinical features of NMO (including ON, etc.), but related to the presentation of LESCL alone. Concerning the sixth point, we remind the fact that AQP4 antigen is present throughout the CNS. Besides, 10% of NMO patients have MS-typical brain plaques as an atypical finding. This proportion shows a four- to five-fold increase when reported in a Japanese population [5, 22]. This point further highlights the value of an early AQP4 antibody test in comparison to imaging techniques. In conclusion, we underline the importance of distinguishing NMO from MS at very initial stages that is possible by the AQP4 antibody test. Such an early differentiation can play a pivotal role in the management of the clinical course of the disease. For this test, specially, cases who firstly present with ON and paraparesia (similar to our case) are addressed as the first-line candidates.

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Disclosure Statement

The authors have no proprietary interest in the materials presented herein.

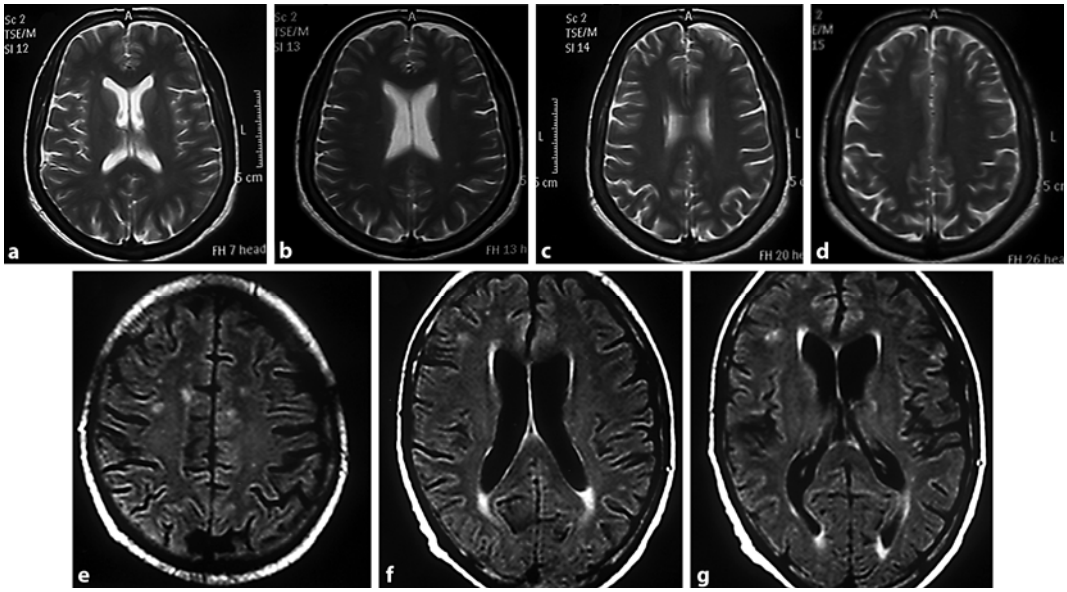

Fig. 1. The second MRI series of the brain in 2005. Axial T2-weighted (**a–d**) and FLAIR sections (**e–g**) show several periventricular and subcortical plaques.

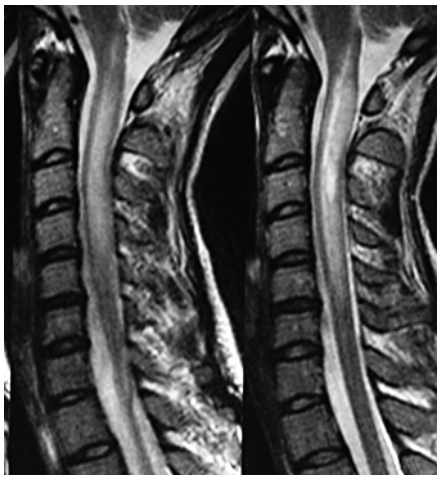

Fig. 2. Sagittal T2-weighted spinal MRI shows large extending lesions in the upper cervical region.

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