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Case Report

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Co-occurrence of myasthenia gravis and demyelinating diseases of the central nervous system: A case report and review

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Abstract

Myasthenia gravis and demyelinating diseases are disorders that affect the neuromuscular junction and the central nervous system respectively. Although both conditions are rare, reports of the coexistence of these two pathologies are increasing. We describe one patient with MG develop relapsing and remitting demyelinating diseases after thymectomy.

Keywords: Demyelinating diseases of the central nervous system; Myasthenia gravis; Acetylcholine receptor antibody; Multiple sclerosis; Neuroimmunology.

Introduction

Even though polyautoimmunity exists between different autoimmune diseases, the co-occurrence of Myasthenia Gravis (MG) and demyelinating diseases of the Central Nervous System (CNS) is rare; however, this rare combination occurs more frequently, as repeatedly reported, than expected by random association [1-3]. In this article, in addition to presenting a unique female patient with a previous diagnosis of MG, who presented with possible Multiple Sclerosis (MS), we aimed to review the literature to find the common immunological mechanisms involved in the pathogenesis of MG and possible MS. The following case illustrate this extremely rare combination of diseases, which also shared a clinical course of remissions and of exacerbations, and have been treated with immunosuppressive therapy.

Case presentation

This is 38-year-old women with a past medical history of MG diagnosed in 2006 (at age 23) following initial presentation with fluctuating difficulty speaking, chewing and swallowing. Thymectomy was realized in 2007 and thymic histology revealed benign thymoma. Then she was symptomatically stable on pyridostigmine. She was taking pyridostigmine for 8 years, until she self-discontinued the medication due to no visible symptoms. However, the patient did not perform any requested laboratory test and lost to follow-up.

In April 2021, she developed tingling sensation in the limbs and right face, and dizziness followed by nausea and vomiting. She also experienced the double vision. Neurological examination showed nystagmus, right external rectus muscle palsy, right

facial paresis, and decreased sensation to pinprick in the right face. Generalized hyperreflexia and bilateral Hoffmann sign also revealed evident. Hematological tests, biochemistry screening were normal, and serological tests for HIV and HTLV were negative. While a test for anti-acetylcholine receptor (AChR) antibody was positive (9.68 nmol/L; normal ≤0.45 nmol/L). The thyroid function was abnormal with low level of thyroid stimulating hormone (0.119 mIU/L; normal 0.27-4.2 mIU/L). Anti-nuclear antibody test was weakly positive (1:100; normal<1:40), but the other serum antibody tests (anti-SSB/La, anti-RNP, Sm and SSA/Ro) were negative. Cerebrospinal fluid analysis was normal with a normal electrophoretic protein pattern. The tests of demyelinating disease of central nervous system auto-antibodies (MOG, AQP4, MBP, GFAP), oligoclonal bands (OCB) of Cerebrospinal Fluid (CSF), autoimmune encephalitis related auto-antibodies (NMDA, AMPA1, AMPA2, LGI 1, GABAB, CASPR2-Ab-IgG) and anti-glial fibrillary acidic protein antibodies (GFAP-Ab) were negative. Brain CT showed a lesion with low density in the right corona radiata. Brain MRI revealed lesions of hyperintense on FLAIR and T2-weighted images in the brainstem and the right corona radiata (Figure 1). Dynamic brain MR enhancement suggested uneven enhancement of the right brachium pontis (Figure 2). Spinal MR showed a suspicious lesion of hyperintense on FLAIR at T1-T2 (Figure 3). Visual Evoked Potential (VEP) was abnormal on both sides. Concurrent MG and demyelinating diseases of the Central Nervous System (CNS) was formally diagnosed, although MG symptoms started first. The demyelinating diseases of the CNS was tended to the diagnosis of possible Multiple Sclerosis (MS) according to the 2017 McDonald criteria for diagnosis of MS [1]. The patient was treated with intravenous dexamethasone and oral pyridostigmine (180 mg/day), with improvement of double vision, dizziness and paresthesia. Mycophenolate Mofetil (MMF) 250 mg twice/day was then associated. At discharge she was treated with prednisone 30mg QD, MMF 250 mg BID and pyridostigmine 60mg TID. During the following 2 months, the patient underwent to regular follow up and manifested no obvious symptoms. The prednisone was gradually decreased.

Several days after the last follow-up visit, she was admitted with numbness in her left face, dizziness, nausea and vomiting. Her neurologic examination was notable for nystagmus, impaired pain and light touch sensory examinations in the left face. Brain MRI showed a new lesion of hyperintense on FLAIR and T2-weighted images in the left of medulla oblongata (Figure 4). The patient was diagnosed with relapse of demyelinating diseases of the CNS combined with MG. Intravenous methylprednisolone pulse therapy was started, with substantial improvement of numbness, dizziness, nausea and vomiting. She was discharged on prednisone 50 mg QD, MMF 750 mg in the morning and 500mg in the afternoon. On her continuous follow-up visit, the patient had full recovery. Brain MRI was repeated in November 2021, which didn't show any new active lesions (Figure 5).

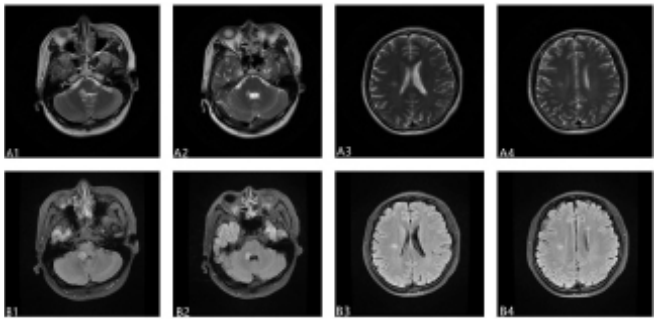

Figure 1: Brain MRI revealed lesions of hyperintense on T2-weighted(A1-A4) and FLAIR (C1-C4) images in the brainstem and the right corona radiata(B1-B4).

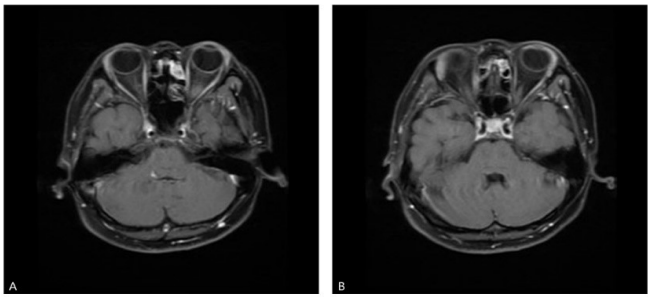

Figure 2: Dynamic brain MR enhancement suggested uneven enhancement of the right brachium pontis (A-B).

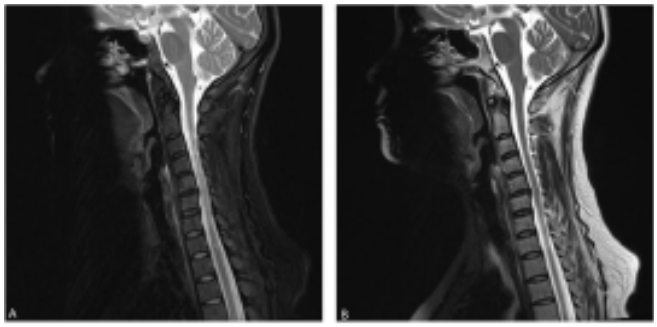

Figure 3: Spinal MR showed a suspicious lesion of hyperintense on FLAIR at T1-T2s (A-B).

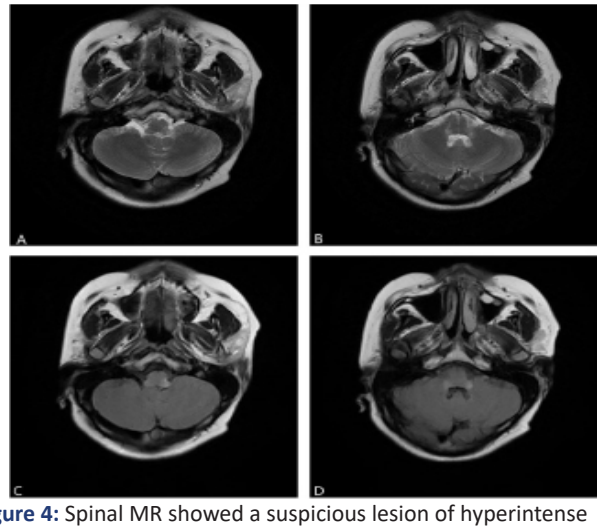

Figure 4: Spinal MR showed a suspicious lesion of hyperintense on FLAIR at T1-T2s (A-B).

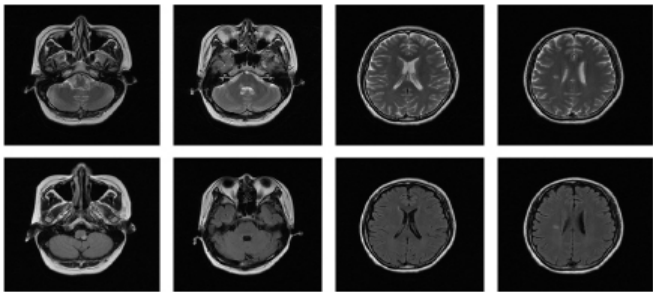

Figure 5: Brain MRI was repeated in November 2021, which didn't show any new active lesions.

Discussion

Here, we describe the coexistence of MG and demyelinating diseases of the CNS (possible MS) in a female patient with long follow-up. Polyautoimmunity exists between different autoimmune diseases. which reflects possible common pathogenic mechanisms [2,3]. Previous researches show that a similar immunogenetic background predisposes to susceptibility to different autoimmune diseases, whereas diverse triggering and unknown genetic factors cause different clinical diseases [3,4]. In this article, we primarily intend to review and find a similar immunological background and theories for the co-occurrence of MG and demyelinating diseases of the CNS which affect the neuromuscular junction and the CNS respectively.

MG is an autoantibody-mediated neurological disease that affects the postsynaptic membrane at the neuromuscular junction [5]. Localized or general muscle weakness is the major manifestation of MG and the autoantibodies consist of AChR antibodies, anti-muscle specific tyrosine kinase (MuSK) antibodies or anti-lipoprotein receptor-related protein 4 (LRP4) antibodies [4]. The thymus plays an important role in AChR antidody-mediated MG, with thymoma in 10% of patients or with thymic follicular hyperplasia in moce than 80% of patients with early-onset MG [5]. Autoantigen specific cells are produced due to abnormal positive or negative T cell selection in thymus, then they leave the thymus and induce MG or other autoimmune diseases [4]. Therefore, thymectomy is a treatment option for nearly all patients with thymoma and in many AChR antibody-mediated MG [5].

Demyelinating diseases of the CNS are a group of diseases characterized by the loss of nerve myelin sheath and relatively mild damage of the neuronal cell and axon. The most common diseases consist of MS and Neuromyelitis Optica Spectrum Disorders (NMOSD), frequently presenting with similar clinical courses [6-8]. Genetic and environmental factors, as well as autoimmunity play causal roles in both diseases [3,9]. Traditionally, it is believed that MS belongs to a T-cell-mediated disease and NMOSD caused by humoral dysimmunity [6]. Whereas recent studies demonstrated that the interplay between T and B cells in immune responses participate in the pathogenesis and progression in MS [8] and NMOSD [7]. Many studies have proposed that humoral immune-mediated pathogenesis in MS, for the reasons that the OCB in the CSF, existence of B cell-rich aggregates in the meninges, and effective treatment of CD19/20monoclonals depleting B cells in patients[8,10].Study suggested that CD72 acts as an inhibitory co-receptor of B cells in MG [11],and finding was supporting the hypothesis of B cell activation in the antibody-mediated process of MS[11-13].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 [14]. 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.

Our patient development demyelinating diseases of the CNS nearly 15 years following the diagnosis of MG and 14 years following thymectomy. A recent study showed that the mean-age for MG was 27.66 ± 10.33 years old and for NMOSD manifestations was 41.78 ± 14.68 years old [15]. The clinical onset of MG can present before or after the diagnosis of MS [5], while most patients especially those taking thymectomy are diagnosed with MG before clinical onset of NMOSD, often by more than a decade [16,17]. In addition, most patients have a mild clinical course of MG in concurrent MG and demyelinating diseases of the CNS, congruent with our patient [5]. Some case reports also described the clinical onset of MG during or after treatment of MS with interferon beta [18,19], glatiramer acetate [20]and alemtuzumab [21]. Whether interferon beta, glatiramer acetate and other immunomodulatory drugs are triggering factors directly causing MG via deviation of immune response towards a predominantly Th2 reaction, or in an already predisposed patient, is unknown [18,20].

Our patient was diagnosed with concurrent MG and demyelinating diseases of the CNS (possible MS). Her AChR antibody was positive, while auto-antibodies (MOG, AQP4, MBP, GFAP) and OCB of CSF were negative. There are up to 10% of MS patients lack OCB [22].

Thyroid function of our patient was abnormal, also antinuclear antibody test was weakly positive. For patients' coexistence of MG and MS, there are other co-occurring autoimmune diseases (Graves disease, iritis, systemic lupus erythematosus, asthma and polyarthritis) [23]. Thyroiditis, Sjogren syndrome, systemic lupus erythematosus or antiphospholipid syndrome are common autoimmune diseases in patients' coexistence of MG and NMOSD [16]. T regulatory cells (Tregs), generated mainly in the thymus have the ability to suppress abnormal effector CD4+ T (Teff) cells and sustain self-tolerance[24]. Different immunological mechanisms for loss of self-tolerance, especially Tregs take part in the development of autoimmune responses such as MG and demyelinating diseases of the CNS [5]. Nowadays, there are Tregs augmentation therapies, by enhancing Treg suppressive activity and/or numbers, enhancing suppression of Teff cells, increasing Treg migration, or enforcing self-tolerogenic signals have been studied as therapeutic strategies [5].

Gerli et al. reported 12.5% of thymectomized MG patients occurred additional autoimmune diseases [12]. Compared with healthy controls and MG patients without thymectomy, the frequencies of antinuclear, anti-double-stranded DNA, and anti-cardiolipin antibodies were significantly higher in thymectomized MG patients [17]. In addition, it is hypothesized that a decrease in Tregs in the adult thymus following thymectomy in MG [25-28].

Melanoma cell adhesion molecule (MCAM)-expressing T cells reportedly consist of an interleukin (IL)-17–producing pathogenic Th cell subset in MS, Experimental Autoimmune Encephalomyelitis (EAE), and other inflammatory diseases [27]. MCAM+ mTh cells were elevated in the CSF of relapsing patients with MS and in both the PB and CSF of patients with NMOSD,the frequency of MCAM+ Th cells increases in the peripheral blood and the CSF and accumulates in the CNS lesions

of patients with MS [29,30]. These results indicate that MCAM contributes to the pathogenesis of MS and NMOSD through different mechanisms, MCAM could be a therapeutic target of the CNS IDDs, and further study is needed to elucidate the underlying mechanism of MCAM in the CNS IDD pathogenesis [31].

Human leuocyte antigen (HLA), as a primary susceptibility gene, is involved in diverse autoimmune disorders [32]. It was reported that HLA-DRB1*16 was a risk allele of AChR antibody-positive MG in Italy, while HLA-DRB1*16:02 for AQP4 antibody-positive NMOSD in Japan. Besides, HLA-DRB1*15:01 was regarded as a risk allele for MG and NMOSD [32]. Hence, there might be unrevealed specific susceptibility alleles in patients with comorbidity of MG and demyelinating diseases of the CNS.

Co-occurrence of MG and demyelinating diseases of the CNS exist more frequently than expected by random association, which shows the complexity of confirming an optimal diagnosis in cases of poly-autoimmunity. The case highlighted the importance of continuous follow-up and periodic reevaluation for newly emerging untypical neurologic symptoms, which may invoke a new co-existing immune disease. Further research is needed to clarify the immunopathogenesis and genetic mechanisms in patient's co-occurrence of MG and demyelinating diseases of the CNS, which will promote the generation of a unified treatment.

Declarations of interest: None

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References

1. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurology. 2017; 17: 162-173.
2. Nacu A, Andersen JB, Lisnic V, Furlund Owe J, Gilhus NE. Complicating autoimmune diseases in myasthenia gravis: a review. Autoimmunity. 2015; 48: 362-368.
3. Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, et al. International Consensus Guidance for Management of Myasthenia Gravis 2020 Update. Semin Neurol. 2020.
4. Yc A, Chang L, Wang C, Han X, Mu L, et al. Metformin attenuates autoimmune disease of the neuromotor system in animal models of myasthenia gravis. International Immunopharmacology. 2019; 75: 105822.
5. Dehbashi S, Hamouda D, Shanina E. Co-occurrence of multiple sclerosis and myasthenia gravis: A case report and review of immunological theories. Mult Scler Relat Disord. 2019; 34: 135-136.
6. Hartung H-P, Graf J, Aktas O, Mares J, Barnett MH et al., Diagnosis of multiple sclerosis: revisions of the McDonald criteria 2017 - continuity and change. Current Opinion in Neurology. 2019; 32: 327-337.
7. Probert F, Yeo T, Zhou Y, Sealey M, Arora S, et al. Determination of CSF GFAP, CCN5, and vWF Levels Enhances the Diagnostic Accuracy of Clinically Defined MS From Non-MS Patients with CSF Oligoclonal Bands. Front Immunol. 2022; 12: 811351.
8. Zhang X, Ge R, Chen H, Ahiafor M, Liu B, et al. Follicular Helper CD4+ T Cells, Follicular Regulatory CD4+ T Cells, and Inducible Costimulator and Their Roles in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis. Mediators of Inflammation. 2021; 2021: 1-10.
9. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurology. 2017; 17: 162-173.
10. Husser-Kinzel S, Weber MS. The Role of B Cells and Antibodies in Multiple Sclerosis, Neuromyelitis Optica, and Related Disorders. Front Immunol. 2019; 10: 201.
11. Lu J, Li J, Zhu T-Q, Zhang L, Wang Y, et al. Modulation of B Cell Regulatory Molecules CD22 and CD72 in Myasthenia Gravis and Multiple Sclerosis. Inflammation. 2013; 36: 521-528.
12. Xu M, Hou R, Sato-Hayashizaki A, Man R, Zhu C, et al. Cd72c is a modifier gene that regulates Faslpr- induced autoimmune disease. J Immunol. 2013; 190: 5436-5445.
13. Kamal M, Katira A, Gordon J. Stimulation of B lymphocytes via CD72 (human Lyb-2). Eur J Immunol. 2010; 21: 1419-1424.
14. Rang X, Liu Y, Wang J, Wang Y, Xu C, et al. Identification of multiple sclerosis-related genes regulated by EBV-encoded microRNAs in B cells. Mult Scler Relat Disord. 2022; 59: 103563.
15. Shahmohammadi S, Doosti R, Shahmohammadi A, Mohammadianinejad SE, Sahraian MA, et al. Autoimmune diseases associated with Neuromyelitis Optica Spectrum Disorders: A literature review. Mult Scler Relat Disord. 2018; 27: 350-363.
16. Leite MI, Coutinho E, Lana-Peixoto M, Apostolos S, Waters P, et al. Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. Neurology. 2012; 78: 1601-1607.
17. Jarius S, Paul F, Franciotta D, de Seze J, Münch C, et al. Neuromyelitis optica spectrum disorders in patients with myasthenia gravis: ten new aquaporin-4 antibody positive cases and a review of the literature. Mult Scler. 2012; 18: 1135-1143.
18. Bibic VC, Brust TB, Jodie MB. Neuromyelitis optica spectrum disorder presenting with concurrent autoimmune diseases. Mult Scler Relat Disord. 2018; 28:125-128.
19. Blake, Murphy. Onset of myasthenia gravis in a patient with multiple sclerosis during interferon-1b treatment. Neurology. 1997; 49: 1747-1748.
20. Frese A, Bethke F, Lüdemann P, Stögbauer F, et al. Development of myasthenia gravis in a patient with multiple sclerosis during treatment with glatiramer acetate. Journal of Neurology. 2000; 247: 713.
21. Gratacòs M, Caronna E, Raguer N, Sastre-Garriga J , et al. Myasthenia gravis following alemtuzumab therapy for multiple sclerosis. Neurology. 2018; 91: 622-624.
22. Stich O, Kluge J, Speck J, Rauer S, et al. Oligoclonal restriction of antiviral immunoreaction in oligoclonal band-negative MS patients. Acta Neurologica Scandinavica. 2015; 131: 381-388.
23. Anagnostouli M, Vakrakou AG, Zambelis T, Boufidou F, Nikolaou C, et al. Myasthenia gravis, atypical polyneuropathy and multiple autoimmune phenomena in the same patient, with HLA-immunogenetic profile expectable for Greek chronic inflammatory demyelinating polyneuropathy: a case report. Int J Neurosci. 2020; 132: 593-600.
24. Danikowski KM, Jayaraman S, Prabhakar BS. Regulatory T cells in multiple sclerosis and myasthenia gravis. Journal of Neuroinflammation. 2017; 14: 1-16.

25. Castro-Suarez S, Guevara-Silva E, Caparó-Zamalloa C, Cortez J, Meza-Vega M. Neuromyelitis optica in patients with myasthenia gravis: Two case-reports. Mult Scler Relat Disord. 2020; 43: 102173.

26. Czaja KG. Killer cell immunoglobulin-like receptors and their ligands: assessment of potential diagnostic and immunotherapeutic value. 2014.

27. Breuer J, Korpos E, Hannocks M-J, Schneider-Hohendorf T, Song J, et al. Blockade of MCAM/CD146 impedes CNS infiltration of T cells over the choroid plexus. Journal of Neuroinflammation. 2018; 15: 236.

28. Kanagawa O. Secondary rearrangement of TcR alpha chain in vivo: shaping and reshaping T cell repertoire. CBD SEMINAR. 2015.

29. Dagur PK, Mccoy JP. Endothelial-binding, proinflammatory T cells identified by MCAM (CD146) expression: Characterization and role in human autoimmune diseases. Autoimmunity Reviews. 2015; 14: 415-422.

30. Ken F, Fitzgerald K, Baker J, Regnstrom K, Gardai S, et al. Laminin-411 Is a Vascular Ligand for MCAM and Facilitates TH17 Cell Entry into the CNS. Plos One. 2012; 7: e40443.

31. Ikeguchi R, Shimizu Y, Kondo A, Kanda N, So H, et al. Melanoma Cell Adhesion Molecule Expressing Helper T Cells in CNS Inflammatory Demyelinating Diseases. Neurol Neuroimmunol Neuroinflamm. 2021; 8: e1069.

32. Kimura K, Okada Y, Fujii C, Komatsu K, Takahashi R, et al. Clinical characteristics of autoimmune disorders in the central nervous system associated with myasthenia gravis. J Neurol. 2019; 266: 2743-2751.