Case Report

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A perplexing case report of concomitant multiple sclerosis and myasthenia gravis

Mustafa Al-Mollah[a], Moaiad Hussein[a,*], Jamil Qiqieh[a], Hardeep Sidhu[c], Nosaiba Ryalat[b], Yacoub Bahou[a]

Introduction and importance: The co-occurrence of multiple sclerosis (MS) and myasthenia gravis (MG) within the Middle East and North African Region (MENA) has been scarcely reported in current literature. This rare case report explores the pathophysiological mechanisms and potential avenues of treatment modalities. Such insights can potentially facilitate the development of more efficacious and targeted treatment modalities and perhaps pave the way for disease prevention.

Case description: Twenty-nine-year-old female patient presented with diplopia of two weeks duration associated with occasional blurred vision in the left eye. On physical examination, she was discovered to have marked left eye ptosis. A visual evoked potential (VEP) test was performed, which revealed asymmetrical delay. MRI imaging revealed a few white matter hyperintense foci noted at both periventricular regions and the corpus callosum with the characteristic appearance of Dawson's fingers, and thus MS was diagnosed. An anti-acetylcholine receptor antibody test returned positive, confirming the diagnosis of concurrent MG.

Clinical discussion: Proposed pathophysiological mechanisms underlying the concurrent manifestation of both diseases include, among others, the involvement of HLA haplotype and non-HLA genotypes, as well as the immunogenetic influence of specific transcription factors. Notable HLA haplotype genes include DRB1 and HLA-DQ5 genes. In contrast, non-HLA genes include the interleukin-4 receptor (IL4RA) and factor forkhead box P3 (FOXP3).

Conclusion: Considering the similar immunological background of the two diseases, ideally, a single therapeutic modality could be used for management. This will hopefully simplify the patient's treatment regimen and may ultimately reduce the treatment cost and patient burden.

Keywords: case report, multiple sclerosis, myasthenia gravis

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating central nervous system disorder that is traditionally diagnosed according to the McDonald criteria via dissemination of demyelination in both time and space[1,2]. Due to its immunologic background, it is more commonly associated with other autoimmune disorders, of particular interest is Myasthenia Gravis. Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction (NMJ) characterized by muscle weakness. Autoantibodies generated towards post-synaptic nicotinic acetylcholine receptors result in a significant decrease in the number of receptors; thus, precipitating the risk of depleting acetylcholine stores during repetitive stimulation[3]. Despite MS mainly being a T-cell-mediated disorder and MG being B-cell-mediated disorder, there is evidence that supports both cell-mediated and humoral immunity being involved in the pathogenesis of both diseases[4]. This article presents the first-ever reported case of concurrent MS and MG in the Hashemite Kingdom of Jordan. This case report has been written to be in line with the CARE criteria.

HIGHLIGHTS

- Multiple sclerosis and myasthenia gravis are demyelinating diseases affecting the central and peripheral nervous system, respectively, with rare co-occurrence.
- Multiple sclerosis presentation can overlap with myasthenia gravis proposing a significant clinical challenge in diagnosis.
- Multiple sclerosis and myasthenia gravis have been shown to share a common genetic and immunological basis for their pathophysiology.
- This case report demonstrates one of the first presentations of such co-occurrence in the MENA region.

Case presentation

A 29-year-old medically and surgically free recent university graduate female patient from Jordan presented to a tertiary healthcare center clinic with diplopia of two weeks duration associated with occasional blurred vision in the left eye. The

Departments of [a]Internal Medicine, [b]Radiology, University of Jordan Hospital, Amman, Jordan and [c]Baba Farid University of Health Sciences—School of Medicine, Faridkot, Punjab

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**Corresponding author. Address: University of Jordan, Queen Rania St., 11972 Amman, Jordan. Tel.: +00 96 279 926 0001. E-mail: moaiad.husseinmed@gmail.com (M. Hussein).*

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patient denied having a fever, a recent history of viral infection, dysphagia, dyspnea, nausea/vomiting and was vitally stable. On physical examination, she was discovered to have marked left eye ptosis. However, there was no facial asymmetry, weakness, nystagmus, dysdiadochokinesia, or dysmetria. Also, the patient has no prior family history of any neurologic disease.

Based on these findings, a series of tests were conducted which costs were covered by governmental university insurance. A visual evoked potential (VEP) test was performed, which revealed asymmetrical delay. The patient was admitted to the hospital and was scheduled for anti-acetylcholine receptor antibody testing. While awaiting results, brain MRI with and without contrast was ordered. Twenty-four hours post-admission, the patient remained medically stable. MRI imaging revealed a few white matter hyperintense foci noted at both periventricular regions and the corpus callosum, which did not show restricted diffusion or abnormal postcontrast enhancement with the characteristic appearance of Dawson's fingers on FLAIR and T2 weighted images, suggesting a diagnosis of MS (Fig. 1) (Fig. 2) (Fig. 3) (Fig. 4).

Therefore, a lumbar puncture was indicated to test for oligoclonal bands in the cerebrospinal fluid (CSF). About 8 ml of a CSF sample was sent for analysis and chemistry. In addition, serum oligoclonal bands were also requested. CSF analysis revealed a normal protein level of 27.9 mg/dl (normal range: 15–60 mg) and a normal glucose level of 89.7 mg/100 dl (normal range: greater than 2/3 of the blood sugar level of the patient). CSF cytology showed a percentage of 40% of white blood cells and 100% of lymphocytes. These results further supported an impression mostly of a multiple sclerosis case despite the absence of oligoclonal bands. Other laboratory tests ordered for the patient were unremarkable, urine analysis results were insignificant, and the patient had a serum level of C-reactive protein (CRP) of 0.2 mg/l as referenced in Table 1 for the patient's basic chemistry and liver function test findings (Table 1) (Table 2).

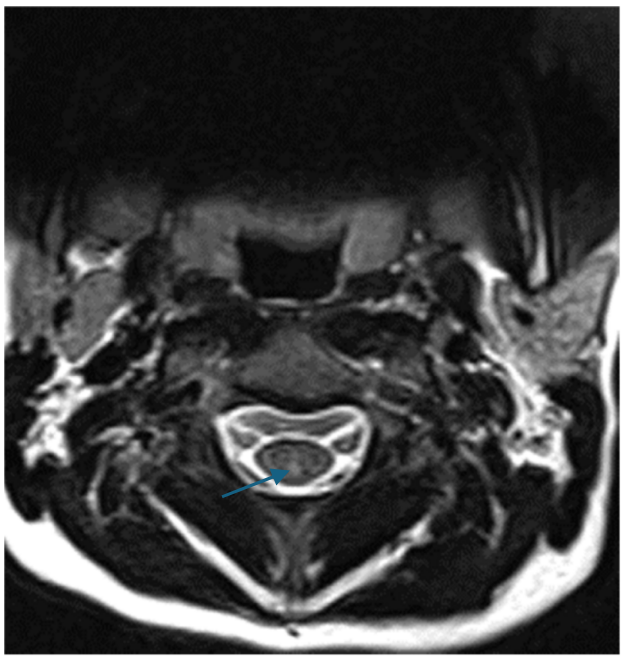

Figure 1. Axial view of the cervical MRI with an arrow pointing at a C2 cervical lesion opposite to C2 vertebra.

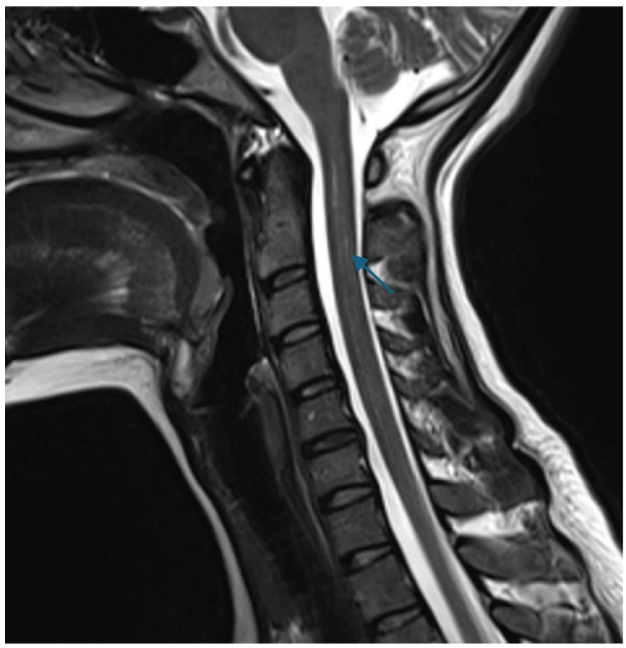

Figure 2. Sagittal view of the cervical MRI with an arrow pointing at a C2 cervical lesion opposite to C2 vertebra.

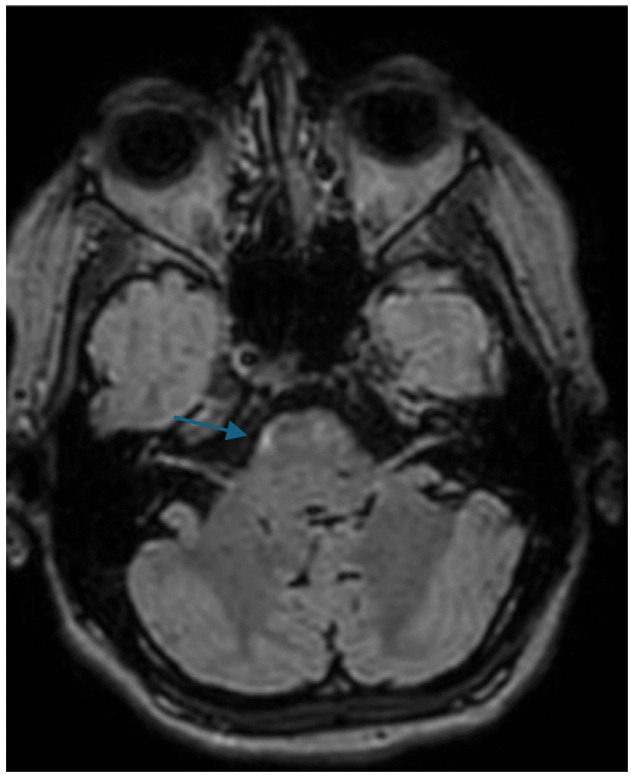

Figure 3. Axial view with a pointing at flaring on the ventral aspect of the right hemipons.

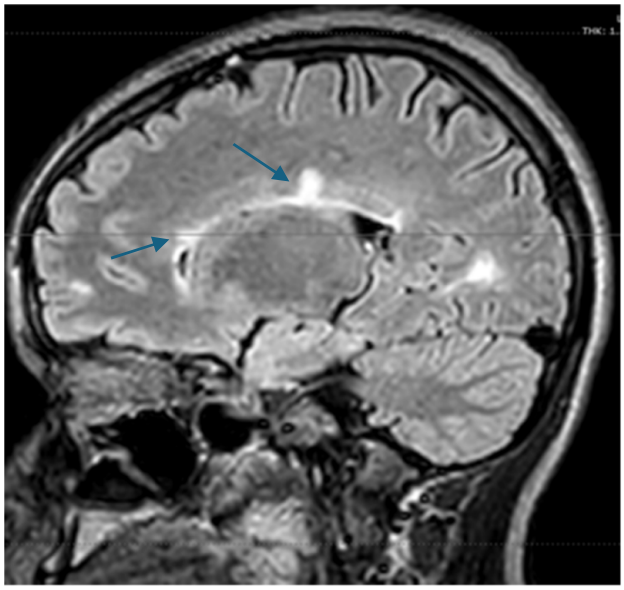

Figure 4. Sagittal view with arrows pointing at multiple callous septal and periventricular lesions/Dawson fingers.

Forty-eight hours post-admission, the patient was started on pulse therapy of 1 g intravenous (IV) methylprednisolone daily for 5 days. Following completion of the treatment, the patient was seen and evaluated, and she was vitally stable and fit for discharge. She was asked to start on MS disease-modifying therapy with sphingosine-1-phosphate receptor modulator Fingolimod and to return to the neurology clinic a week later for a follow-up as the results of the anti-acetylcholine receptor antibody and varicella-zoster IgG antibodies were still pending.

On the first visit to the neurology clinic following discharge, the patient presented with fatigable muscle weakness, double vision, and dysphonia. The anti-acetylcholine receptor antibody test returned positive, confirming the diagnosis of concurrent MG. This was followed by a repetitive nerve stimulation testing, which was negative. Moreover, a chest computed tomography (CT) scan was preformed to look for any mediastinal masses suggestive of a thymoma. Fortunately, there was no evidence of thymoma or other mediastinal masses. The patient was prescribed a trial of pyridostigmine, which improved her symptoms while waiting for approval for fingolimod therapy.

Table 1

Patient's basic chemistry and liver function test laboratory findings

Parameter	Value	Units	Reference values
ALT	23.3	U/l	10–35
AST	19.9	U/l	13–35
Alkaline phosphatase	45.2	U/l	35–129
Gamma glutamyl transferase	9.27	U/l	5–39
Bilirubin			
Direct	0.312	mg/dl	< 0.3
Total	0.638	mg/dl	< 1.1
Creatinine	0.628	mg/dl	0.6–1.2
Urea	15.2	mg/dl	15–46
Serum electrolytes			
Sodium	136.2	mmol/l	135–152
Potassium	4.37	mmol/l	3.5–5.3
Random blood sugar	84.0	mg/dl	70.0–110.0
Proteins			
Total protein	6.27	g/dl	6.2–8.7
Albumin	4.1	g/dl	3.5–5.2
C-reactive protein	0.2	mg/dl	< 0.3

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase.

Table 2

Patient's hematologic studies results

Hematologic studies			
RBC count	4.89	million/mm^3	4.0–5.2
Hemoglobin	13.8	g/dl	12.0–16.0
Hematocrit	41.9	%	36–46
MCH	28.2	pg/cell	26–34
MCHC	32.9	g/dl	31–37
RDW	14.3	%	4.6–13.5
MCV	85.8	μm^3	80–100
Leukocyte count	6.03	10^9/l	4.5–11.0
Segmented neutrophils	56.8%	%	50–70
Eosinophils	1.0%	%	0–4
Basophils	0.5%	%	0–2
Lymphocytes	33.7%	%	20–44
Monocytes	6.0%	%	2–9
Platelet count	218 000	/mm^3	140 000–440 000
Mean platelet volume (MPV)	9.1	fl	7.2–11.1

MCH, Mean Corpuscular Hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean Corpuscular Volume; RDW, Red cell Distribution Width.

Discussion

The co-occurrence of MS and MG within the Middle East and North African Region (MENA) has been scarcely reported on within current literature. In addition, the heterogeneity of the MENA region poses a significant barrier to statistically analyze these pathologies. However, an exceedingly large number of studies have noted a significant rise in the prevalence and incidence of these autoimmune disorders. For example, the prevalence of multiple sclerosis within the Hashemite Kingdom of Jordan has been gradually increasing over time to such an extent it is now classified as a medium to high-risk country. One study conducted in 2003–2004 reported a prevalence of 39/100 000 in the capital Amman[5], which is significantly higher than the prevalence of 7/100 000 reported in 1977[6]. In contrast, a study conducted in Libya revealed that the incidence of myasthenia gravis is similar to the worldwide average incidence of 5.3/1 000 000[7].

To our knowledge, this study presents the first-ever reported case of co-occurrence of MG and MS in the Arab world, this is most likely due to the analogous presentation of both diseases in addition to the normal CSF protein and glucose values which are typically seen in both MS and MG[8]. The most prominent overlap in symptoms occurred as ocular and bulbar manifestations[2]; facial paresthesia and optic neuritis occurred in 15.3% and 23.1% of patients, respectively, in MS, while ptosis and diplopia occurred in 69.2% and 30.8% of patients respectively in MG[9]. The diagnosis is even more burdensome in patients presenting with only ocular MG; This subtype occurs in around 10–15% of cases[3]. Moreover; our case of MS of the relapsing-remitting subtype falls in concordance with the most common presentation of MS as stated by multiple previous studies[9,10], as well as with

the prevailing type of MS in Jordan[5]. In our case, MG was diagnosed one month after diagnosing MS, this is not a usual occurrence as in comparison to one of the largest studies conducted in Vancouver British Colombia all the patients diagnosed of MS followed by MG had a 4–9-year interval in between the diagnoses[11].

Moreover, there are common non-HLA genes linked to both Multiple Sclerosis and Myasthenia Gravis. This includes the gene for interleukin-4 receptor (IL4RA) and the gene coding for the muscle nicotinic acetylcholine receptor α-subunit, which alters the binding of the interferon regulatory factor 8 gene (IRF8). Interestingly, this is also associated with altered cytokine levels of type I interferon[12,13]. It is well established that certain immune diseases are associated with particular positive serologic markers although it is not uncommon to find some serologic markers positive in multiple different autoimmune diseases[14]. A classic example is antinuclear antibodies (ANAs). Within the context of multiple sclerosis and myasthenia gravis, ANAs have been detected in patients with either MG or MS[15].

Several statistics within the region have also demonstrated the manifestation of autoimmune diseases in patients diagnosed with MS such as psoriasis and thyroid disease[16]. These results can possibly be explained by the consensus that MS is an immunological disease that shares a common pathophysiology with other autoimmune conditions[2]. A recent multi-centered retrospective cohort study conducted on a sample of MS patients concluded that the prevalence of MG was 0.34%. Upon further comparison, this proved to be higher than the MG prevalence in the general population, indicating that their association is more than just a coincidence[9]. The increase in the co-occurrence of MS and MG has been mainly attributed to the immunogenetic aspect of both diseases[4]. Moreover, both diseases share a similar younger peek of bimodal age distribution with matching HLA typing (A1, A2, DR3, B8)[15].

Immunogenetic studies have attempted to elucidate the aberrant immunoregulatory correlation between multiple sclerosis and myasthenia gravis. For instance, several studies have linked a polymorphism of the transcription factor forkhead box P3 (FOXP3) gene with an increased risk of developing MS. Consequently, this can potentially tie to a modified risk of developing MG as the frequency of certain alleles of FOXP3 such as the FOXP3 IVS9 + 459 G allele was associated with lower risk of MG[12,17]. This potential link can be explained by the role of the (FOXP3) gene in influencing the number and function of $CD4^+$ $CD25^+$ T-reg cells[17]. However, more studies must be conducted to ascertain the role of the (FOXP3) gene in modifying the risk of developing MG and MS.

In addition, certain proposed HLA genes linking both MS and MG have also been reported within the literature. The prevalence of different alleles of the DRB1 gene were found to be increased in patients with MG[12]. The DRB1*15 allele, in particular, has been associated with increased risk in late-onset MG in COHORT studies conducted in Italy and Norway as well as increased risk for developing MS in Middle Eastern populations[12,18]. However, this association was not as strong for Caucasian populations. Another HLA gene that is potentially relevant is the HLA-DQ5 gene, as a higher prevalence of a certain set of polymorphisms of the HLA-DQ5 gene was found in MS patients in Kuwait[19]. Furthermore, different alleles of the HLA-DQ5 gene have also been associated with MG with positive antibodies for Muscle-specific tyrosine kinase (MuSK-MG)[12].

In conclusion, this rare case manifests the opportunity to explore a special subset of a patient population previously not well established. Considering the similar immunological background of the two diseases, ideally, a single therapeutic modality could be used for management. This will hopefully simplify the patient's treatment regimen and may ultimately reduce the treatment cost[20]. Currently, there is still no approved treatment modality that can simultaneously manage both of these disorders. Of the suggested drugs that proved to be beneficial in the treatment of MG and MS is Rituximab, a B cell depleting anti-CD20 antibody, this highlights the role of B cells in their pathophysiology[21]. The use of Tregs augmentation therapies has also shown significant potential in the treatment of both diseases[2]. Additionally, some studies suggest an association between the treatments used for MS and MG and the adverse effects of developing the converse disease. For instance, the use of IFN-B and Glatiramer acetate for the treatment of MS seemed to induce the development of MG and the use of thymectomies in MG seemed to precipitate central demyelinating diseases such as MS[4,16].

Ethical approval

The research was exempted from review by the Institutional Review Board under the reference number 5367/1.10.2023.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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This study did not receive any funding support.

Author contribution

M.A.-M.: investigation, writing—original draft. M.H.: writing—review and editing, validation, visualization. J.Q.: writing—original draft, resources. H.S.: writing—review and editing, validation. N.R.: conceptualization, writing—original draft. Y.B.: conceptualization, writing—original draft, visualization, validation.

Conflicts of interest disclosure

Not applicable.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Dr Yacoub Bahou.

Data availability statement

Not applicable.

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