Case Report

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An unusual initiation of an ocular form of MuSK-positive myasthenia gravis after magnesium administration: a rare case report

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Introduction and importance: The primary clinical symptom in people with myasthenia gravis (MG) is muscle weakness that gets worse with activity and gets better with rest; often, the first symptoms are ocular ones, such as ptosis and double vision. On the other hand, individuals with anti-muscle-specific tyrosine kinase may present with unusual symptoms. Nonetheless, it is hypothesized that muscle-specific tyrosine kinase antibodies may be present when no antibodies are present, along with bulbar and respiratory symptoms.

Case presentation: A 26-year-old pregnant patient was referred to the Neurology Department after experiencing tongue enlargement. A neuro-ophthalmic assessment revealed ptosis with lateral diplopia in the right eye, bulbar palsy, facial weakness, weakness in the palate and pharyngeal reflex, dizziness, and hearing loss in her right ear. The patient was given magnesium sulfate for 2 days since pre-eclampsia was suspected; however, this treatment exacerbated the development of symptoms and was discontinued. Her MG symptoms gradually improved after starting medication. Nonetheless, bilateral weakness in the neck and limb flexion persisted. Following a few days of therapy, there were no indications of diplopia, swallowing was normal, and the muscular weakness was somewhat improved.

Clinical discussion: The patient was put on drug treatment for MG (predlon 60 mg daily, amioran 50 mg twice daily, and mistenon).

Conclusion: Treating severe MG patients with a customized approach aims to manage their symptoms and improve their quality of life. Reduce muscle weakness, eradicate circulating antibodies, and suppress the abnormal immunological response. Minimizing side effects while attaining ideal symptom control is the ultimate objective.

Keywords: anti-muscle-specific tyrosine kinase, case report, immunological, muscle, myasthenia gravis

Introduction

Neuromuscular junction (NMJ) disorders comprise a variety of dysfunctions that lead to muscle weakness[1]. MG is the most common NMJ disorder, presenting with a highly diverse clinical spectrum[2]. MG is an autoimmune disease in which antibodies are produced against the acetylcholine receptor (AChR), thereby hampering AChR function on the muscle membrane[3].

Despite advancements, the mortality rate for MG hovers around 5–9%, With a slight inclination for men[1]. The disease predominantly affects women in their reproductive age and is more common before age 40 with a female:male ratio of 3:1, compared with that in men, highly appears after age 50 with a male:female ratio of 3:2[1,4]. Muscle weakness that worsens with exertion and improves with rest is the core clinical symptom in patients with MG; usually it would be ocular manifestations like double vision and ptosis being the initial symptoms[1]. While anti-MuSK patients may exhibit atypical clinical features involving select muscle groups, including the bulbar, face, respiratory system, and neck muscles, with relative preservation of the eye and limb muscles[5]. MG diagnosis relies on a blend of history, clinical examination,

HIGHLIGHTS

- Muscle-specific tyrosine kinase (MuSK) antibody-positive myasthenia gravis (MG) is a rare clinical disease.
- There have been limited reports in the literature where magnesium administration was observed as the initial manifestation of MG.
- Ocular manifestations are a less common presentation in patients with MuSK autoantibody-related MG.
- It is essential to keep MG in mind when evaluating a pregnant patient with symptoms similar to MG.
- Early diagnosis and avoidance of medications that exacerbate muscle weakness are important to prevent myasthenic crisis, which has high morbidity and mortality rates.

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pharmacological, serological, and electrodiagnostic tests[6]. Serological tests involve acetylcholine antibodies, which are present in 85% of patients. However, in the absence of antibodies and the presence of bulbar and respiratory symptoms, the presence of MuSK antibodies is suggested[6]. Computed tomography (CT) is recommended to rule out thymoma in MG patients[5]. The treatment methods used to treat MG are plasmapheresis, immunosuppressive therapy, and anticholinesterases[6]. In this paper, we discuss a pregnant patient's case who appeared to have pre-eclampsia and was managed with magnesium sulfate, which led to complications like ptosis, dizziness, and other symptoms. Finally, she turned out to have hitherto undiagnosed MG. Few cases in the literature have been reported where magnesium administration was observed as the initial manifestation of MG.

Case presentation

Two days postpartum, a 26-year-old pregnant patient was referred to the Neurological Department with a sensation of tongue swelling. Then 2 weeks ago, the patient developed symptoms of difficulty swallowing, dysarthria, tinnitus, and headache. Her blood pressure was 90/180. The patient was conscious and responsive. Sensation and tonicity in her four limbs were normal with tandem gait disorder. Neuro-ophthalmic evaluation noted ptosis with lateral diplopia in the right eye, bulbar palsy, facial weakness, dizziness, hearing loss within her right ear and the palate, and the pharyngeal reflex showed weakness without deviation of the uvula. The patient had four previous cesarean deliveries with lumbar anesthesia with gestational hypertension treated with alpha-methyldopa, and aspirin during pregnancy and edema of the lower extremities. Pre-eclampsia was suspected, so the patient was given magnesium sulfate for 2 days, which increased the development of symptoms, so it was stopped. Patient underwent a brain CT scan, which was normal. Then, the next day, she showed diplopia with bilateral eye abduction and facial paralysis. The pupils were reactive, and there was no papilledema. Also MRI study of the brain was within normal (Figs 1, 2). When her blood pressure was measured, it was 70/140. She was put on aspirin and atorvastatin, observed increasing the symptoms in the evening and improved in the morning. Referred to MG, and neostigmine was given with an intramuscular injection. Laboratory blood tests, C-reactive protein, rheumatoid factor, and thyrotropin-stimulating hormone were within normal ranges. Finally, to confirm the diagnosis, AChR antibody testing was negative, which depressed and a value of 0.25. CT scan of the chest with injections to exclude thymoma and the result was negative. Then, the MuSK-antibody tested positive with an elevated value of 18.6. The patient was put on drug treatment for MG (predlon 60 mg daily, amioran 50 mg twice daily, and mistenon) and noted a gradual improvement in bulbous and ocular symptoms, but neck and limb flexion were weak bilaterally. After a few days of treatment, no signs of diplopia, normal swallowing, and muscle weakness partially improving.

The work has been reported in line with the SCARE criteria[7].

Discussion

MG is an autoimmune disorder of the NMJ mediated by autoantibodies and causes impaired neuromuscular transmission and weakness in skeletal muscle[1,4,8]. The estimated prevalence of MG is 5–150 cases per million population, with the incidence ranging from 2.5 to 20 cases per million person-years[4].

Symptoms can manifest at any age, but during the second and third decades of life, the highest incidence presents in women,

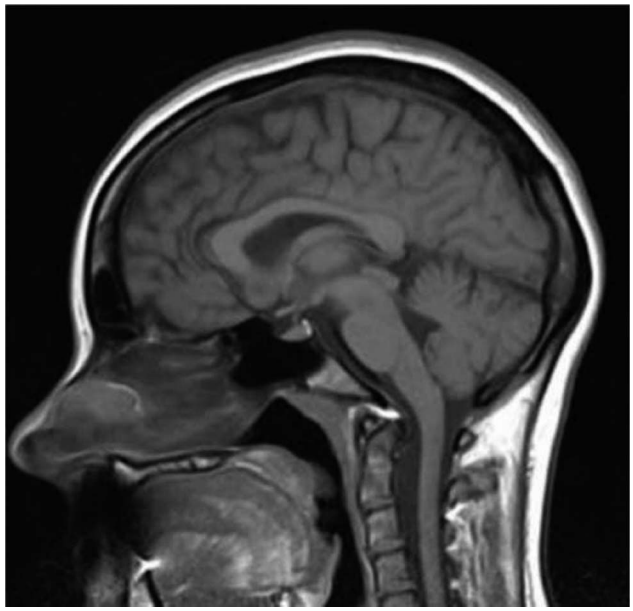

Figure 1. MRI study of the brain showing cerebral hemispheres on sagittal view.

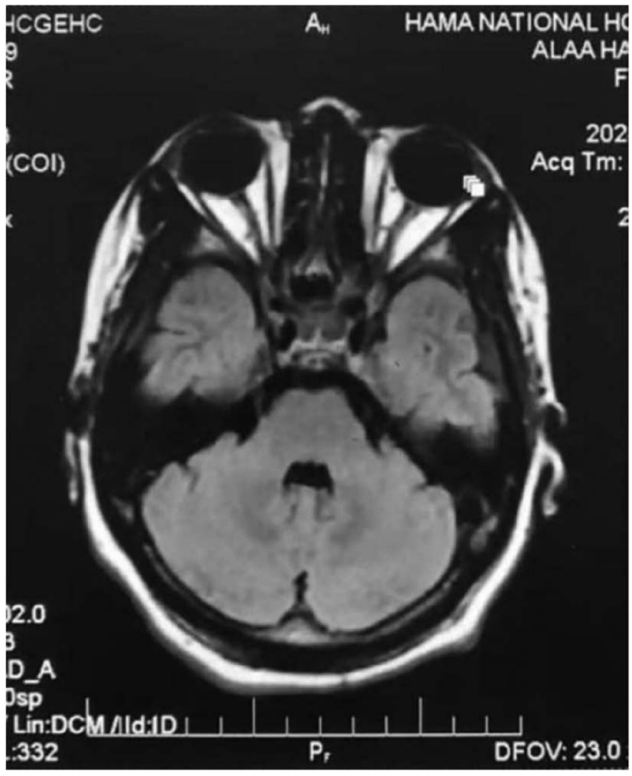

Figure 2. MRI study of the brain showing brainstem on cross-view.

while during the sixth and seventh decades, the highest incidence occurs in men[1,4]. In our case, MG was diagnosed in a woman in her third decade. Emotional stress, surgery, and traumatism are some of the predisposing factors that are found in the majority of patients with MG. In addition, it is important to avoid many drugs or use them caution, such as beta-blockers, dantrolene, magnesium, and others, because they can exacerbate symptoms in patients with MG[4,9]. In our case, 3 weeks after the patient underwent cesarean surgery, the disease was detected. In addition, our patient started suffering from MG manifestations 2 days postpartum, where the patient was treated with magnesium sulfate because of pre-eclampsia suspicion. Therefore, the treatment was stopped. There have been limited reports in the literature where magnesium administration was observed as the initial manifestation of MG.

MG is clinically defined by the presence of fluctuating and fatigable weakness in the skeletal muscles[3,5]. This weakness is primarily attributed to a deficiency in AChR functionality on the muscle membrane[3,10]. Symptoms exhibit variability in both location and intensity across affected individuals[3]. The term "fatigable weakness" signifies that strength fluctuations stem from successive contractions of the affected muscle[5]. Therefore, symptoms exacerbation occurs following repetitive muscle use, particularly towards the end of the day[11]. The occurrence of permanent muscle damage is rare, often leaving maximal muscle strength relatively intact[11]. Clinical examinations of patients with MG may reveal no abnormalities[11]. Complaints related to altered sensitivity, such as numbness, tingling, or pain, are uncommon due to the absence of involvement of sensory nerves[5]. A clinical examination of our patient revealed normal sensation in both upper and lower limbs. MG is commonly classified as either ocular (characterized by diplopia and ptosis resulting from extraocular muscle weakness and levator palpebrae superioris dysfunction[5,11]) or generalized (encompassing limb muscles, the bulbar and oropharyngeal region, and respiratory muscles)[3,5,11]. Our patient presented with difficulty swallowing, dysarthria, tinnitus, and headache, while neuro-ophthalmic evaluation noted ptosis, lateral diplopia in the right eye, bulbar palsy, facial weakness, dizziness, and hearing loss within her right ear. In approximately 85%of MG cases, symptoms initially present as ocular manifestations, with weakness predominantly confined to the ocular muscles in about 10–15% of instances (ocular form MG)[3,5]. Progression in the remaining cases leads to affecting the face, oropharyngeal musculature, and/or limb muscles, causing symptoms of bulbar weakness featuring dysarthria/dysphonia and dysphagia (generalized MG)[5]. Infrequent occurrences of respiratory muscle weakness can lead to a critical condition necessitating respiratory support[11]. Maximum weakness commonly appears within the first year[5]. Ocular symptoms commonly mark the AChR subtype of MG (AChR-MG) onset, with most patients eventually developing generalized symptoms[1]. In MuSK antibody-associated MG, patients present with atypical characteristics and pronounced involvement of bulbar, facial, respiratory, and neck muscles while sparing ocular and limb musculature[5]. Exclusive ocular symptoms are rare in anti-MuSK-positive cases[5]. Our positive anti-MuSK MG patient started with ocular symptoms.

The diagnostic approach to MG necessitates an initial assessment based on a congruent clinical presentation. Following this, it is advisable to determine the serum autoantibodies, which are the most specific diagnostic tests[5,12]. MG is associated with a spectrum of nine identified antibodies[13]. Notably, anti-AChR, anti-MuSK, and anti-lipoprotein receptor-related protein 4 (anti-LRP4) antibodies represent the three well-defined pathogenic antibodies[13]. The selection of appropriate markers should be tailored to individual clinical contexts[12]. Employing an exhaustive antibody panel for all patients is not only costly but also unnecessary[13]. Anti-AChR binding antibodies, present in approximately 80–85% of generalized cases, constitute the most prevalent and highly specific antibodies[5]. These antibodies, mainly of immunoglobulin (Ig)G1 and IgG3 subclasses, disrupt NMJ transmission, resulting in postsynaptic membrane impairment[5,13]. AChR antibodies testing in our patient was negative. The detection of anti-MuSK is recommended in scenarios where anti-AChR antibodies yield negative results[12]. MuSK, a postsynaptic protein pivotal for NMJ development and stability, serves as the target for these specific antibodies, primarily of the IgG4 subtype[5]. Anti-MuSK antibodies are identified in 5–8% of MG cases[12]. The reference values for MuSK antibodies are typically ≤ 0.02 nmol/l[7]. In our patient the MUSK-antibody in our patient was tested positive with an elevated value of 18.6. MuSK-antibody antibodies are rarely found in positive AChR-antibody patients[13]. In cases of dual AChR/MuSK-antibody negativity with severe disease onset, assessment for anti-LRP4 antibodies is advised[12]. Electromyography and cholinesterase inhibitor response assessment are pivotal in confirming diagnoses for seronegative patients who require thorough differential diagnosis from other neuromuscular transmission disorders[12]. Electrodiagnostic evaluations should target clinically affected muscles[5,14]. Should clinical indicators strongly suggest MG without confirmatory test results, the response to pyridostigmine may serve as a supportive diagnostic measure – particularly valuable in cases of ocular MG or when precise antibody tests are unavailable[5]. The symptoms of our patient revealed a positive response to pyridostigmine. In individuals with MG, CT evaluations are imperative to rule out thymoma presence[5]. In such instances, MRI offers no additional diagnostic advantage[5]. Challenges in diagnosis often arise in cases with slow onsets and absent fluctuations[15]. Approximately 15% of MG patients exhibit secondary autoimmune diseases, a phenomenon more common in early-onset MG and those with thymic hyperplasia[5]. Thyroiditis emerges as the most prevalent comorbidity, followed by systemic lupus erythematosus and rheumatoid arthritis[5]. Consequently, thyroid function assessments should be conducted at MG diagnosis[5]. Thyrotropin-stimulating hormone test of our patient was within normal range.

The goal of MG management is to improve patients' muscular strength and quality of life via the control of illness activity, the observation of treatment-related side effects, and the implementation of personalized supportive strategies. An individualized therapy that takes into account the illness's subtyping based on thymus pathology and related antibodies, the location and degree of weakness, individual features, and comorbidities is recommended by the current comprehension of MG pathogenesis[11].

MG's management strategy should include the following steps: the first step is to determine the contraindications to medication. The second step is treatment of the main reason that contributed to the development of MG in the patient. The third step is improvement of MG symptoms through providing anticholinesterase therapy, Igs, and possibly plasmapheresis, as well as steroids or other immunosuppressive drugs that improve

symptoms in most patients. The fourth step, the procedure of thymectomy, should be considered either to treat the disease and to prevent the development of complications and to reduce medical doses to avoid its side effects. In nonthymomatous, generalized MG patients with AChR-antibody, aged 18–50 years or if the medication therapy is not sufficient or has severe side effects either in patients with AChR-antibody + generalized MG or in patients with generalized MG without detectable AChR-antibody. In patients who are seropositive for anti-MuSK, antibodies to low-density anti-LRP4, or agrin antibodies, Current evidence does not encourage thymectomy[4,8,9]. CT and MRI for our patient, who is seropositive for anti-MuSK, revealed normal findings. Therefore, thymectomy was not considered. Fast-acting therapies such as plasma exchange and intravenous Ig are usually used in individuals suffering from acute severe MG either when rapid intervention is essential or in patients who fail to respond effectively to immunosuppression as periodic treatments. Because of their short-lived (4–12 weeks) effects, other immunotherapy is typically required. The bioavailability of ACh in the synaptic cleft is improved by anticholinesterases, commonly referred to as cholinesterase inhibitors. The recommended anticholinesterase for oral therapy is pyridostigmine bromide, typically used as the first line of treatment for MG patients. Anticholinesterases are effective against all subgroups of MG, with the exception of patients with anti-MuSK antibodies, where the degree of weakness alleviation, the ideal dose, and tolerability vary across individuals. Adding disease-modifying medication, like corticosteroids, azathioprine, mycophenolate mofetil, or thymectomy, is usually recommended when the weakness and clinical changes continue following pyridostigmine dosage optimization. Pyridostigmine, which may trigger muscular cramps and fasciculations up to a cholinergic crisis accompanied by severe muscular weakening, is typically ineffective and intolerant in patients with MuSK MG. Therefore, anticholinesterase medications should be included in those patients. If anticholinesterases do not have a beneficial impact on patients with MuSK MG, there is no symptomatic medication treatment available. Nevertheless, 3,4-diaminopyridine may be beneficial[11]. The patient, in our case, was put on azathioprine, predlone, and pyridostigmine. After the first week of the therapy, the patient developed proximal muscle weakness in the extremities, neck muscle weakness, and exertional dyspnea with gradual improvement of flaccid dysarthria, dysphagia, and ocular symptoms. After the second week, the muscle weakness in the extremities began to ameliorate partially, and the patient was significantly relieved from bulbar and ocular symptoms.

Modern therapeutic interventions of MG include subcutaneous Igs, selective depletion of MG-specific autoantibodies in place of total IgG apheresis, comparison of novel prednisone reducing techniques, study of the usage of 3,4-diaminopyridine or amifampridine phosphate and autologous hematopoietic stem-cell transplantation. In patients with MG, a transient, rapid drop in serum IgG levels may occur when using the novel complement inhibitors and FcRn-blocking medications, either separately or in combination. This treatment could be implemented in conjunction with either new or older, slower-acting immunosuppressive medications to prevent the long-term development of autoantibodies[11].

Conclusion

This paper aims to emphasize the importance of having a high suspicion for MG in the third trimester of gestation or postpartum, although it is a rare and unexpected disease at this stage. Therefore, it is significant for the medical team to consider MG as a potential mechanism in the pregnant woman who presents with dysarthria, ptosis, or other manifestations of this illness. Especially if necessary to manage the patient with magnesium sulfate when pre-eclampsia is suspected, even if there is no prior history of weakness. Early diagnosis and avoidance of medications that exacerbate muscle weakness can help minimize the frequency of myasthenic crises and reduce the morbidity and mortality associated with complications arising from MG.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the parents of the child for publication of this case report and any accompanying images and videos. A copy of the written consent is available for review by the editor of this journal.

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