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Comorbid Human Immunodeficiency Virus (HIV) and Muscle-Specific Kinase (MuSK) Myasthenia Gravis: A Case Report and Literature Review

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Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 44
Final Diagnosis: MuSK myasthenia gravis
Symptoms: Difficulty swallowing • double vision
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Rare co-existance of disease or pathology

Background: HIV infections with concomitant immunologically-mediated disorders have been frequently described but there has been little research on the association between HIV and myasthenia gravis.
MuSK myasthenia gravis coexisting with HIV is an even a rarer entity and can occur as a part of immune restoration disease. We report the case of a patient with asymptomatic HIV infection who presented with new-onset MuSK myasthenia gravis.

Case Report: A 44-year-old African-American woman with HIV since 2004 and on highly active antiretroviral therapy (HAART) presented to the ED with complains of double vision and difficulty swallowing for 2 weeks. The patient was intermittently on HAART therapy. On examination, she had bilateral ptosis, weak orbicularis oris and orbicularis oculi, along with mild lateral gaze palsy of the left eye. Her CD4 count was 383 and the viral load was undetectable. An MRI of the brain produced normal results and a CT chest did not show thymus enlargement. Due to worsening symptoms and high suspicion for myasthenia gravis, she was started on IVIG at 0.4 mg/kg/day for 5 days, and her symptoms markedly improved. She was found to have strongly positive MuSK antibody and negative Ach receptor antibody. Repetitive nerve stimulation showed a 13% decrease in the right median nerve, which confirmed the diagnosis. She was subsequently discharged to home on pyridostigmine. Azathioprine was added at clinic follow-up. The patient continues to improve.

Conclusions: As the use of antiretroviral therapy increases, immune reconstitution syndromes have become more common. Rare associations like HIV and MuSK myasthenia gravis are being increasingly reported. The use of immunosuppressants in the treatment of these conditions should be carefully evaluated.

MeSH Keywords: HIV • Immune Reconstitution Inflammatory Syndrome • Immunomodulation • Myasthenia Gravis

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903108

Background

Immune restoration disease, also known as immune reconstitution syndrome, is a potential complication of antiretroviral therapy. Different autoimmune conditions have been described as a part of this syndrome, but there have been few reports on the association between HIV and myasthenia gravis. MuSK Myasthenia Gravis coexisting with HIV is even rarer and can occur as a part of immune restoration disease. We report the case of a patient with asymptomatic HIV infection who presented with new-onset MuSK myasthenia gravis.

Case Report

A 44-year-old African-American female with past medical history of HIV since 2004 and who was on antiretroviral therapy (ART) presented to the ED stating that for the last 2 weeks she had been experiencing double vision, difficulty swallowing, and progressive dysphagia, which were all worse in the evening. She had been on antiretroviral therapy consisting of emtricitabine 200 mg QD, tenofovir 300 mg QD, and Ritonavir 100 mg QD. Although she was diagnosed and started on ART in 2004, she was subsequently lost to follow-up and had very high viral load (19 068 copies/ml) with CD4 count of 53 until 2012. With highly active antiretroviral therapy, her CD4 count had increased to 325 by 2014. She had undergone cesarean section 3 weeks prior in a different facility and 1 week prior to the presentation she was treated with magnesium sulfate for preeclampsia. Review of systems was negative. On examination, she had bilateral ptosis, weak orbicularis oris and orbicularis oculi, and mild lateral gaze palsy of the left eye. Other cranial nerves were intact. Motor, sensory, coordination, and deep-tendon reflexes were normal. Her initial workup was normal, CD4 count was 383, and viral load was undetectable. Routine blood tests, serum immunity marker, TSH, ANA, RF, and anti-thyroid antibody were normal, and a brain MRI did not show any neurological abnormalities. A CT chest did not show any significant enlargement of the thymus. While getting the workup, the patient had unexpected worsening of symptoms and based on clinical suspicion for myasthenia, IVIG was started at 0.4 mg/kg/day for 5 days as per neurology recommendation. She markedly improved with improvement of diplopia and dysphagia, and the course of IVIG was completed. Her Ach receptor antibody was negative and MuSK antibody was strongly positive. EMG/NCS showed normal findings except for a 13% decrease in the right median nerve; earlier, she had refused EMG/NCS of the facial nerve. She was subsequently discharged to home on pyridostigmine 60 mg TID, which was increased to 60 mg QID with addition of azathioprine 50 mg qd in her follow-up visit at the neurology clinic. She continues to improve in her follow-up.

Discussion

Myasthenia gravis (MG) is the most common disorder of neuromuscular transmission. Antibodies to the muscle-specific receptor tyrosine kinase (MuSK) are present in up to half of those with generalized myasthenia gravis who are acetylcholine receptor antibody (AChR-Ab)- negative. MuSK is a receptor tyrosine kinase that mediates agrin-dependent AChR clustering and neuromuscular junction formation during development. MuSK antibody-positive myasthenia gravis may have a different cause and pathologic mechanism than AChR-Ab-positive disease [1,2].

Although it is one of the best-characterized and understood autoimmune disorders, comorbid HIV and myasthenia gravis is rare. Very little is known about this association, mostly through case reports [3]. Comorbid HIV and MuSK MG is even rarer, with only 3 cases previously reported [4–6]; these cases are summarized in Table 1. Clinical features of MuSK resemble AChR-Ab myasthenia, but these patients may additionally have increased incidence of diplopia, ptosis, dysarthria, and prominent respiratory muscle weakness, and are less responsive to acetylcholinesterase inhibitors [7]. All the cases listed in Table 1 had similar findings along with negative Ach R antibody and were subsequently treated with immunomodulators like cyclosporine, azathioprine, and Rituximab.

HIV infection can modify the manifestation and natural history of MG. Acute HIV infection might act as a trigger for MG [8]. Antigenic mimicry between subcapsular/medullary thymic tissue and HIV core p17 and p24 proteins have been documented, suggesting that autoreactivity against thymic tissue may be the etiology of MG in HIV-infected patients [10]. It has been thought to be associated with immune restoration disease (IRD) due to the restoration of dysregulated immune response against pathogen-specific antigens [10].

All these case reports have described MG in HIV as part of immune restoration disease, in which MG was manifested as CD4 count improved after ART. A similar pattern is seen in the presentation of our patient, in whom the improvement in the CD4 count with antiretroviral therapy coupled with provocation by pregnancy and use of magnesium sulfate for preeclampsia led to presentation of the symptoms. A consistent finding in patients with MuSK myasthenia gravis is that they have a much lower frequency of thymic pathology than patients with AChR-Ab-positive myasthenia [11]. This finding is consistent in all the aforementioned cases summarized in Table 1, including our patient. Therefore, it is imperative to recognize autoimmune disorder as a manifestation of immune restoration disease. Further research is needed to identify the pathogenesis of this association.

Table 1. Comparison of case reports on HIV and MuSK myasthenia gravis.

Case report	Kurokawa et al.	Kuntzer et al.	Ragunathan et al.
Year reported	2008	2011	2015
Age	58	21	39
Sex	M	F	F
Time from HIV to MG	5 years	2 years	1 year
CD4 cell count at diagnosis of MG	ND	575	520
Ptosis	+	+	+
Bulbar sign	+	+	–
Limb weakness	–	+	–
Respiratory failure	–	–	–
Repetitive nerve stimulation test	+	+	–
Anti-Ach R Ab	–	–	–
Thymic hyperplasia	–	ND	ND
ART	Efavirenz, Tenofovir, Emtricitabine	Zidovudine, lamivudine, Efavirenz/Tenofovir	Tenofovir/Emtricitabine, Darunavir, Raltegravir
MG medication	Pyridostigmine, prednisone, cyclosporine	Pyridostigmine, prednisone, Thymectomy, IVIg, Plasmapheresis, Rituximab	Prednisone, Azathioprine, Plasmapheresis

M – male; F – female; ND – not mentioned or not done; '+' – positive; '–' – negative; Anti-AchR-Ab – anti-acetylcholine receptor antibody; ART – antiretroviral therapy; IVIg – intravenous immunoglobulin.

Management of patients who have both an immunosuppressive condition like HIV and an autoimmune condition like MuSK myasthenia gravis is challenging. Immunosuppressants and immunomodulators have been successfully used in the treatment of MuSK MG in HIV patient [4–6]. As in other cases of myasthenia gravis with worsening symptoms and impending respiratory failure, our patient was managed with IVIg, which improved her symptoms. She was also started on acetylcholinesterase inhibitors and subsequently started on azathioprine during her follow-up. Kurokawa et al. has described the use of cyclosporine [4] and Kuntzer et al. described the use of Rituximab for the treatment of this condition [5].

Conclusions

In the era of antiretroviral therapy, immune restoration disease and immune reconstitution syndrome are not uncommon. Rare associations like HIV and MuSK myasthenia gravis are being increasingly reported as advances in HIV treatment continue. Guidelines for the management of myasthenia gravis and its subtypes are described in the literature but not when they are associated with immunodeficiency states like HIV. Therefore, use of immunosuppressants and immunomodulators in these cases is based on case reports and expert opinions, and is not entirely without risk. Regardless in the lack of studies on treatment of MG in HIV patients, the use of steroids, immunosuppressants, and thymectomy must be carefully evaluated in each patient.

Conflicts of interest

None.

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