CASE REPORT

Muscle-specific Tyrosine Kinase Antibody-positive Myasthenia Gravis Unmasked by Fluoroquinolone: A Case Report

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Abstract

Introduction: Muscle-specific tyrosine kinase (MuSK) myasthenia gravis (MG) is a severe, subtype of MG with different pathogenesis, atypical clinical features, lack of symptom fluctuations, and acetylcholinesterase inhibitors failure making MuSK-MG diagnosis challenging. Such patients may suffer a worsening of symptoms upon exposure to a variety of medications such as fluoroquinolones. Fluoroquinolones of any generation may interfere with neuromuscular transmission and may lead to MG symptoms by simply unmasking a pre-existing mild case. This case report describes the development of myasthenic crisis and respiratory distress following the use of levofloxacin in a patient who was initially diagnosed as tuberculous meningitis with no previous diagnosis of MG.

Case description: A 24-year-old woman presented with 1 month history of low-grade fever and headache without any raised intracranial pressure features or neck stiffness. All her routine laboratory investigations and brain imaging were normal. Cerebrospinal fluid analysis showed normal protein and sugar levels, zero cell count with mild cartridge-based nucleic acid amplification test (CB-NAAT) positivity for mycobacterium tuberculosis. She was started on routine anti-tubercular therapy (ATT) initially, later changed to modified ATT with levofloxacin, rifampicin, and ethambutol in view of deranged liver function tests. One month later, she returned with complaints of double vision, drooping of eyelids, unsteadiness while walking, dysphagia to solids and liquids, and shortness of breath. On examination, patient had bilateral ptosis and restricted extraocular movements in all directions. Curtain sign was present. Single breath count was eight. As the patient's clinical condition worsened despite adequate ATT regimen and in view of mild CB-NAAT positivity, evaluation for alternate diagnosis was considered. Ice pack test and neostigmine challenge test were done and both were positive. Repetitive nerve stimulation (RNS) showed more than 10% decremental response in facial and limb muscles. Acetylcholine receptor and MuSK antibody tests were sent. A working diagnosis of MG with myasthenic crisis was made and patient was started on intravenous immunoglobulin (IVIG) at a dose of 2 gm/kg for 5 days and oral pyridostigmine. Antibody testing came positive for anti-MuSK antibody. As the patient did not show any improvement to IVIG, she was given injection rituximab 1 gm and simultaneously started on mycophenolate mofetil. Even with rituximab, patient did not show adequate response, so she was taken up for plasma exchange with which her symptoms improved dramatically and was continued on mycophenolate mofetil.

Conclusion: Muscle-specific tyrosine kinase-MG is a subtype of MG with atypical clinical presentations causing a delay in diagnosis. In such cases MuSK-Ab testing confirms the diagnosis. Fluoroquinolone exposure may result in potentially life-threatening myasthenia gravis in patients with underlying disease. Our case shows that levofloxacin can unmask MuSK-MG, which has not been much reported in the literature. Response to acetylcholinesterase inhibitors is often unsatisfactory from that expected in MG patients. Among all immunotherapies, plasma exchange can be considered as the cornerstone of treatment for MuSK-MG which was evident in our case where inadequate response was showed to IVIG and rituximab.

Keywords: Auto-immune, Case report, Fluoroquinolones/adverse effects, Human, Muscle-specific tyrosine kinase receptor, Myasthenia gravis.

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Introduction

Muscle-specific tyrosine kinase (MuSK)-myasthenia gravis (MG) is a severe form of MG that has distinct pathology and atypical clinical symptoms. The onset of MuSK-MG is usually acute, and it mostly affects the facial and bulbar muscles. It is common to experience frequent early respiratory crises and rapid progress of symptoms within a few weeks. The diagnosis of MuSK-MG is challenging due to the atypical start, absence of symptom variations, and poor response to acetylcholinesterase inhibitors (ACEI). Fluoroquinolones and other medications can lead to a worsening of symptoms in these patients. Fluoroquinolones of any generation may interfere with neuromuscular transmission and may lead to MG symptoms by simply unmasking a pre-existing mild case and it should be avoided in patients with MG. The purpose of this case report is to document the occurrence of myasthenic

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crisis and respiratory distress resulting from taking levofloxacin in a patient initially diagnosed as tuberculous meningitis with no prior history of MG.

Case Description

A 24-year-old woman presented with 1 month history of low-grade fever and headache without any raised intracranial pressure features or neck stiffness. All her routine laboratory investigations and brain imaging were normal. Cerebrospinal fluid analysis showed normal protein and sugar levels, zero cell count with mild Cartridge-based nucleic acid amplification test (CB-NAAT) positivity for Mycobacterium tuberculosis. She was initially started on routine anti-tubercular therapy (ATT), later changed to modified ATT with levofloxacin, rifampicin, and ethambutol in view of deranged liver function tests. One month later, she returned with complaints of double vision, drooping of eyelids, unsteadiness while walking, dysphagia to solids and liquids, and shortness of breath.

On examination, the patient had bilateral ptosis and restricted extraocular movements in all directions. Curtain sign was present. The single breath count was eight. As the patient's clinical condition worsened despite adequate ATT regimen and in view of mild CB-NAAT positivity, evaluation for alternate diagnosis was considered. Ice pack test and neostigmine challenge test were done and both were positive. Repetitive nerve stimulation showed more than 10% decremental response in facial and limb muscles. Acetylcholine receptor (AchR) and MuSK antibody tests were sent.

A working diagnosis of MG with myasthenic crisis was made and the patient was started on intravenous immunoglobulin (IVIG) at a dose of 0.4 gm/kg for 5 days and oral pyridostigmine. Antibody testing came positive for the anti-MUSK antibody. As the patient did not show any improvement to IVIG, she was given injection rituximab 1 gm and simultaneously started on mycophenolate mofetil. Even with rituximab, patient did not show an adequate response, so she was taken up for plasma exchange with which her symptoms improved dramatically and was continued on mycophenolate mofetil.

Discussion

The first description of muscle-specific kinase antibody (MuSK-ab) as an autoantibody causing MG occurred in 2001, which led to the description of a distinct type of MG disease.[1] About 5–8% of patients with MG and 30% of patients with MG who do not have AChR antibody (AChR-ab) are affected by it.[2,3] MuSK activation is proven to cause AChR clustering on the postsynaptic membrane of the neuromuscular junction.[4] Muscle-specific kinase-abs are mainly found in the non-complement activating IgG4 subclass[5] and function by stopping the interaction between the MuSK–LRP4 complex and consequently inhibiting the AChR clustering. Muscle-specific kinase-MG's unique pattern thus be partly based on the pathological mechanism that is not identical to that of AChR-ab.

Women in their third decade are the most likely to experience this disease, with predominant involvement of the facial and bulbar muscles and much more prone to crisis. In most cases, the onset is sudden and progresses quickly in a few weeks. It has been shown that up to 80% of patients with MuSK-MG have involvement of the bulbar muscles. Muscle-specific kinase-MG symptoms can be overlooked in the initial part of the disease because they can be atypical and lack fluctuations, unlike AChR-ab-associated MG. In this case, the patient's initial atypical symptoms and lack of symptom fluctuations made the diagnosis challenging.

There is a wide range of medications that have been linked to a worsening of symptoms in patients with known MG. The connection between MG and medication effects is intricate. MG may occur occasionally as a result of certain medications, such as penicillamine and interferon, while drugs like aminoglycoside antibiotics and quinine can cause MG symptoms by simply revealing a mild MG case.

Fluoroquinolones are commonly employed antibiotics that have minimal side effects. Nausea, abdominal discomfort, headache, and dizziness are the most common side effects. Ciprofloxacin, norfloxacin, pefloxacin, ofloxacin, and trovafloxacin have been implicated in the exacerbation of MG.[6]

Despite the fact that fluoroquinolones have been reported to have similar effects, there have been very few cases involving levofloxacin. As this case illustrates, levofloxacin, along with other quinolones, has the potential to trigger symptom attacks in subclinical MG and results in myasthenic crisis.

The response to treatment in patients with MG often differs from what is expected, making it challenging to achieve a regression of symptoms. Muscle-specific kinase-MG is insensitive to conventional therapy like ACEI and thymectomy.[7,8] Treatment with ACEI could be detrimental to MuSK-MG. Furthermore, the response to standard doses of pyridostigmine is lackluster and has severe intolerance due to side effects.[9]

The main therapeutic approach for MuSK-MG involves immunosuppression. Immunotherapies include IVIG, rituximab, and plasma exchange as the primary treatments for MuSK-MG. In our case, the patient did not show adequate response to both IVIG and rituximab but showed excellent response to plasma exchange.

Conclusion

Muscle-specific kinase-MG is a subtype of MG that presents with atypical clinical manifestations, which can lead to delayed diagnosis. If the diagnosis is challenging, MuSK-ab testing can provide confirmation of the disease in these situations. Exposure to a variety of medications such as fluoroquinolones may result in potentially life-threatening MG in patients with underlying disease. Our case is a one-of-a-kind example, demonstrating that levofloxacin can also trigger MuSK-MG, which has not been widely reported in research. Treatment for these patients is challenging and different from the treatment of patients with AChR-MG. Muscle-specific kinase-MG responds poorly to ACEI and has the potential to be harmful in MuSK-MG. Among all immunotherapies, plasma exchange can be considered as the cornerstone of treatment for MuSK-MG which was evident in our case where inadequate response was shown to IVIG and rituximab.

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can disperse preformed agrin-independent AChR clusters. PLoS One 2013;8(11):e80695. DOI: 10.1371/journal.pone.0080695.
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