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MYASTHENIA GRAVIS OF ANTI-MUSK ORIGIN: CASE REPORT

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ABSTRACT
Myasthenia Gravis (MG) is a complex autoimmune neuromuscular disorder. While the classical form associated with anti-acetylcholine receptor antibodies (anti-AchR) is the most common, it is crucial to consider atypical forms, particularly those associated with anti-MuSK antibodies. These atypical forms are often more severe, resistant to treatment, and can present with diverse symptoms, which can be difficult to distinguish from other neuromuscular disorders. In these atypical forms, the detection of anti-MuSK antibodies becomes a key diagnostic element, especially when conventional tests, such as electromyography (EMG), do not yield conclusive results. This article presents a clinical case of a 29-year-old female patient who consulted for fluctuating symptoms, including diplopia, ptosis, exercise-induced fatigue, and swallowing disorders associated with dysphagia and nasal regurgitation. After excluding the presence of a thymoma via thoracic CT scan, a neurophysiological examination (EMG) was performed, but it did not reveal any significant abnormalities. The search for anti-acetylcholine antibodies (anti-AchR) was negative, but testing for anti-MuSK antibodies was positive at a dilution of 1/80, leading to a diagnosis of Myasthenia Gravis associated with anti-MuSK antibodies, a rare form of the disease. The discussion highlights the complexity of diagnosing Myasthenia Gravis, particularly in the atypical forms associated with anti-MuSK antibodies, which can be challenging to diagnose due to symptoms that resemble those of other neuromuscular disorders and negative results from conventional tests. While neurophysiological tests such as EMG are commonly used, they may be normal in atypical forms, making the search for specific antibodies essential for accurate diagnosis. Indirect Immunofluorescence (IFI) thus offers a complementary and more precise method, allowing for better understanding and management of Myasthenia Gravis in its less common forms. Although IFI is a specialized technique requiring specific equipment and expertise, its integration into routine laboratories could significantly improve the diagnosis of atypical forms of the disease, especially in settings where access to other specialized tests is limited. In summary, IFI represents an indispensable tool for the diagnosis of Myasthenia Gravis, particularly in atypical cases where standard tests fail to identify the pathology. Close collaboration between clinicians and laboratory specialists remains essential to ensure prompt and effective management of patients.

KEYWORDS: Myasthenia Gravis, Antibodyanti-MUSK, Routine Laboratory Tests in the Diagnosis of Myasthenia Gravis.

INTRODUCTION

Myasthenia Gravis (MG) is a relatively rare autoimmune neuromuscular disorder, with an estimated prevalence of between 10 and 20 cases per 100,000 inhabitants. MG typically affects young adults (especially women between the ages of 20 and 40) and the elderly (primarily men over 60 years old). It is responsible for fluctuating muscle weakness, particularly in the ocular muscles and the muscles involved in swallowing and respiration. Idiopathic forms are the most common, but geographic and ethnic variations can be observed, with a higher incidence in some European and North American countries. Recognizing this condition is essential, as appropriate treatment can significantly improve quality of life and reduce morbidity associated with the disease.[1]

Myasthenia Gravis is mainly divided into two major categories: the classical form, associated with anti-acetylcholine receptor antibodies (anti-AchR), and the atypical form, often linked to the presence of anti-MuSK antibodies (MuSK: Mucin-Specific Kinase), a protein

crucial for the formation and maintenance of the neuromuscular junction, particularly for the accumulation and stability of acetylcholine receptors by promoting the aggregation of these receptors at the muscle membrane at the neuromuscular junction through interaction with another group of proteins called Lrp4 (Low-Density Lipoprotein Receptor-Related Protein 4), which acts as a co-receptor for MuSK. The classical form is the most common and is typically characterized by symptoms affecting the ocular muscles (ptosis and diplopia), as well as swallowing and breathing disorders. In contrast, forms associated with anti-MuSK antibodies tend to present with more severe and treatment-resistant symptoms, sometimes including severe manifestations such as respiratory and swallowing difficulties. Additionally, rare forms associated with autoantibodies against other components of the neuromuscular junction, such as LRP4, have been reported, increasing the clinical diversity of the disease.[2]

The diagnosis of Myasthenia Gravis primarily relies on a combination of clinical and biological tests. The detection of specific antibodies, particularly anti-AchR and anti-MuSK antibodies, is crucial for confirming the diagnosis. However, while the search for anti-AchR antibodies is positive in approximately 85% of classical cases, it may be negative in atypical forms, making the identification of anti-MuSK antibodies essential, especially in cases where neurophysiological tests (such as electromyography, EMG) are normal or non-revealing. Furthermore, thoracic imaging is used to look for a thymoma, although the latter is more frequently associated with the classical form of the disease.[3]

Despite advancements in diagnostic methods, the role of routine laboratories in diagnosing Myasthenia Gravis, particularly its atypical forms, remains a major challenge. The technique of indirect immunofluorescence (IFI) plays a crucial role in this context, enabling the specific detection of anti-AchR and anti-MuSK antibodies, especially in the atypical forms of the disease where conventional tests may be negative. IFI offers enhanced sensitivity for identifying these autoantibodies, even when other biological or neurophysiological tests, such as electromyography, fail to provide a conclusive diagnosis. Integrating this method into routine laboratories could, therefore, improve the early detection of rare and atypical forms of Myasthenia Gravis, particularly in regions where access to specialized tests is limited. Moreover, close collaboration between clinicians and laboratory specialists remains essential for correctly interpreting IFI results and ensuring optimal patient management.[3]

CASE REPORT

A 29-year-old female patient presented in April with fluctuating symptoms, including diplopia, ptosis, and swallowing difficulties accompanied by dysphagia and nasal regurgitation of fluids. The symptoms had progressively worsened over the previous weeks. In addition to the ocular and muscular symptoms, the patient reported exercise-induced fatigue, a key sign in many neuromuscular disorders.

To exclude a thymoma, a thoracic CT scan was performed, with normal results, thus eliminating this common cause of Myasthenia Gravis. A neurophysiological examination (EMG) was also conducted but showed no significant abnormalities, which is common in the early or atypical forms of the disease. The lack of conclusive clinical findings led to the performance of immunological tests.

A test for anti-acetylcholine antibodies was negative. However, the search for anti-MuSK antibodies was positive at a dilution of 1/80 (normal value <1/10), confirming the diagnosis of Myasthenia Gravis associated with anti-MuSK antibodies (see image below).This result underscores the importance of searching for specific antibodies in atypical forms of Myasthenia Gravis through IFI, owing to its high sensitivity.

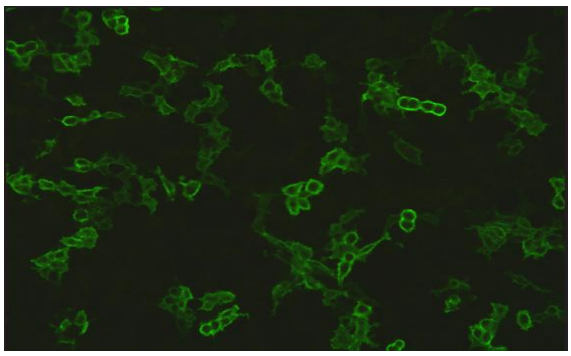

Image viewed under UV fluorescence microscope with a X40 objective. The substrate consists of cells transfected with the MuSK (Mucin-Specific Kinase) protein to which the patient's serum is added, with a dilution of 1/10. Positive result with high intensity (3D or 1/80) of anti-MuSK antibodies.

DISCUSSION

Myasthenia Gravis is an autoimmune disease characterized by impaired neuromuscular transmission due to autoantibodies. The classical form of the disease is associated with anti-acetylcholine receptor antibodies (anti-AchR), which inhibit the action of acetylcholine, a key neurotransmitter for muscle contraction.[4] However, a less common form of Myasthenia Gravis, which may be more difficult to diagnose, is the one associated with anti-MuSK antibodies, a protein at the neuromuscular junction that plays a crucial role in transmitting nerve impulses to the muscle.[5]

Epidemiologically, Myasthenia Gravis typically affects young adults, with a higher prevalence in women aged 20 to 40 years, and in older individuals, primarily men over 60 years old. The forms associated with anti-MuSK antibodies are rare but tend to affect younger patients, as observed in our case with a 29-year-old female patient.

These rare forms are often more severe and present more serious symptoms, such as swallowing difficulties, respiratory issues, and muscle problems, which further complicates their diagnosis.[6]

Forms of Myasthenia Gravis associated with anti-MuSK antibodies are often more challenging to diagnose due to their low frequency and variability in clinical presentation. The search for specific antibodies, such as anti-MuSK antibodies, is therefore fundamental for an accurate diagnosis, especially in the atypical forms of the disease, such as the one observed in this case.[7]

Indeed, although neurophysiological tests such as EMG may be useful, they are not always sensitive, particularly in the early stages of the disease. The absence of abnormalities in the EMG in this case demonstrates that this test may not be sufficient for diagnosing Myasthenia Gravis, especially in forms with anti-MuSK antibodies, where neuromuscular involvement is less pronounced in the early stages of the disease.[8]

Furthermore, the absence of a thymoma in this patient, although common in classical Myasthenia Gravis, does not necessarily exclude the disease, particularly in forms associated with anti-MuSK antibodies. Myasthenia Gravis with anti-MuSK antibodies does not have a strong association with the presence of thymoma, unlike the classical form. This highlights the importance of a broader diagnostic approach, including the search for atypical forms when clinical signs suggest Myasthenia Gravis, but conventional tests are negative.[9]

The technique of indirect immunofluorescence (IFI) is particularly useful in atypical forms of the disease, where the search for anti-AchR antibodies may be negative. IFI is used to detect anti-MuSK antibodies by preparing cells that express the MuSK protein (Muscle-specific kinase) and incubating the patient's serum with these cells. After incubation, a secondary antibody labeled with a fluorochrome is applied, allowing the visualization of anti-MuSK antibodies under a fluorescence microscope. This method is highly precise and sensitive, enabling the detection of even low concentrations of antibodies. However, IFI requires specialized equipment and experienced personnel, which may pose a constraint in certain laboratories.[10] The use of IFI in diagnosing Myasthenia Gravis thus allows for more precise and rapid detection, particularly for less common and difficult-to-diagnose forms.[11]

IFI also allows direct detection of anti-MuSK antibodies through fluorescence, greatly improving diagnostic specificity in atypical forms.[12] Its use reduces the risk of false negatives compared to conventional tests, such as EMG, especially when these tests fail to detect abnormalities.[13]

However, IFI has certain limitations. In addition to requiring specific equipment, this technique may also suffer from inter-laboratory variability and subjective interpretations, especially in cases of weak fluorescence intensity.[14] Moreover, the high cost of reagents and equipment necessary for IFI may limit its use in certain regions or for specific patients, potentially affecting the speed of diagnosis.[15]

Despite these limitations, IFI remains the method of choice to confirm the diagnosis of Myasthenia Gravis in cases where conventional tests are insufficient. Furthermore, it contributes to better management of atypical cases, providing clinicians with crucial information on the presence of anti-MuSK antibodies, thus enabling more targeted and personalized treatment. In our case, although anti-AchR antibodies were negative, the search for anti-MuSK antibodies was positive at a dilution of 1/80 (normal value <1/10), confirming the diagnosis of atypical Myasthenia Gravis associated with anti-MuSK antibodies.

CONCLUSION

This clinical case highlights the importance of searching for specific antibodies in atypical forms of Myasthenia Gravis. Although Myasthenia Gravis associated with anti-MuSK antibodies is rarer, it can present with symptoms similar to those of the classical form and requires thorough differential diagnosis. This case also underscores that laboratory tests for detecting these antibodies, particularly using the indirect immunofluorescence (IFI) method, are crucial for an accurate diagnosis, especially when conventional tests, such as electromyography (EMG), are negative. In our case, the presence of anti-MuSK antibodies at a dilution of 1/80 confirmed the diagnosis of atypical Myasthenia Gravis, emphasizing the importance of IFI in identifying these rare forms and facilitating targeted treatment.

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