



Myasthenia gravis with myasthenic crisis: a case report

Miastenia gravis com crise miastênica: relato de caso

Miastenia gravis con crisis miasténica: reporte de un caso

Fernando Cotrim Gomes¹, Paulo Roberto Nolli Filho¹, Gabriel Anselmo Frota¹, Geanne Muniz Meira¹, Fernando Lucas Santos¹, Lyster Dabien Haddad², Luís Felipe José Ravic de Miranda¹

ABSTRACT

Objective: To present a favorable outcome in a Myasthenia gravis (MG) patient with myasthenic crisis and discuss its main diagnostic challenges. **Case detail:** We report the case of a previously healthy 80-year-old male who first presented with dysphagia that quickly progressed to a generalized myasthenic syndrome leading to ICU admission and intubation over the course of less than two months. He was investigated firstly for thymoma, followed by Parkinson's disease and Lambert-Eaton syndrome before closing on MG. He was successfully stabilized after a month-long ICU stay intercurring with multiple infections and respiratory failure. Currently presenting no sequelae or recurrence. **Final considerations:** Myasthenia gravis is an important autoimmune neuromuscular disorder that affects the neuromuscular junction. It has many possible signs and symptoms, depending on the most affected muscle group. Although there is no cure for it, an early diagnosis allows an approach and treatment that provides a better quality of life, and the prevention of related complications. We discuss how to assess the main differential diagnoses, including Parkinson's disease, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Lambert-Eaton Syndrome, and others, to help clinicians facing a similar patient and avoid a poor outcome on a fast-paced progression case such as the one we report.

Keywords: Myasthenia Gravis, Diagnosis, Neuromuscular Junction Diseases.

RESUMO

Objetivo: Apresentar evolução favorável em paciente com Miastenia gravis (MG) com crise miastênica e discutir seus principais desafios diagnósticos. **Detalhamento do caso:** Relatamos o caso de um homem de 80 anos, previamente hígido, que apresentou inicialmente quadro de disfagia que evoluiu rapidamente para síndrome miastênica generalizada, levando à internação em UTI e intubação em menos de dois meses. Ele foi investigado primeiro por timoma, seguido por doença de Parkinson e síndrome de Lambert-Eaton antes de fechar em MG. Ele foi estabilizado com sucesso após um mês de internação na UTI intercorrendo com infecções múltiplas e insuficiência respiratória. Atualmente sem sequelas ou recidivas. **Considerações finais:** A miastenia grave é uma importante desordem neuromuscular autoimune afetando a junção neuromuscular. Tem muitos sinais e sintomas possíveis, dependendo do grupo muscular mais afetado. Apesar de não ter cura, um diagnóstico precoce permite uma abordagem e tratamento que proporcionem uma melhor qualidade de vida, e a prevenção de complicações relacionadas. Discutimos como avaliar os principais diagnósticos

¹Federal University of Minas Gerais (Department of Internal Medicine), Belo Horizonte - MG.

²Felicio Rocho Hospital /Unimed University Hospital, Belo Horizonte - MG.

diferenciais, incluindo doença de Parkinson, Esclerose Lateral Amiotrófica, Esclerose Múltipla, Síndrome de Lambert-Eaton e outros, para ajudar os médicos a enfrentar um paciente semelhante e evitar um resultado ruim em um caso de progressão rápida, como aquele que relatamos.

Palavras-chave: Miastenia grave, Diagnóstico, Doenças da Junção Neuromuscular.

RESUMEN

Objetivo: Presentar un resultado favorable en un paciente con Miastenia gravis (MG) con crisis miasténica y discutir sus principales desafíos diagnósticos. **Detalle del caso:** Presentamos el caso de un hombre de 80 años previamente sano que primero presentó disfagia que progresó rápidamente a un síndrome miasténico generalizado que condujo a la admisión e intubación en la UCI en el transcurso de menos de dos meses. Primero fue investigado por timoma, seguido por la enfermedad de Parkinson y el síndrome de Lambert-Eaton antes de cerrar con MG. Se estabilizó con éxito después de una estadía de un mes en la UCI intercalada con múltiples infecciones e insuficiencia respiratoria. Actualmente no presenta secuelas ni recurrencia. **Consideraciones finales:** La miastenia gravis es un trastorno neuromuscular autoinmune importante que afecta la unión neuromuscular y tiene muchos signos y síntomas posibles. Aunque no tiene cura, un diagnóstico precoz permite un abordaje que proporciona una mejor calidad de vida y la prevención de las complicaciones relacionadas. Discutimos cómo evaluar los principales diagnósticos diferenciales, como la enfermedad de Parkinson, la esclerosis lateral amiotrófica, la esclerosis múltiple, el síndrome de Lambert-Eaton y otros, para ayudar a los médicos con pacientes similares en un caso de progresión rápida.

Palabras clave: Miastenia gravis, Diagnóstico, Enfermedades de la unión neuromuscular.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder characterized by the degradation of postsynaptic components of the neuromuscular junction (NMJ), leading to muscle fatigue on minor exertion and improvement upon rest (GILHUS NE, 2016). The most frequently involved target is the acetylcholine receptor (AChR), followed by the MuSK protein and the low-density lipoprotein receptor-related protein 4 (LPR4) (VINCENT A, et al., 2018). Thus, a variety of phenotypes may be identified, depending on which antibodies are to be found in each case (GILHUS NE, et al., 2016).

MG can manifest in patients of all ages, but has a classical age-of-onset distribution predominantly between 20 to 45 years among female patients and 50 to 75 among male ones (HERNANDEZ FUSTES OJ, et al., 2020). It has two main clinical presentations. First: there is the ocular one, affecting around 10% of patients, whose symptoms are restricted to the ocular muscles, namely the levator palpebrae superioris and the recti muscles. Its main symptoms are, therefore, diplopia and ptosis. The second one is the generalized form of the disease, in which other muscle groups may be affected, and thus present fatigue, commonly with a proximal-distal progression (THANVI BR, 2004). Although it is considered a rare disease, with an estimated prevalence of 10 cases per 100.000 people, MG is the most common NMJ affecting disease, and an increase in diagnosis frequency has been observed in recent years. That is mostly attributed to successfully overcoming the past sub notification, rather than an actual increase in incidence (HEHIR MK and SILVESTRI NJ, 2018). Diagnosis is based on the combination of clinical data, serum analysis for autoimmune antibodies and neurophysiological testing, such as the electromyography.

MG treatment is based on acetylcholinesterase inhibitors, and in many acute cases an association with immunosuppressive steroids is necessary. For chronic patients, drugs such as azathioprine is recommended. Thoracic MRI is recommended to rule out thymoma as a possible diagnosis, which prompts thymectomy procedure if confirmed. MG frequently presents with a favorable prognosis, with a low mortality rate of around 0.06 deaths per million people every year. Such cases are usually related to the development of myasthenic crisis (MC), the generalized worsening of the fatigue symptoms that may lead to respiratory failure which can affect 15 to 20% of MG patients (HEHIR MK and SILVESTRI NJ, 2018).

Besides, a small percentage of patients may present with the refractory form of the disease, which usually affects women at an early onset age, acute crises and severe symptoms with numerous relapses (GARCIA-GARCIA J, et al., 2020). In this report we present an MG patient with myasthenic crisis, in which dysphagia was his main clinical sign, and to discuss the main differentials to help future decision making in similar cases.

CASE DETAIL

This manuscript was approved by the Ethics Committee – Plataforma Brasil under the decision code 5543994 and CAAE number: 59242021.7.0000.5149. We report the case of an 80-year-old caucasian male patient, previously working as an agricultural manager, with a personal history of tuberculosis, former smoker, and GOLD-3 chronic obstructive pulmonary disease, having stage 1 compensated high blood pressure, and major depression. Daily use of Escitalopram 10mg, Metformin 1g, azatioprin 50mg, atorvastatin 10mg, pantoprazole 40mg, Tiotropium bromide 2.5mg, and olodaterol 2.5mg.

In the previous year he had had herpes zoster, complicated with decreasing strength in his left leg – Grade II. After several weeks of physiotherapy, his strength in the same leg increased to grade IV. He was treated with the antiviral Acyclovir. In April/2021, the patient showed signs of impaired chewing force and dysphagia and underwent a video swallowing study. The study identified signs consistent with neurogenic oropharyngeal dysphagia for both solids and liquids, which can be suggestive of Parkinsonism, MG and other neurologic affections. Some days later he presented with ptosis and dysarthria, which further raised the suspicion of MG.

He thus performed an ice pack test, a non-invasive, bedside diagnostic test for MG, which came back positive. Lab tests were requested to assess the presence of related antibodies, and to screen for other possible causes, apart from a family history check. Then, he was forwarded to the neurologist, who continued the investigation with a Thorax MRI, to exclude the presence of a thymoma, which has a high incidence among MG patients, and an electromyography, to discard a Lambert-Eaton Syndrome, which reported denervation affecting the L2-L4 myotome topographies suggesting moderate to severe both acute and chronic axon impairment. In the meantime, patient serum tested positive for anti-acetylcholine receptor antibody showing 1.58nm/L (reference value <0.4), closing the diagnosis of MG.

At that time this investigation was being conducted, however, the patient's health had deeply worsened. In June/2021, he was admitted at a hospital presenting with generalized asthenia, suggestive of myasthenic crisis. Then, immunoglobulin was immediately prescribed. Furthermore, he was diagnosed on admission with a urinary tract infection, and ceftriaxone was started. He presented with respiratory function worsening which led to his taking to the Intensive care unit (ICU) and intubation with the use of the Trillogy-100 respiratory support device on the following day. Five days later there was a failed attempt at extubating the patient, and subsequent tracheostomy. During his stay, he repeatedly presented new infectious episodes with different foci, which required treatment with ceftriaxone for 7 days for an UTI, followed by meropenem for 6 days, linezolid for 11 days, polymyxin B for 2 days and finally levofloxacin for 10 days for pneumonia. On June 15th, after a month-long stay, he was successfully extubated and discharged from the ICU.

Decannulation was successfully performed on July 7th, and two days later he was in good general condition. The patient was neurologically stable, with good acceptance of oral nutrition, walking and with preserved physiological functions. He was discharged from hospital care and instructed to take prednisone 20mg/day and to schedule a follow-up appointment 20 days later, along with general rehabilitation orientation, currently using pyridostigmine 240mg/day.

DISCUSSION

MG is the main NMJ related disease group, with varying affected muscles, symmetry, and severity of symptoms (GILHUS NE and VERSCHUUREN JJ, 2015). Its wide range of clinical presentations may be mistaken for other neurological and muscular similar affections, as a wide range of muscle groups can be affected in varying order, and thus some differential diagnosis must be considered during the investigation.

In the presence of dysphagia and bradykinesia, Parkinson's disease (PD) should be considered as a possibility. Around 7 to 10 million people worldwide are estimated to be affected and over sixty thousand new cases are diagnosed yearly, making it one of the most common neurodegenerative diseases, and it affects the dopaminergic pathways connected to the mesencephalic Substantia Nigra, with repercussions for muscle control and balance (BEITZ JM, 2014).

Its average age of onset is estimated to be around 60 years old and its prevalence progressively increases in older groups, male patients are 1.5 times more likely to present with it, and its early clinical presentation is frequently similar to that of MG, with early motor symptoms and bradykinesia (GROVER S, et al., 2022). Thus, given our patient's profile and initial presentation, PD was an important differential diagnosis to investigate. If under suspicion of PD, the clinical diagnosis can be rapidly verified, as it is associated with a fast positive response to the use of dopaminergic precursor drugs, such as levodopa, an agent capable of crossing the blood-brain barrier, with an effective use to control bradykinetic symptoms. In the present clinical case, despite the existence of dysphagia and tiredness as possible symptoms of PD, there was no favorable response to the experimental use of levodopa, which helped us to exclude it according to the criteria established by the "International Parkinson and Movement Disorder Society" in 2015 (POSTUMA RB, et al., 2015).

Another differential diagnosis of MG is Amyotrophic Lateral Sclerosis (ALS), an adult-onset progressive neurodegenerative disorder involving motor neurons of both cortex and spinal cord. The disease presents with mixed signs of upper and lower motor neuron syndromes: swallowing problems, weaknesses in the hands and legs, muscle cramps, loss of motor control, and difficulty in usual daily activities. The average incidence of motor neuron disease (MND) has grown from sixties and seventies by up 46 % and now stands at about 1,89 per 100.000/year, and the most well-established risk factors for it are age and family history. The increased incidence could reflect refined El Escorial criteria as well as increased life expectancy and accuracy of death certificate collection. The fact that one of the early common signs of ALS is progressive bulbar palsy, along with the patient's demographic characteristics makes it a relevant differential diagnosis in the reported case. An important factor for the differentiation between ALS and MG is the more stable progression of the motor symptoms, with rare fluctuations in ALS patients, as opposed to the MG ones (SINGH N, et al., 2018)

One autoimmune entity to take into consideration when assessing a myasthenic syndrome is Multiple Sclerosis (MS), especially given that, for reasons yet unclear, there is a relatively high co-occurrence of the disease in MG patients, higher than would be expected at random (DEHBASI S, et al., 2019). Although affecting different immune targets, both MS and MG are hypothesized to be related to similar mechanisms for loss of self-tolerance, and may course with similar motor symptoms. MS is the most common cause of non-traumatic disability among young adults but it has a highly variable age of onset and presentation, so although being more common in women, one must keep a high suspicion level (POZZILLI C, et al., 2023). Being a central-affecting condition, however, there are some aspects of its diagnosis that easily differentiate it from MG, with important radiological findings on a cranial or spinal MRI that could not be mistaken for a peripheral disease, which appear to correlate with outcomes. Lab tests, in this case, are most useful for differentiating it from other possible differential diagnoses (DOBSON R and GIOVANNONI G, 2018).

Penicillamine-induced myasthenia develops in a small number of patients taking the drug penicillamine to treat rheumatoid arthritis or Wilson disease. Among other drugs, de novo MG can also be caused or exacerbated by the use of tyrosine kinase inhibitors, interferons, immune checkpoint inhibitors and statins, with different rates of related side effects. Other substances like some neuromuscular blockers, corticosteroids, class Ia antiarrhythmics, L type calcium channel blockers, magnesium, antipsychotics and some classes of antibiotics, such as fluoroquinolones, macrolides and aminoglycosides can generate MG-like symptoms (SHEIKH S, et al., 2021).

The treatment of hypercholesterolemia with statins may provoke myasthenia syndrome or exacerbate existing symptoms of MG, but fortunately, its effect is commonly self-resolved after discontinuation of the medicine. Thus, when assessing patients with respiratory, muscular and oculomotor symptoms, while MG must be considered, a thorough investigation of his current and previous pharmaceutical treatments must be collected to exclude drug induced symptoms. These can be developed by two main pathological mechanisms:

firstly, some medications can lead to auto-immune responses affecting the neuromuscular joint, thus simulating the same process that is observed in MG patients, such is the case for immune checkpoint inhibitors as those used to treat some forms of cancer. Secondly, some drugs may interfere in the neuromuscular synaptic. In such cases, the discontinuation of treatment is frequent enough to completely heal the patient, otherwise other possibilities should be considered (ADELMANN HM, et al., 1995)

When facing a patient presenting with a myasthenic syndrome with cephalocaudal progression, starting with dysphagia as in the presented case, another clinical entity to be considered is botulism, an infection by the anaerobe microbial clostridium botulinum. Although rare, with around 100 yearly cases in the US, this disease is potentially fatal, as the botulinum toxins bind to NJ nerve endings irreversibly and impair the transmission of acetylcholine, leading to similar symptoms to those of MG but usually with a much faster progression (HA JC and RICHMAN DP, 2015).

The main forms of botulism are foodborne, commonly associated with home-canned or raw fermented products, and wound related infection. Thus, the patient's history including time and progression of the symptoms, as well as eating habits, plays a vital role in allowing a quick diagnosis and preventing worsening of their condition. As the history of this reported case suggested no risk factors for it, it was not included among the initial suspicions. If that remains uncertain, the diagnosis for botulism can be confirmed by lab tests presenting the parasite or the toxins in serum and stool tests (CARRILLO-MARQUEZ MA, 2016).

Lambert-Eaton Syndrome (LES), an important differential diagnosis in this case, is a dysfunction of the NMJ resulting from a paraneoplastic or autoimmune cause. It usually courses with proximal muscle weakness and autonomic dysfunction, such as dry mouth, impotence and constipation. The presentation seems to be a consequence of the action of autoantibodies on voltage-gated calcium channels (VGCC) of the P/Q type present in presynaptic receptors on nerve endings and lower acetylcholine (ACh) release.

More than 50% of cases of this syndrome are related to small cell lung carcinoma, which also expresses VGCC. LES is a rare disease whose incidence varies from 1/10 to 1/40 of the incidence of MG and its prevalence is 46 times lower. The paraneoplastic form of the disease, related to lung carcinoma, usually appears around 60 years of age and 65% to 75% of those affected are men.

The non-neoplastic form of LES has an age and sexual distribution similar to MG, being found at all ages, and there are 2 peaks of incidence: the first at 35 years and another at 60 years. The clinical triad usually consists of asthenia, autonomic dysfunction, and loss of reflexes. Symptoms appear insidiously and gradually increase. The main manifestations are lower limb weakness (60%), generalized fatigue (18%), myalgia or stiffness (5%), xerostomia (5%), upper limb weakness (4%), diplopia (4%) and dysarthria (2%). Weakness usually progresses in a proximal-distal and caudal-peripheral manner, until reaching the subocular region.

The pattern is therefore different from that of MG, which is usually cranial-caudal. The diagnosis of Lambert-Eaton Syndrome is based on clinical signs and symptoms and its confirmation is made by the detection of specific antibodies to VGCC and by electrophysiological studies. Effective treatment of symptomatic LES is performed with 3,4-diaminopyridine. AChE inhibitors usually do not improve the condition, but they can alleviate xerostomia (MICHAEL KEOGH, et al., 2011; NA ZHANG, et al., 2021)

The clinical differentiation between MG and LES presents obstacles related to the similar distribution of muscle weakness. Thus, in the reported patient, the differentiation was established through electromyography, in which the study of motor conduction after isometric muscle contraction of 20s did not show an increase (>100%) in amplitudes and the low-frequency repetitive stimulation test Frequency (3HZ) at rest and after exertion of the median, ulnar and facial nerves showed an abnormal decrease (>10%), especially in the facial nerve in addition to the median one. In patients with LES, an increase greater than 100% is expected in repetitive high-frequency nerve stimulation or after maximal voluntary contraction. On the other hand, the presence of an electromyographic response with a reduction in muscle potential amplitude of at least 10% after repetitive stimulation at 3-5 Hz configures an inclusion criterion in the diagnosis of MG, confirming that the postsynaptic dysfunction of the neuromuscular junction presented by this patient is compatible with MG (WIRTZ PW, et al., 2002; PASCUZZI RM and BODKIN CL, 2022).

CONCLUSION

We can infer the importance of considering the possible differential diagnoses in a suspected MG case, regarding the clinical similarity between them and the specific procedures for the diagnosis, clinical approach and treatment of each one. The diagnosis of MG should always be suspected first by the clinical signs and symptoms and confirmed with complementary workup, especially by serological tests and electromyography. The correct diagnosis and as early as possible becomes imperative, because even though there is no cure for MG, the treatment can provide a good quality of life for the patient and avoid complications of the disease.

REFERENCES

1. ADELMAN HM et al. D-penicillamine-induced myasthenia gravis: diagnosis obscured by coexisting chronic obstructive pulmonary disease. *Am J Med Sci*. 1995; 309(4): 191-3.
2. BEITZ JM. Parkinson's disease: a review. *Front Biosci (Schol Ed)*. 2014; 6(1): 65-74.
3. CARRILLO-MARQUEZ MA. Botulism. *Pediatr Rev*. 2016; 37(5): 183-92.
4. DEHBASHI S et al. Co-occurrence of multiple sclerosis and myasthenia gravis: A case report and review of immunological theories. *Mult Scler Relat Disord*. 2019; 34: 135-136.
5. DOBSON R, GIOVANNONI G. Multiple sclerosis - a review. *Eur J Neurol*. 2019; 26(1): 27-40.
6. GARCIA-GARCIA J et al. A series of patients with refractory myasthenia gravis. *Neurologia (Engl Ed)*. 2020; S0213-4853(20): 30293-0.
7. GILHUS NE et al. Myasthenia gravis - autoantibody characteristics and their implications for therapy. *Nat Rev Neurol*. 2016; 12(5): 259-68.
8. GILHUS NE, VERSCHUUREN JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol*. 2015; 14(10): 1023-36.
9. GILHUS NE. Myasthenia Gravis. *New England Journal of Medicine*. 2016; 375(26): 2570-2581.
10. GROVER S et al. Genome-wide Association and Meta-analysis of Age at Onset in Parkinson Disease: Evidence From the COURAGE-PD Consortium. *Neurology*. 2022; 16; 99(7).
11. HA JC, RICHMAN DP. Myasthenia gravis and related disorders: Pathology and molecular pathogenesis. *Biochim Biophys Acta*. 2015; 1852(4): 651-7.
12. HEHIR MK, SILVESTRI NJ. Generalized Myasthenia Gravis. *Neurologic Clinics*. 2018; 36(2): 253-260.
13. HERNANDEZ FUSTES OJ et al. Myasthenia Gravis with Elderly Onset at Advanced Age. *Cureus*. 2020; 12(1): 29.
14. MICHAEL KEOGH, et al. Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database of Systemic Reviews*. 2021; 2: 1465-58.
15. NA ZHANG, et al. 3,4-diaminopyridine treatment for Lambert Eaton myasthenic syndrome in adults: a meta-analysis of randomized controlled trials. *BMC Neurology*. 2021; 21(1): 371.
16. PASCUZZI RM and BODKIN CL. Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome: New developments in diagnosis and treatment. *Neuropsychiatr Dis Treat*. 2022; 18: 3001-3022.
17. POSTUMA RB et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015; 30(12): 1591-1601.
18. POZZILLI C et al. Diagnosis and treatment of progressive multiple sclerosis: A position paper. *Eur J Neurol*. 2023; 30(1): 9-21.
19. SHEIKH S et al. Drugs That Induce or Cause Deterioration of Myasthenia Gravis: An Update. *J Clin Med*. 2021 6; 10(7): 1537.
20. SINGH N et al. Clinical Mimickers of Amyotrophic Lateral Sclerosis-Conditions We Cannot Afford to Miss. *Ann Indian Acad Neurol*. 2018; 21(3): 173-178.
21. THANVI, B R. Update on myasthenia gravis. *Postgraduate Medical Journal*. 2004; 80(950): 690-700.
22. VINCENT A et al. Serological and experimental studies in different forms of myasthenia gravis. *Ann N Y Acad Sci*. 2018; 1413(1): 143-153.
23. WIRTZ PW et al. Difference in distribution of muscle weakness between myasthenia gravis and the Lambert-Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatry*. 2002; 73(6): 766-8.