CASE REPORT: RESPIRATORY FAILURE – DON'T FORGET MYASTHENIA!

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ABSTRACT

Myasthenia gravis (MG) is a rare autoimmune disease in which antibodies bind to acetylcholine receptors in the postsynaptic membrane at the neuromuscular junction. Muscle-specific kinase (MuSK) antibody-associated MG patients often have severe symptoms, including bulbar dysfunction, respiratory insufficiency and atrophy of the facial and tongue muscles. Fluctuating character and the similarity of symptoms to those of other disorders make MG one of the most challenging medical diagnoses. Initial misdiagnosis of MuSK-MG can lead to worsening of symptoms. The diagnosis is confirmed by positive results on pharmacological testing, electrodiagnostic testing and serum antibody assay. Symptomatic, immunoactive, and supportive approaches to therapy have very good effect and the prognosis is improved with precocious interventions.

Key words: Myasthenia gravis, autoantibodies, respiratory insufficiency.

RESUMO

A miastenia gravis (MG) é uma doença autoimune rara na qual os anticorpos se ligam aos receptores de acetilcolina na membrana pós-sináptica da junção neuromuscular. Pacientes com MG associado ao anticorpo músculo quinase específico (MuSK) freqüentemente apresentam sintomas graves, incluindo disfunção bulbar, insuficiência respiratória e atrofia dos músculos faciais e da língua. O caráter flutuante e a semelhança dos sintomas com os de outras doenças tornam a MG um dos diagnósticos médicos mais desafiadores. O diagnóstico incorreto de MuSK-MG pode levar ao agravamento dos sintomas. O diagnóstico é confirmado por resultados positivos em testes farmacológicos, testes de eletrodiagnóstico e análise de anticorpos séricos. As abordagens sintomáticas, imunoativas e terapias de supeorte têm um efeito positivo na sintomatologia e o prognóstico é melhorado com intervenções precoces.

Key words: Miastenia gravis, autoanticorpos, insuficiência respiratória.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder in which muscle weakness occurs as a result of impairment of neuromuscular transmission (CARR et al, 2010). The knowledge on myasthenia gravis pathogenesis has greatly increased, and it is now recognized to have wide clinical phenotypes based on the presence of the different autoantibodies (MANTEGAZZA et al, 2018). MG is caused by autoantibodies that target the postsynaptic membranes of neuromuscular junctions (NMJs), cholinergic synapses that connect nerve terminals and skeletal muscle fibers (MORI et al, 2013).

In Brazil the incidence of MG varies from 1 to 9 per million inhabitants (MINISTÉRIO DA SAÙDE, 2015). Symptoms are characterized by fluctuating weakness that improves with rest and worsens with exercise, infections, menstruation, anxiety, emotional stress and pregnancy. Weakness can be limited to specific muscle groups (ocular, facial, bulbar muscles) or be generalized (GILHUS, 2016).

These antibodies can be divided in three different classes: antibodies against acetylcholine receptors (AChR), muscle-specific kinase (MuSK) and lipoprotein receptor-related protein 4 (LRP4) (GILHUS, 2016). The majority of abs positive myastehnic patients have AChR antibodies, with an initial ocular symptomatology converging to a generalized form within one year and good resposnse to acetylcholinesterase inhibitors (AChE-I) (MANTEGAZZA et al, 2018).. Approximately 5-8% of the total number of patients with myasthenia gravis (MG) has antibodies against the muscle specific tyrosine kinase (MuSK) receptor. These patients exhibit a distinct clinical phenotype and may differ from “typical” MG associated with antibodies against the acetylcholine receptor (AChR) (FURUTA et al, 2015). MG associated with MuSK antibodies has some distinct clinical features, including prevalent involvement of cranial and bulbar muscles and frequent intolerance of (AChE-I). Cramps and fasciculations may also occur in patients with MG following treatment with AChE-I, particularly in patients with MuSK-MG (SIMON et al, 2013).

MG remains one of the most challenging medical diagnoses due to its fluctuating character and to the similarity of its symptoms to those of other disorders (JUEL et al, 2007). The initial clinical course might be interpreted as fatigue, tiredness or laziness. So, the complication with respiratory insufficiency may lack a previous clinical history that would help with the diagnosis. We would like to present a case that exemplify these “false” acute presentation for myasthenia.

METHODS

Medical Reports review.

CASE REPORT

A 45-year-old woman went to the general physician complaining of dyspnea, she was no longer able to perform her dance classes. She had an unremarkable spirometry and showed night desaturation in the polysomnography. She started domiciliary oxygen at night and was referred to a pneumologist.

Before the consultation, she had an acute episode of ventilatory insufficiency associated with a decrease in consciousness level (gasometer analysis: SpO2: 92%, PCO2: 90mmHg, PaO2: 72.2 mmHg). She went to the emergency room and was submitted to mechanical ventilation. Pulmonary thromboembolism was ruled out after angiotomography. The tomography revealed a pneumonic infiltration, she was treated with antibiotics. A bronchospasm therapy with use of venous hydrocortisone was added after the evidence of wheezing on auscultation. She got better after the whole treatment without oxygen dependence and went back home. The medical team listened to her family that reported she was feeling weak for about one year and was also sadder since her husband was diagnosed with cancer, always with an unhappy face. So, it was suggested that her respiratory failure was secondary to a psychogenic disorder and she was referred to the psychiatry. Two weeks later, she started to feel the same symptoms again, and needed to use night oxygen.

She has referred to our team at the occasion. The first examination showed a restricted gaze upwards and restricted adduction on the bilateral gaze with a bilateral ptosis with no fluctuation during the day. The palate elevation and nausea reflex were impaired, with an inefficient swallow. Global force, sensibility, coordination and tendon reflexes were preserved. The gasometer showed high CO2 pressure (60 – 70 mmHg), her spirometry showed a restrictive and obstructive pattern and the manovacuometry was normal. The electromyography showed no alterations even after the repetitive stimulation. The ice test was negative, the pyridostigmine test showed a slightly improvement of the upward gaze and lateral gaze. The laboratory exams revealed normal thyroid, liver and kidney function, normal creatine phosphokinase (cpk) (91 U/L) and lactate (0,2 – 2,4 mg/dL) value. We ordered the anti-acetylcholine dosage and decided to use the pyridostigmine for a myasthenia therapeutic test.

On the next day, she presented a tongue fasciculation. There was no improvement with pyridostigmine and the anti-acetylcholine was negative. The ventilatory function was getting worst. Therefore, we decided to ask for an anti-musk dosage and tried an empirical treatment with immunoglobulin (there were no availability of plasmapheresis – our first option). After, 2g/kg of immunoglobulin she presented no improvement.

The dosage of anti-musk was positive and we started prednisone – 1mg/Kg. She continued with BIPAP, showed an initial decline in the ventilatory function followed by an improvement. Nowadays she is using azathioprine, gradually tapping the prednisone and need no more oxygen supplementation.

DISCUSSION

In this report, we described a case of a patient with myasthenia gravis MuSK positive with missed signs of her clinical presentation and a misdiagnosis. Some important clinical aspects regarding her case will be discussed in order to focus the relevant signs and symptoms to guide a diagnosis of myasthenia.

The clinical presentation of MuSK-MG patients can be atypical and symptom fluctuation, which is a clinical hallmark of MG, can be minimal or absent (EVOLI et al, 2013). Respiratory muscle weakness can occur in up to 40% of MG patients leading to dyspnea or orthopnea. Roughly 15% to 20% of patients with MG will experience myasthenic crisis, defined as respiratory failure necessitating either noninvasive positive pressure ventilation or mechanical ventilation until clinical improvement occurs. Respiratory muscle weakness is typically associated with concurrent bulbar and neck muscle weakness and more predominant in MuSK + patients (HEHIR et al, 2018) (MORI et al, 2013) (EVOLI et al, 2012), as showed by our patient.

Patients with both defined and undiagnosed neuromuscular disorders are frequently admitted to hospital services and clinicians must be able to recognize and intervene appropriately when respiratory failure develops. Early recognition of acute neuromuscular respiratory failure (NRF) and determination of the cause is imperative, as there are survival implications (HOCKER, 2017).

In general, failure of the lung caused by a variety of lung diseases (e.g. pneumonia, emphysema and interstitial lung disease) leads to hypoxaemia with normocapnia or hypocapnia (hypoxaemic or type I respiratory failure). Failure of the pump (e.g. drug overdose) results in alveolar hypoventilation and hypercapnia (hypercapnic or type II respiratory failure). Although

there is coexistent hypoxaemia, the hallmark of ventilatory failure is the increase in PCO2 (ROUSSOS et al, 2003).

When the diaphragm and intercostal muscles become sufficiently weak that they cannot lift the ribcage, accessory muscles attached to the ribcage are enlisted to move it and assist with ventilation. These compensatory mechanisms provide only partial compensation, resulting in microatelectasis at the lung bases. At this stage, the patient may be tachypneic and examination of the arterial blood gas (ABG) will show a respiratory alkalosis with normal or mildly reduced PO2. As the muscles fatigue, generalized hypoventilation develops. The patient compensates by increasing their respiratory rate further (rapid shallow breathing) and thus testing of the blood gas at this stage will reveal a normal PCO2. Further muscular fatigue leads eventually to hypercapnia and respiratory acidosis (HOCKER, 2017). Mechanical defects of the chest wall (flail chest and acute hyperinflation), neuromuscular diseases (bilateral diaphragmatic paralysis, myasthenia Gravis, botulism and Guillain-Barre´ syndrome) and pharmacological agents such as curare may result in acute hypercapnia (ROUSSOS et al, 2003).

A diurnal fluctuation of myasthenic symptoms may not be evident in some patients. The often negative edrophonium test and/or negative repetitive nerve stimulation study may make the MuSK-MG diagnosis less obvious. It is important to differentiate MuSK-MG from amynotrophic lateral sclerosis (ALS), since both can present tongue atrophy and fasciculation as reported in the case. In MuSK-MG upper motor neuron dysfunction is usually absent, creatine kinase level is typically normal and the denervation is rarely seen on needle electromyography (MORREN et al, 2018).

Moreover, it is important to emphasize the possible co-existance of myasthenia and depression, that is present in our case. Since the fatigability present in myasthenic patients can resemble a sad face or apathy, it is always important to evaluate if the depression really explain all the symptoms of the patient.

For cost effectiveness, MuSK-Ab testing should be reserved for patients who have tested seronegative for AChR-Abs or patients who have tested positive for AChR-Ab but respond poorly to treatment (MORREN et al, 2018). Therefore, only the anti-acetylcholine dosage were ordered initially and the MuSK dosage was reserved for after the poor response to the convetional treatment

Therapeutic management of MG is based on the use, most often in combination, of acetylcholinesterase inhibitors (AChE-I) as symptomatic medication, thymectomy, pharmacological immunosuppression, and short-term immunomodulation with plasma-exchange and intravenous immunoglobulin (IVIg). Pyridostigmine is the AChE-I agent most

commonly used, is generally well tolerated and represents the first-line treatment in MG, (HEHIR et al, 2018). Thymectomy is indicated in all patients with thymoma to treat a potentially malignant tumor; moreover, it is currently performed in generalized AChR-MG , it appears to increase the likelihood of medication free remission and reduce the patients hospitalization (WOLFE et al, 2016, 2019). Several lines of evidence suggest that thymectomy may not be beneficial for MuSK-MG. The MuSK-Ab level remains unchanged after thymectomy in contrast to its reduction after successful immunosuppression. Histological findings of the thymus gland removed from patients with MuSK-MG were often normal for age or atrophic (REDDEL et al, 2014). Thymus alteration appear to be definitely uncommon in MuSK-MG, supporting the view that the thymus does not play a pathogenic role in this form of MG (EVOLI et al, 2013).

Immunosuppressive treatment reduces the level of pathogenic antibodies through different effects on immune system and is performed in patients with disabling symptoms, not satisfactorily controlled with AChE-Is. It includes corticosteroids, alone or in combination with a variety of drugs as antimetabolites (azathioprine, mycophenolate mofetil), calcineurine inhibitors (cyclosporine, tacrolimus), alkilating agents (cyclophosphamide) and rituximab (SANDERS et al, 2016). Plasma exchange removes antibodies and cytokines from circulation, while IVIg has complex effects on the immune system mostly mediated through interference with idiotype network and modulation of T and B cell activation. Both plasma-exchange and IVIg induce rapid, though short-term improvement, and are mainly employed in association with pharmacological immunosuppression, in treating disease exacerbation phases and in preparation for thymectomy (EVOLI et al, 2013).

Regarding our case, the next day after starting the pyridostigmine the patient showed no improvement and presented a tongue fasciculation together with ventilatory function deterioration. In MuSK-MG animal models, clinically appropriate doses of pyridostigmine exacerbated weakness, end plate AChR loss and impaired end plate electrophysiological measures in the diaphragm muscle. Hypersensitivity to ACEI merits extra caution when treating patients with MuSK-MG who are at risk for myasthenic crisis because increased bronchial and oropharyngeal secretions could further aggravate impaired breathing and/or swallowing (MORREN et al, 2018).

Immunosuppression is the mainstay treatment in all forms of MG. This is particularly true in MuSK-MG, where weakness severity and poor response to AChE-Is imply prompt and aggressive treatment (EVOLI et al, 2012).Currently, the 3 most effective treatments for MuSK MG are corticosteroids, plasmapheresis, and rituximab (MORREN et al, 2018).There is a

general agreement that MuSK-MG responds well to steroids and dramatically to plasma-exchange. The association of high-dose prednisone (1 to 1.5 mg/kg body weight/day) and plasma-exchange (five exchanges of 40 to 50 ml/body weight each on alternate days) is the treatment of choice in patients with respiratory crisis or severe bulbar weakness, as in other forms of MG (EVOLI et al, 2013).

However, after the positive dosage of anti-MuSK ab the patient showed no improvement with the use of immunoglobulin and we had to start the prednisone. Her ventilatory function has improved and the oxygen supplementation is no longer needed. Response to corticosteroids is relatively fast, usually within 2–3 weeks. Because of the rapid onset of action, corticosteroids are often the first line immunotherapy for MuSK-MG. However, the maintenance corticosteroid dose may be higher in MuSK-MG compared with that used for AChR- MG (MORREN et al, 2018).

CONCLUSIONS

The early diagnosis of acute neuromuscular respiratory failure and the determination of the cause are extremely relevant, because they can interfere on the patients' survival and comorbidities. Neuromuscular diseases should be always investigated in type II respiratory failure, considering that the determination of the cause required strenuous investigation, alternated with empirical attempts at treatment, demonstrating the importance of recognizing the possible differential diagnoses for controlling the disease course.

Myasthenia gravis remains a challenging diagnosis for doctors, since it has different spectra of clinical manifestations, in addition to a fluctuating course and characteristics similar to other diseases, which makes it even more relevant to raise it as a diagnostic hypothesis by attending physicians.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEGMENTS

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