

Refractory Myasthenia Gravis: Clinical Description and Literature Review

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Abstract

Case Report

Myasthenia is an autoimmune disease due to the presence of auto-antibodies leading to a blockage of the neuro-muscular junction. The anti-MuSK form is rarely observed and can lead to an acute respiratory failure requiring care in intensive care unit. It can be refractory to the immunosuppressant first-line treatment. In this case, plasmatic exchanges can lead to a better clinical evolution. We report a case of favorable evolution.

Keywords: Myasthenia, autoimmune disease, refractory.

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INTRODUCTION

Myasthenia is an autoimmune disease inducing a fatigability and a weakness of skeletal striated muscles, due to auto-antibodies against acetylcholine postsynaptic receptors, leading to a blockage of the neuro-muscular transmission [1]. Many types of auto-antibodies [acetylcholine receptor (AChR, the most frequent), muscle-specific kinase (MuSK), and lipoprotein receptor-related protein 4 (LRP4)] are involved in the pathogenesis [2]. The clinical forms with anti-Musk are rare, found in about 5% of the cases in young patients with a female predominance [3]. They are responsible of severe forms usually refractory to the standard treatment [4-9]. We report the case of a 25-years old female patient admitted in intensive care unit for a severe refractory form with a favorable evolution after plasma exchanges.

REPORT

Ms.NK, is presenting since one year, a muscular fatigability after exertion, a weight loss of 24 Kgs, a nasal speech, a rhinolalia, a dysphagia to solids without any episode of “wrong way” and a painful ophthalmoplegia of the right eye with a both sides lateral gaze binocular diplopia.

She was born prematurely of a twin pregnancy and has a history of anxio-depressive troubles. She is hospitalized in neurology where the clinical examination reveals a goiter without heart murmur. The CTA scan of neck and thorax shows a thyroid goiter

without compression of the pharyngolaryngeal tract. Some hours after her admission, she presents a respiratory deterioration with desaturation and severe hypercapnic acidosis needing her transfer to intensive care.

At the admission, the parameters were: blood pressure 115/84 mmHg, heart rate 100 bpm, respiratory rate 18 b/min, SpO₂ 100% in ambient air, Glasgow Coma Scale 15, temperature 37°C.

The neurological examination finds a right eye adduction deficit with orbital pain, a binocular diplopia, a bulbar damage with rhinolalia, dysphagia, nasal speech, a weakness of respiratory muscles. Arterial blood gases assessment under 2L/min oxygen finds a severe uncompensated respiratory acidosis with a pH of 7.24; PaCO₂ of 94,5 mmHg and bicarbonates of 33 mmol/l. The patient benefits from non-invasive ventilation and, in front of the conscience disturbance, an orotracheal intubation under propofol without neuromuscular blocking agent and a mechanic ventilation. The electromyograph shows, after a 3 Hz frequency repetitive stimulation, the presence of a V-XII reproducible reduction at the bilateral oral floor and to a high frequency stimulation (40 Hz), a significative increase at the same location more pre-synaptic characteristic. The research of anti-AChR antibodies is negative and the anti-MuSK antibodies were positive to 20.1 U/L (N < 0.4). The autoimmune assessment, especially the research of anti-gangliosides antibodies and the antinuclear factors, is negative.

There is no anemia and the TSH, the B12 vitamin dosage are normal. The neck and thoracic CTA scan show a thymic residue normal for the age. A head MRI is performed showing a diffuse leptomeningitis infra and supratentorial without pachymeningitis nor encephalitis signs and abnormal contrast enhancement of cranial nerve pairs. The lumbar puncture is normal with a cerebrospinal fluid (CSF) protein of 0.15 g/l, CSF glucose of 0.74 g/l and LDH of 20 UI/L, leukocytes $1/\text{mm}^3$ and the culture negative.

A cure with immune globulins at 0.4 g/kg is carried out for three days, a treatment with anticholinesterase drug (Pyridostigmine 60 mg 4 times/day) and a corticoid therapy with oral prednisone 1 mg/kg are also given. She does not present any clinical improvement after 5 days of treatment and the weaning of ventilatory assistance remains difficult with many unsuccessful attempts of spontaneous ventilation despite a test with intravenous prostigmin and atropine. The evolution is marked by a cholinergic acute crisis due to the Pyridostigmine with important vomiting efforts complicated by a Mallory Weiss syndrome, a tachycardia, an hypersialorrhea and a bronchial hypersecretion justifying the discontinuation of Pyridostigmine and gastric protection with omeprazole. After an unsuccessful second cure of immune globulins (3 doses), a treatment with 4 sessions of plasma exchanges results in the improvement of the ventilation with a recovery of an effective spontaneous ventilation, the disappearance of the binocular diplopia and extubating at day 12. She will be treated with Cloxacillin during 7 days for a Staphylococcus aureus ventilator-associated pneumonia with a good clinical evolution. She is transferred in neurology at day 17 with persistence of a dysphonia and a diplopia in the right-lateral gaze with a myasthenia score of 82/100. She will then be treated by immunosuppressive drugs (Azathioprine 100 mg/day), corticoid therapy and a low-dose of Ambenonium chloride in specialized neurological follow-up with a total functional recovery (myasthenia score of 100/100).

DISCUSSION

Anti-MuSK myasthenia gravis is observed between 0 and 70 years with a higher peak of frequency between 21 and 30 years [10]. The female predominance is reported but Evoli and al study has shown that there is no significant difference between genders for the anti-MuSK positive or seronegative forms [3, 10]. The action mechanism of anti-MuSK antibodies is not yet clearly defined because autoantibodies are of the sub-type IgG4 and do not activate the complement cascade. However, in murine models, the anti-MuSK antibodies lead to a disorganization of the pre and post synaptic neuro-muscular junction [11] hence the pre-synaptic damage found in our patient with the presence of increases on the electromyograph. A thymic damage is generally not in cause in its forms of myasthenia [10].

On a symptomatic aspect, the bulbar damage is found in 100% of the positive anti-MuSK cases, the respiratory damage is also observed significantly [10]. Our patient was presenting a bulbar and respiratory damage with an acute hypercapnic respiratory failure requiring a mechanic ventilation. The clinic severity score is established by the classification of Myasthenia Gravis Foundation of America (MGFA) [12]. Our patient was presenting a severe gravity score (class V) as reported by Evoli and al in their comparative study with some anti-MuSK seropositive patients having moderate gravity score (class II) and severe (V) with a significant difference [10].

The treatment requires immunosuppressive drugs in the majority of anti-MuSK forms [4, 5,7-9, 10]. The anticholinesterase drugs are ineffective in the anti-AchR seronegative forms as in the anti-MuSK forms since it is a presynaptic blockage of the neuro-muscular junction. So, the anticholinesterase treatments are often poorly tolerated because of the onset of a cholinergic crisis by exceedance of acetylcholine, which was the case of the patient.

The association Prednisone and Azathioprine provides a better remission in those patients [10]. The treatment of the acute crisis, besides the symptoms' treatment like the mechanic ventilation in respiratory deficiency, requires the use of immunomodulators: immune globulins or plasma exchanges. A randomized study has shown that there was no efficiency difference between immune globulins and plasma exchanges in patients suffering from a moderated or severe myasthenia and regardless of the type of responsible antibodies [13].

However, some refractory forms to the first-line treatment of the myasthenic crisis are described especially the anti-MuSK form [5-9]. In our case, the immune globulins cure associated to the prednisolone and to anticholinesterase did not result in a clinical improvement. Only plasma exchanges were efficient in our patient resulting in the mechanic ventilation cessation and a significant functional recovery.

CONCLUSION

The anti-MuSK myasthenia is rare and may be discovered late during an acute crisis justifying an admission in intensive care unit. The presence of an amplitude increase on the electromyogram does not eliminate the diagnosis of myasthenia and must make search this particular form of the sickness. The treatment is difficult in the refractory forms to usual therapeutics. The plasma exchanges can be very useful and improve the vital and functional prognosis.

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