HOW TO MANAGE MUSK ANTIBODY-POSITIVE MYASTHENIC CRISIS DURING PREGNANCY?

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Myasthenia gravis (MG) is an autoimmune disease that is characterised by the formation of antibodies against acetylcholine receptors in the postsynaptic membrane of the neuromuscular junction. The course of the disease cannot be predicted during pregnancy. A subtype of MG with positive muscle-specific receptor tyrosine kinase (anti-MuSK) antibodies exhibits more localised clinical characteristics and a poor response to treatment compared with the disease subtype that involves positivity for acetylcholine receptor antibodies. Myasthenic crisis is more frequently observed in anti-MuSK-positive myasthenia patients. Anti-MuSK-positive myasthenic crisis management is very difficult and a risky situation during pregnancy.
The reported case was 30 years old, female, 9 weeks pregnant and musk antibody positive. She stopped her treatment without asking her doctor because she was planning pregnancy in the 6-month period before her hospitalization. She was intubated for a long time in the intensive care unit due to myasthenic crisis and was very resistant to treatment. During this period, her pregnancy was terminated due to fetal anomaly. Plasmapheresis, IVIg and immunosuppressive treatments were applied. Our patient was discharged after a period of about 10 weeks. We share our treatment management.

Keywords: *muscle-specific receptor tyrosine kinase, intravenous immunoglobulin, plasmapheresis, cyclophosphamide, myasthenic crisis*

HOGYAN KEZELJÜK A TERHESSÉG ALATT JELENTKEZŐ MUSK-ANTITEST-POZITÍV MYASTHENIÁS KRÍZIST?

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A myasthenia gravis (MG) a neuromuscularis junctio postsinapticus membránjában lévő acetilkolin-receptorok ellen létrejövő antitestekkel jellemezhető autoimmun betegség. A terhesség alatti betegséglefolyás nem jósolható meg. Az izomspecifikus tirozinkináz-receptor antitestekkel (anti-MuSK) jellemezhető MG-altípus lokalizáltabb klinikai karakterisztikummal bír és rosszabbul reagál a kezelésre, mint az acetilkolin-receptorok elleni antitestekkel jellemezhető altípus. Az anti-MuSK-pozitív myastheniás betegalcsoportban gyakoribb a myastheniás krízis (MC). Az anti-MuSK-pozitív MC kockázatos állapotot jelent terhesség alatt, és kezelése nagyon nehéz. A bemutatott esetben egy 30 éves, 9 hetes terhes, anti-MuSK-pozitív nőbeteg kezelését ismertetjük. A beteg a kórházunkba kerülését megelőző 6 hónapban, mivel terhességet tervezett, orvosa megkérdezése nélkül abbahagyta MG-ellenes kezelését. Az intenzív osztályon a beteget MC miatt hosszú ideig intubálták, és a kezelésre alig reagált. Terhességét magzati anomália miatt ez alatt az időszak alatt terminálták. Terápiája plazmaferézis, IVIg és immunszuppresszáns kezelés volt. 10 hetes kezelés után bocsátottuk otthonába. Esetbemutatásunkban részletesen ismertetjük kezelését.

Kulcsszavak: *izomspecifikus tirozinkináz-receptor, intravénás immunglobulin, plazmaferézis, ciklofoszfamid, myastheniás krízis*

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Approximately forty to seventy percent of seronegative myasthenia gravis (MG) patients have antibodies to muscle-specific receptor tyrosine kinase (anti-MuSK)[1]. MG patients with anti-MuSK antibodies have a more complicated clinical course. In this myasthenia type, bulbar symptoms are prominent, ocular disorders are rare and usually no thymoma is detected. Response to conventional therapy is poor and may cause recurrent myasthenic crisis[2]. In anti-MuSK-positive MG patients, respiratory crises are more common than in anti-acetylcholine receptor- (AChR) positive patients. Weakness can be seen in muscles that are not usually symptomatic in MG, such as paraspinal and upper oesophageal muscles. Increased sensitivity to anti-cholinesterase, non-responsiveness and even clinical worsening has been reported in MuSK-positive MG[3].

This patient group usually consists of females aged less than 40 years. Since it affects women mostly during the childbearing years, treatment management becomes more important[4, 5].

The effect of pregnancy on myasthenia gravis varies from woman to woman and also from pregnancy to pregnancy in the same female patient[6, 7]. Since the disease course in pregnancy cannot be predicted, a multidisciplinary approach is required in the treatment of these patients[7].

Coexistence of anti-MuSK-positive MG and pregnancy is rare, and treatment management poses difficulties for clinicians due to the lack of guidelines[8]. We report our case with the purpose of reviewing myasthenic crisis treatment management in anti-MuSK-positive pregnant women.

Case report

The patient, with no known chronic disease, was admitted to our clinic for the first time at the age of 28 with complaints of generalized muscle weakness, diplopia, and dysphagia. She had a decrement response in the repetitive nerve stimulation test **(Figure 1)** and she had an anti-MuSK antibody titer: 4.92 nmol / l. Thymus was normal in computed tomography. The patient was followed up in our clinic with a diagnosis of MuSK antibody positive MG.

Prednisolone 1 mg / kg / day (per os) was started for the patient. Initially, clinical follow-up was taken every 15 days. She received prednisolone 1 mg / kg / day and monthly IVIg for a while. After the treatment, the patient's complaints improved significantly.

After her status remained stable, steroid treatment was tried to be reduced. However, due to increase in her complaints, the steroid dose was fixed at 32 mg / kg / day.

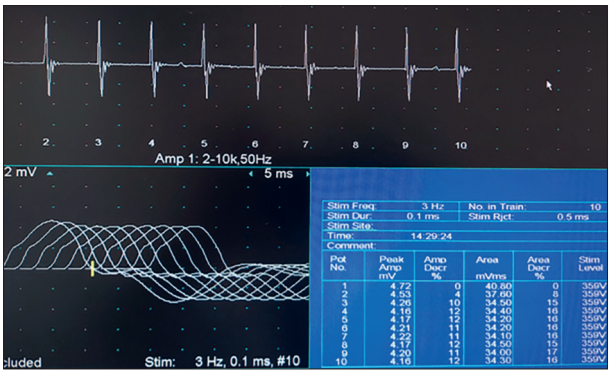

Figure 1. *Decrement response in repetitive nerve stimulation test recorded in the right trapezius muscle*

She was 30 years old and 9 weeks pregnant when she applied to our clinic again with complaints of respiratory distress and generalized weakness. She had not come to our clinic for control within the last 6 months. She stated that this was because she was planning a pregnancy and so she had not used her medications for 3-4 months without asking her doctor.

On neurological examination, there was prominent bilateral ptosis. Motor examination revealed 5- / 5 muscle weakness in the proximals of all four extremities and 3- / 5 in neck flexion. In the pulmonary function test examination, it was seen that the percentage of vital capacity decreased to 78%. She needed nasal oxygen support. At the same time, she had difficulty in swallowing. In obstetric ultrasonography, a cystic structure in the posterior area of the foetal neck extending to the back region was observed.

Anti-cholinesterase (Pyridostigmine 240 mg/day) and intravenous prednisolone (500 mg/day) treatment were initiated. The respiratory distress of the patient intensified on day 3 after admission, and hypoxaemia was detected in the arterial blood. The patient was transferred to the neurology intensive care unit, intubated, and mechanical ventilation was initiated. Intravenous immunoglobulin (IVIg, 0.4 g/kg/day) was administered for five days. Anti-cholinesterase treatment was discontinued due to side effects. As the patient did not benefit from the IVIg therapy, plasmapheresis (six doses) was conducted. The patient exhibited partial benefits from the treatment and was able to be extubated. Afterwards, the departments of obstetrics, gynaecology and neurology came to a decision to terminate the pregnancy, thus the pregnancy was terminated with the family's consent.

The patient was discharged home with oral cortisone treatment (1mg / kg / day). Three days later, after developing respiratory failure at home, she was re-admitted to our clinic due to myasthenic crisis (MC). The patient was admitted to the neurology intensive care unit. She was intubated and mechanical ventilation was started.

Oral cortisone treatment (1mg / kg / day) was continued. During the intubation period, nutrition was provided through nasogastric tube. Oral medications were administered through the tube. IVIg treatment (0.4 g/kg/day) was administered for five days. The treatment was partially beneficial. However, extubation efforts were not successful. Thus, tracheostomy was performed, and the patient remained connected to the mechanical ventilator for a while (about 10 weeks). Intravenous (IV) cyclophosphamide (500 mg/m^2) was administered. Apparent respiratory improvement was observed after 10 days of the treatment. The motor weakness decreased, and the patient was extubated.

Discussion

Symptoms in MG are usually in remission during the second or third trimester, probably due to the hormone-mediated immunosuppression that occurs in the normal course of pregnancy[9]. Santos et al. reports that pregnancy does not cause side effects in patients with MuSK-positive MG[5], but in our anti-MuSK-positive MG patient bulbar weakness and myasthenic crisis developed during the first trimester. However, this situation may have been caused by our patient's discontinuation of immunosuppressive treatment 3 months before pregnancy.

Termination of pregnancy does not change the relative risk or severity of myasthenic exacerbation, but the exacerbation of the disease often decreases after spontaneous abortion[10]. The pregnancy of our patient was terminated at the 11th week due to fetal anomaly, with the joint decision of the obstetrics, gynaecology and neurology departments. The severity of the symptoms in our patient increased after the termination of pregnancy and mechanical ventilation had to be initiated due to respiratory failure.

Treatment of myasthenic patients with positive anti-MuSK antibodies is more difficult because they respond poorly to conventional therapeutic approaches[7, 11]. Increased sensitivity and intolerance in response to anti-cholinesterase agents have been reported in anti-MuSK-positive MG patients, and the possibility of reaching unresponsiveness to the treatment is high[12]. In this case, following acetylcholinesterase inhibitor treatment, an increase in bronchopulmonary–oropharyngeal secretions and worsening of the myasthenic symptoms occurred.

MC is a life-threatening neurological disease and is characterized by respiratory or bulbar weakness. Plasmapheresis, immunosuppressants and IVIg have great importance in the treatment[3, 13]. Corticosteroids, plasmapheresis and IVIg have fewer potential risks and can be relatively safer to use during pregnancy[6, 7]. Currently available information indicates that immunosuppressives such as azathioprine and cyclosporine A are relatively safe in pregnancy. It is reported that rituximab can also be used carefully during pregnancy according to the benefit / harm ratio. It is emphasized that other immunosuppressives such as mycophenolate mofetil, cyclophosphamide and methotrexate are contraindicated[14, 15]. However, the treatment should be chosen considering the severity of the disease and its side effects on the fetus. In this context, cyclosporine A and cyclophosphamide are used in refractory cases during pregnancy[16].

Lin et al. reported that the symptoms of a 48-year-old female patient with high levels of anti-MuSK antibodies, extremity weakness, severe bulbar and respiratory weakness and a lack of response to conventional immunosuppressive treatments remarkably improved following high-dose cyclophosphamide administration. These authors emphasised that high-dose cyclophosphamide may be an effective alternative for patients with refractory disease[17].

In summary, our case demonstrates the need for careful monitoring and a multidisciplinary approach in MuSK-positive MG patients during pregnancy. It should be explained to these patients that the disease activation that may occur in case of discontinuation of their medication may adversely affect the pregnancy and the development of the fetus. In the cases that are unresponsive to plasmapheresis and IVIg treatment, the addition of immunosuppressive agents, such as cyclophosphamide, will increase the success of the treatment during MC.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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