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Anti-musk Myasthenic Crisis in the Puerperium: The Management Dilemma

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Authors' contributions

This work was carried out in collaboration with all authors. Author PAT developed the idea and wrote the manuscript. Author YAA developed the idea and wrote the manuscript. Author OOD developed the idea and wrote the manuscript. Author PM reviewed the manuscript and author BLAT reviewed the manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Myasthenia gravis (MG) is a chronic neuromuscular junction (NMJ) dysfunction with a wide spectrum of neurological manifestations. MG is as a result of autoantibodies directed against NMJ at the postsynaptic level involving nicotinic or other postsynaptic antigens. The newly identified subtype of MG with antibodies against the muscle-specific receptor tyrosine kinase (Anti-MuSK) shows an unpredictable response to current MG treatment. The initial presentation of this disease entity often poses a diagnostic challenge and a treatment dilemma to the clinician. We present a case of life threatening Anti-MuSK-positive myasthenic crisis occurring during puerperium which required a temporary surgical airway and percutaneous endoscopic gastrostomy tube for feeding. She had dysphonia for 7 years but was not diagnosed. The complications and management dilemma of this case report are highlighted.

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Keywords: Myasthenia gravis; myasthenic crisis; anti-MuSK; puerperium.

1. INTRODUCTION

Myasthenia gravis (MG) is a chronic neuromuscular junction (NMJ) dysfunction with a female preponderance before 40 years. MG presents with a wide spectrum of neurological manifestations which tend to be fatigable. Deficiencies in the neuromuscular junction are found in the congenital forms whilst the acquired forms are due to autoimmune reactions [1].Clinical findings of fatigable painless muscle weakness, characteristic electromyographic features and autoantibody analysis are important for MG diagnosis. There are 2 main types of MG - the acetylcholine receptor MG (AChR MG) that is more common, and the antibodies to muscle-specific receptor tyrosine kinase MG (anti-MuSK MG). Although 75-80% of MG clients have positive acetylcholine receptor antibody (anti-AChR), for those with negative anti-AChR about 40% have positive anti-muscle specific receptor tyrosine kinase (anti-MuSK) antibodies [2]. The anti-MuSK subtype of MG usually starts later in life (about 10 years later than the anti-AChR i.e. after 40 years) with a female preponderance [3]. Three phenotypes of the anti-MuSK variant have been described; oculopharyngeal weakness, neck, shoulder and respiratory weakness without ocular involvement and a variant indistinguishable from the anti-AChR positive MG. A peculiar finding with the anti-MuSK is its poor response to treatment with a lower rate of complete remission [4,5]. Many cases of anti-MuSK MG have been described in medical literature but its association with pregnancy is uncommon. The challenges in diagnosis and the dilemma of its management has been described in this case report.

2. CASE REPORT

A 29 year old Para 1 lady who had a 3 week old baby, presented to the emergency room (ER) with shortness of breath (SOB), double vision, inability to lift arms, inability to swallow solid and semi-solid foods and general weakness. The inability to lift her arms started 1 week postpartum and it progressed till she could not even carry her own baby. She could neither feed, bath nor dress herself. Her inability to swallow solid and semi-solid foods had started 2 weeks postpartum. She apparently had double vision in her fifth month of pregnancy and SOB in her third trimester which all resolved spontaneously.

Within 3 weeks of the puerperium, she presented to the ER every week with chest pain, SOB and increased heart rate but all possible investigations led to no conclusive diagnosis. She was thought to have had Pregnancy-induced Hypertension (PIH), thus was given labetalol but the SOB worsened. The labetalol was therefore stopped. Subsequently she was thought to have had an imminent Pulmonary Embolism (PE) because she had a high D-dimer after an episode of a severe chest pain which took her to the ER in the first week postpartum. Computed tomography pulmonary angiogram (CT-PA) scan of the chest however showed no evidence of embolism.

Postpartum Cardiomyopathy was then considered and however cardiologists' work up showed negative results. Echocardiography and electrocardiography were all normal and thus subsequently she was started on diltiazem which worsened the SOB.

At her fourth week of presentation at the ER, the neurologists were consulted and they came up with the following; her past medical history revealed that about the age of 11 years, she had weakness of her ocular muscles that improved after rest. Then at the age of 22 years, she developed hypernasal speech (dysphonia) after losing the ability to speak for about 2 months. She also experienced extreme weight loss and inability to swallow solids and liquids for about 2 months, which were followed by frequent episodes of aspiration and choking while eating or drinking. Her hypernasal speech persisted, but consultation with the ear, nose and throat surgeon and speech therapist yielded no favorable results.

On examination at the ER, she was found to be a young lady who looked wasted, afebrile, anicteric and not pale. She also had ptosis of the left eye, fluctuating course of ocular, bulbar and shoulder weakness and symmetric fatigable weakness that was worse in the arms than the legs. The working diagnosis were as follows;

- Progressive dyspnoea
- Fatigable ptosis
- Bulbar weakness

Investigations done revealed:

- Positive anti-MuSK antibodies for Myasthenia Gravis (negative titres for Acetylcholine receptor (AChR)
- Positive repetitive nerve stimulation test
- Positive ice test on the left eye
- CT scan of chest was negative for thymoma and PE

The final diagnosis made after the investigations was Anti-MuSK Myasthenia Gravis with Myasthenic Crisis.

2.1 Course in the Hospital

The patient followed a complicated course while on admission at the hospital.

She was admitted at the intensive care unit (ICU) for intubation due to worsening respiratory distress. She was also given IV steroids and multiple doses of intravenous immunoglobulin during her 4 weeks of admission at the ICU. She was extubated twice but each time this resulted in worsening of symptoms, thus eventually a tracheostomy was done. She was then transferred to the neurology ward on prednisolone and pyridostigmine. The pyridostigmine was however stopped because of secretion challenges. She was then decannulated 2 weeks afterwards. Nasogastric tube feeding was started and later changed to percutaneous endoscopic gastrostomy (PEG) tube because of the need for long term feeding since multiple barium swallows had shown that she was still at risk of aspirating. She was discharged on a combination of Azathioprine 75 mg daily and Prednisone 60 mg daily with scopolamine patch to be given when needed for management of secretions. Her other medications were calcium carbonate 1 tab daily, vitamin D 1000 units daily, ranitidine 150 mg BID, multivitamin liquid suspension 50 mg daily, alendronate 70 mg weekly, ferrous sulphate 300 mg daily, melatonin 3 mg daily, folic acid 1 mg daily, Tylenol prn, and senna & colaceprn.

2.2 Recovery Phase

The PEG tube was taken out one week after discharge following a barium swallow test that indicated normal swallowing. She was then followed up regularly by the general practitioner and the neurologist. Azathioprine was later stopped and then she was started on monthly intravenous immunoglobulin (IVIg) and prednisolone. She is back in her home country where IVIg is not available. She is having increasing side effects of the steroid i.e. increased intraocular pressure and impaired fasting glycemia. She has been tapered off the steroid and azathioprine titrated to a dose of 100 mg daily. We have observed complete remission of her symptoms for the past 10 months. She is currently on follow up for the side effects of the azathioprine.

3. DISCUSSION

The diagnosis of MG requires a good history, physical findings and demonstrable specific autoantibodies. Pregnancy with MG co-morbidity brings on board a challenge in management. It is difficult to predict if the anti-MuSK MG subtype will follow the clinical course of the AChR MG since only few cases of the anti-MuSK MG in pregnancy have been reported in medical literature.

The disease course varies significantly from one woman to the other and even between pregnancies in the same woman [6,7]. It is known that disease exacerbations are more common in the first trimester and after delivery but the second and third trimesters are usually associated with a remission of symptoms possibly due to the normal immunosuppressive changes taking place during this period [8]. In our case, she had double vision in the second trimester and SOB in the third trimester which resolved spontaneously. There was no exacerbation in the first trimester but she had a flare in the second and third trimesters which is contrary to the clinical course in the AChR positive MG. Our anti-MuSK case shared the features of postpartum exacerbations with the clinical course in the AChR positive MG.

Medical History is very important in the early diagnosis of this disease. The past medical history revealed that she had exacerbations at 11 years, 22 years and in the second and third trimesters but the diagnosis of MG was not made. MG is usually diagnosed late because most of the symptoms are attributed to other more common conditions, especially since they all do not present at the same time.

We have not come across any evidence for the management of MG in pregnancy and even more challenging in the case of the anti-MuSK subtype of the disease. Currently there are no specially

recommended medications for the anti-MuSK positive MG and so all the medications for the AChR positive MG are used by same dosage, route and duration.

The aim of the treatment of MG is to control symptoms and prevent relapses because there is currently no definitive cure for MG. Immunosuppression in some cases leads to complete remission without further recurrence. Treatment modalities include medications or surgery or a combination of both. The options for medications are acetylcholinesterase inhibitors (e.g. pyridostigmine) which directly improve muscle function by prolonging the action of acetylcholine by preventing their breakdown and immunosuppressant drugs (e.g. prednisone and azathioprine) which reduce autoimmune processes. The surgical approach is thymectomy. In emergency cases, plasmapharesis (plasma exchange) or intravenous immunoglobulin (IVIg) can be used as a temporary measure to remove antibodies from blood circulation.

A life-threatening form of MG is known as a Myasthenic Crisis, which arises when the respiratory muscles become very weak, leading to respiratory failure. A crisis or relapse can be triggered by infection of any kind or any form of stress like pregnancy, monthly periods, change in medication, climate change and drugs.

Plasmapheresis is considered a second choice during pregnancy because of its associated increased risk of prematurity and interference with coagulation [9,10]. It is however noted that significant proportion of the patients will respond to steroids and other immunosuppressives [4].

In the case of our patient, the mode of treatment was medical, and the choice was immunosuppression with prednisone and azathioprine, and IVIg when she had a myasthenic crisis. Other forms of immunosuppressive agents were not considered in her case because of her age and the possibility of having a second child.

Our patient on diagnosis received multiple doses of intravenous immunoglobulin and steroid in the first 4 weeks but response was unimpressive and progressed to the extent of requiring tracheostomy as surgical airway and PEG tube for feeding. It is noted that the Anti-MuSK positive disease usually has a poor response to therapy compared to the AChR variant and our case supports that course. Her response to pyridostigmine and prednisolone was remarkable but the pyridostigmine was discontinued on account of hypersalivation. Our patient was discharged on azathioprine and prednisolone but a week later the azathioprine was stopped. There is less evidence supporting its use in anti-MuSK MG. Her monthly IVIg and prednisolone were not sustainable because of relocation to her home country. She is currently in remission on azathioprine alone at 100 mg and this may confer some benefit to the anti-MuSK variant.

Future challenges are alternative medications to use if exacerbations occur on current medications or if untoward side effects of drugs occur. The child had uninterrupted breastfeeding as all medications were safe during this period.

Some 15% of myasthenia gravis cases are associated with thymomas [10]. Thymectomy is not recommended in a non-thymomatous patient as its role is unclear and of little value in the anti-MuSK subtype according to current best available evidence [5,11,12].

The fetal outcome of anti-MuSK MG has not been well documented though there are reports of early spontaneous abortions in some cases questioning the pathogenic effect of anti-MuSK antibodies in utero [8,11]. In our case a healthy baby girl was delivered with no delay in the developmental milestones. Congenital myasthenic syndromes may arise in the newly born child of a MG patient but in our case we have not seen any features suggestive of that and the child is currently on close monitoring.

4. CONCLUSION

The association of anti-MuSK positive MG and pregnancy is uncommon and its management poses a dilemma to the clinician because of lack of clear guidelines and fewer cases to learn from.

5. LEARNING POINTS

1. History taking is very important for the diagnosis and follow up of a myasthenia gravis patient since it can present with bulbar symptoms like dysphonia or dysphagia alone and thus a high index of suspicion is needed to diagnose it early.
2. The pregnant patient with MG requires a multidisciplinary care before and after delivery.

3. The anti-MuSK antibodies test should be performed in all clinical cases suspected of MG but with negative AChR.

DECLARATION OF ORIGINALITY

We declare that this is our own original work.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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