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Case Report

A toddler with juvenile ocular myasthenia gravis: Clinical experience

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Abstract

Background : Myasthenia gravis is an extremely rare autoimmune disorder affecting the neuromuscular junction. The incidence rate is 0.9–2.0 cases per 1 million children per year.[1] Ocular myasthenia gravis presents as ptosis with extraocular motility restriction and is prone to be misdiagnosed as third nerve palsy and is difficult to diagnose in very young children.[2]
Case : A girl aged 2 years 6 months with clinical features with bilateral ptosis and was diagnosed as juvenile ocular myastenia gravis based on history, physical examination and other diagnostic procedures such as chest X–ray within normal limit and no thymoma, the ice test showed positive result, *electromyography* (EMG) showed decrement response >10%, progstigmin test showed positive result, and serum acetylcholine receptor antibody levels was 0.43 nmol/L (reference range : positive as >0.40 nmol/L).
Conclusion : Juvenile ocular myastenia gravis diagnostics can be established using simple examinations such as ice tests,prostigmin test to sophisticated examinations as systemic acetylcholinesterase antibodies. Management begins with a first–line drug, pyridostigmine, that is safe and effective. Disease monitoring and looking for etiology are very important for successful treatment.

Keywords : Ptosis, ocular, myasthenia gravis, juvenile

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder in which acetylcholine receptor antibodies attack the post synaptic membrane of the neuromuscular junction. The incidence rate is 0.9–2.0 cases per 1 million children per year.[1] The average age of onset is 7 years.[3] Ocular types are more common than generalized and the age of onset earlier than generalized type.[4] It is also an uncommon disorder in our institution hence this case report.

The levator palpebral superior and extra–ocular muscles are initially affected in about 70% of cases and these muscles are eventually affected in over 90% of childs. The hallmarks of MG are fluctuation and fatigue. Weakness varies from day to day and from hour to hour, typically increasing toward evening. MG should be considered in every child with ptosis and/or diplopia. Diagnostic tests include serum acetylcholine receptor antibody levels, repetitive nerve stimulation (RNS), Prostigmin test, and the ice test. None of these tests, however, are 100 % sensitive or specific.[5-7] The aim of reporting this case is to examine various tests for the diagnostic enforcement of ocular myastenia gravis based on our clinical experience at our institution.

CASE REPORT

A girl aged 2 years 6 months present in January 2018 with chief complaints upper eye lid ptosis. Symptoms have progressed over the past 2 months, fluctuated and this may be marked towards the evening, whereas it disappears next morning after resting at night. No other complaints, and nor family history with illness like this, thyroid, graves disease, and diabetes mellitus. Notable physical exam findings were left eyelid more ptosis compared to right lid crease with right eye 9 mm, left eye 8 mm (normal 12 mm).

At first admission the child came into pediatric ophtalmologist because of her eyes complaints, the child was diagnosed by ophtalmoplegi and then she was undergone with the procedure of ice test.The result was positive, thus referred to pediatric neurology department. We did *electromyography* (EMG) examination of musculuslevator palpebra, and there was a decremen response greater than 10%, that means postive for myasthenia gravis.To make sure of the diagnosis, the childhas been hospitalized to undergo a prostigmine test. The prostigmine was given 0.025 mg/kg intravenously and we also give atropine sulfate 0.01 mg/kg intramuscularly ± 30 minutes before prostigmine. The clinical improvement response of weakened muscle strengthening had been observed for 15–30 minutes. The following picture showed images from child before and after prostigmin injection (Fig. 1).

From the laboratory finding acetylcholine receptor antibody 0,43 mmol/L (elevated), free T4 and TSHs level was normal. We also did not find thymic mass from chest x ray.

She was diagnosed as Myasthenia Gravis Class 1 (Ocular type) based on classification from *Medical Scientific Advisory Board* (MSAB) of the *Myasthenia Gravis Foundation of America* (MGFA) .

She was initiated on pyridostigmine 7 mg/kg per day, divided into 4 doses for therapy. She did not experience exacerbation of eye lid ptosis, or other weakness and deterioration, and has been recovering within 3 months.

DISCUSSION

Myasthenia gravis is a neuromuscular transmission disorder that causes skeletal muscle fatigue and fluctuating weakness. One study found that incidence myastenia gravis in girl is higher than boy, and ocular types are more common than generalized types. The juvenile type is the most common form in pre–pubertal age (< 12 years old). It did not have a familial pattern and had the characteristics of an autoimmune mechanism.[4]

Pathophysiology of MG through an autoimmune mechanism. The presence of antibodies to the acetylcholine receptor in the nerve muscle link reduces the transmission of nerve impulses to the muscles. HLA antigen *(Human Lymphocyte Antigen)* plays an important role in autoimmune diseases and is often linked with myastenia gravis. The presence of this antigen increases the incidence of MG especially in childs who are seropositive to the acetylcholine receptor.[8]

Myastenia gravis is considered a disease caused by B cells, because cell B is the one that produces anti AChR bodies. But the new findings show that T cells produced by Thymus have an important role in the pathophysiology of myastenia gravis. This is indicated by the large number of childs with myastenia experiencing thymic and thymoma hyperplasia and thymectomy can reduce the clinical sign of myastenia gravis.[9] However, the study showed a sensitivity of 89.5%, specificity of 87.5% and accuracy of 88.6% for CT compare to plain radiography. CT is superior to plain radiography in the diagnosis of thymoma.[10] *(LoE 3)*

Childs with MG often have ophthalmologic signs and symptoms including ptosis, diplopia, ophthalmoplegia and orbicularis weakness. A descriptive study by Xin Huang in 306 juvenile myastenia gravis childs in China showed that ocular symptomps were found in 93.6% of cases.[11] *(LoE 3)*

Ptosis, however, may be caused by a variety of disorders, so the distinction between myasthenic and nonmyasthenic ptosis is critical.

Diagnostic tests to establish the diagnosis of MG include the ice test, *repetitive nerve stimulation* (RNS)/ SFEMG, Prostigmin test and serum acetylcholine receptor antibody levels.

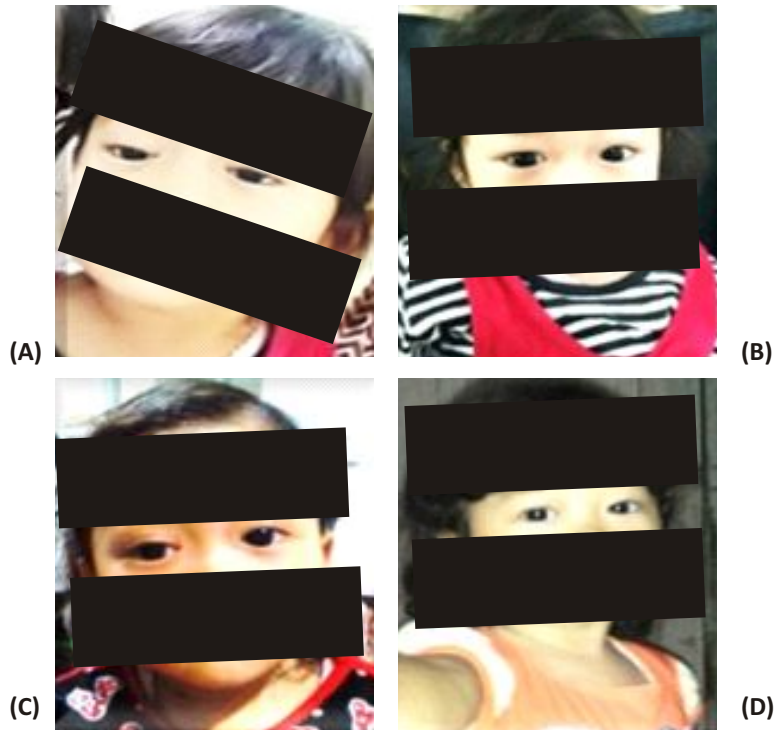

Figure 1. (A) Before prostigmin test, **(B)** After prostigmin test, **(C)** After 2 months treatment, **(D)** After 3 months treatment.

Bronestein and Desmedt later showed that the local cooling improved myasthenic neuromuscular block, whereas warming had the opposite effect. Cooling process can improve neuromuscular transmission so that placement of ice for 5–10 minutes on the eyelid will improve ptosis. Result is positive if there is resolution of ptosis. This test has a sensitivity of 96% while the specificity is 88%.[12,13] *(LoE 3)*

Clinically, the use of ice test is more advantageous than the Prostigmin test because this test is rapid, simple and inexpensive with a high degree of specificity and sensitivity. The ice test is particularly useful in childs whom the use of anticholinesterase agents is contraindicated by either cardiac status orage.[14]

Repetitive Nerve Stimulation has a sensitivity of 82% with a specificity of 100%. However the sensitivity of RNS is different for some sub groups where ocular type sensitivity is only 67%. The recommendation for electrophysiological examination that is recommended to obtain high and better sensitivity is SFEMG *(Single Fiber Electro Myography)*.[15] *(LoE 3)*

In a cohort study by Yew Long (2017) revealed that the SFEMG test has a high sensitivity and ice pack test as a valid, affordable and simple test. If the SFEMG test or icedtest is done separately, it will provide poor specificity so it is recommended to combine the two tests to achieve higher and more reliable specificity.[16] *(LoE 3)*. Testing the orbicularis muscle or the superior rectus levator complex greatly increase the specificity.

The estimated sensitivity of Prostigmin test is 92% and specificity 96% for both type ocular or systemic MG. The Prostigmin test may produce false–positive and false–negative results and also carries with cardiac risk and other complications (including significant bradycardia, loss of consciousness and death).[17] *(LoE 1)*

The sensitivity of the antiacetylcholine receptor antibody test is 50% to 75% in subjects with ocular myasthenia. Although it's specificity is high but the anti-AChR antibody concentration cannot be used to predict individual severity. In children with negative antibodies to the acetylcholine receptor, but symptoms appear at a younger age, there might be such a congenital myastenia gravis and about 40–50% of them have antibodies to muscarinic receptors.[18]

In developing countries like us, antibody testing is still very difficult to do routinely. For that, the ice test and SFEMG test are still the first choice because they are fast, easy, affordable and not invasive. Prostigmin test also helps, but closely monitoring of vital signs is needed, knowing the dangerous side effects of cholinergic that can occur.

Management of juvenile ocular myastenia gravis is intended to reduce the symptoms of the disease and reduce the severity of the disease to develop into a generalized type. The administration of pyridostigmine as an acetylcholinesterase inhibitor is the main choice. Acetylcholinesterase inhibitors retard the degradation of Ach that occurs by enzymatic hydrolysis in the

neuromuscular junction. As a result the effect of Ach is prolonged, leading to a variable improvement in strength. Acetylcholinesterase inhibitors are the first line of treatment due to thir safety and ease to use. It provides only symptomatic therapy and are usually not sufficient in generalized MG. Nonetheless, in some childs this is the only therapy ever needed for good control. For children and younger adolescents, the initial dose is 0,5 to 1 mg/kg every four to six hours, up to daily dose of 7mg/kg. In this child pyridostigmine dose is 1 mg/kg every 4–6 hours. If the acetylcholinesterase inhibitor still does not provide a good response, it can be combined with an immunosuppressant agent such as prednisone. Remission or improvement occurs in 65–75% of childs. Other therapies include thymectomy, azathioprine, cyclosporine and intravenous immunoglobulin. Complications of myastenia gravis are myasthenic crisis and cholinergic crisis.[19,20] *(LoE 1)*

The prognosis of children with MG is better than adults. Many cases had remission without treatment, therapy requires long–term follow up in childs over the age of 3 years. A cross sectional study by Ahigeaki in Japan in 607 MG ocular childs found that regular use of drugs for 2 years would reduce the complications of diplopia and improve the quality of life.[21] *(LoE 2)*. However Bever's research shows that 50–60% of cases with ocular symptoms will develop general weakness in 2 years or more so that adequate management is needed in addition to paying attention to factors that can aggravate the degree of illness.[21] *(LoE2)*

CONCLUSION

Juvenil ocular myastenia gravis is a very rare case, and it can be diagnosed through a few relevant tests for myastenia gravis. The child was given the first line antimyastenic treatment with pyridostigmine. Clinical improvement can be reached after 3 months therapy. Monitoring and management are needed for long term to reduce the risk of recurrence and progression of the disease to be a general type. The other important things of succesfull management myastenia is looking for the etiology. Knowing the etiology, so management therapy would be more precise and effective.

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