OCULAR MYASTHENIA GRAVIS: CASE REPORT OF AN AFRICAN CHILD AND LITERATURE REVIEW.

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ABSTRACT

We report a 7 year old male who presented with a two year history of drooping of both eye lids. Examination revealed bilateral ptosis (with the left eye being more severely affected than the right eye) and bilateral ophthalmoplegia. A diagnosis of Juvenile Myasthenia gravis with ophthalmoplegia was made when symptoms improved with intramuscular Neostigmine administration. He was commenced on oral Neostigmine at a dose of 0.04mg/Kg 6 hourly and is on regular follow up and had a good response.

Background: Myasthenia gravis is an autoimmune disorder affecting the neuromuscular junction and characterized by weakness and fatigability of skeletal muscles. It is non-hereditary and is characterized by autoantibodies which bind to acetylcholine (Ach) receptors at the motor end plate. The resultant effect is impaired Ach function, impaired nerve conduction and muscle weakness.1 Isolated ocular involvement (ptosis) is the most common presentation.1-3 The disease is characterized by easy fatigability of muscles, particularly the extraocular muscles, muscles of mastication, swallowing and respiration.1,3 It is commoner in females and onset is usually after ten years of age. It is unusual in boys. Diagnosis is typically made by Tensilon test. Management modalities include use of anticholinesterases, immunosuppressant drugs, plasmapheresis and thymectomy when indicated. It is also an uncommon disorder in our institution hence this case study and review of literature.

Case report: A seven year old male presented with a two year history of drooping of both eye lids that progressively worsened over time. He complained that “the eyes feel tired” and closes to the extent that he sometimes uses his fingers to support the eyelids. He demonstrated fatiguability after 20-40 seconds

of upward gaze. He admitted to having occasional diplopia and weakness of the facial muscles. There was no history of pain around the eyes or other facial muscles. There was no history of abnormal jerks or movements of the facial muscles. He did not have dysphagia or drooling of saliva. His pregnancy and neonatal histories were unremarkable. All aspects of motor development were normal. He was doing well academically. There was no similar illness in the family. He had several medications from different orthodox and unorthodox facilities including manual massage of his face prior to presentation.

Examination revealed a well kempt boy, with a body weight of 28 kilograms with a head circumference of 51cm. Vital signs were stable; body temperature was 36.80C and blood pressure was 100/60mmHg. He was alert, well oriented in time, place and person. He had bilateral ptosis worse on the left, bilateral ophthalmoplegia with a down ward gaze and inability to sustain an upward gaze for more than 20-30 seconds. He had normal tone in all the limbs. He had no sensory or focal neurological deficits. Examinations of the other systems were all normal. A diagnosis of Ocular Myasthenia gravis with ophthalmoplegia was made. (FIGURE 1).

A clinical diagnosis of ocular myasthenia gravis was made at the bedside when the ptosis improved remarkably after 10 minutes of Neostigmine administration (FIGURE 2) (Consent was obtained from the parent for the use of these photographs). Intramuscular Neostigmine was used because Edrophonium was unavailable. A test dose of 1mg was given. The Neostigmine was well tolerated at the bed side. Ptosis recurred after an hour. He was commenced on oral Neostigmine at a dose of 0.04mg/Kg 6 hourly and Prednisolone tablets. Follow up at the Paediatric Neurology Clinic showed he had made some clinical improvement as the eyes no longer 'tire' out easily and the downward gaze had improved.

Thyroid function tests (T3,T4 and TSH) done were within normal range .We were unable to perform auto-immune screening tests, electromyography (EMG) and anticholinesrease (Anti-Ach) antibody tests in our facility.

Discussion:

The incidence of myasthenia gravis is 3–30 cases per million per year and rising as a result of increased awareness.2 Juvenile myasthenia gravis (JMG) is a rare autoimmune disease which accounts for less than 10 - 15% of all myasthenia gravis cases, with an incidence of 1 - 5 per million per year.2 Incidence and prevalence of juvenile myasthenia gravis vary geographically. Paediatric presentation is more common in Oriental than in Caucasian populations.4 Up to 50% of all cases in Chinese populations present in childhood, mostly with ocular features, with a peak age at presentation of 5–10 years.10 Children with African genetic ancestry, as opposed to European ancestry, show a trend toward ocular presentation. This was the case in our patient. When the symptoms of myasthenia gravis are isolated to the levator palpebrae superioris, orbicularis oculi, and the oculomotor muscles, it is referred to as ocular

MG (OMG). Approximately 15 percent of all patients with MG have isolated OMG as the only manifestation of this disease. Girls are more frequently affected than boys.6 Our patient however was a male child who presented with isolated ocular type. This is reported as the commonest presentation of MG in children.5-7 A high index of suspicion is required to make the diagnosis.

Neostigmine was used for the diagnostic test because Edrophonium was unavailable. The result was an improvement of the ptosis and ophthalmoplegia within 10 minutes. Most patients that require treatment respond to Neostigmine as was seen in our patient. Myasthenia gravis is occasionally associated with hypothyroidism; usually due to Hashimoto thyroiditis.

Pathophysiology

Myasthenia gravis is a chronic disease characterized by rapid fatigability of striated muscle. The most frequent cause is an immune-mediated neuromuscular blockade. Acetylcholine (Ach) is released normally into the synaptic cleft, but the post-synaptic motor end plate is less responsive than normal. There is decreased number of available Ach receptors due to circulating receptor binding antibodies.9 The disease is generally non-hereditary but an autoimmune disorder. A rare familial myasthenia gravis is the autosomal recessive trait which is not associated with plasma anti-Ach antibodies.1,9

The pathophysiology of ocular myasthenia gravis is the same as that due to generalized MG (GMG). 11 It is uncertain why ocular muscles are frequently involved in myasthenia. However, it has been proposed that subtle alterations in the function of extraocular muscles especially the levator palpebrae, under constant activation during eye opening, are susceptible to fatigue. Also, patients with OMG are more likely to be seronegative for acetylcholine receptor antibodies than patients with GMG.11

Clinical manifestation.

Ocular myasthenia gravis (OMG) is characterized by a triad of ophthalmoparesis, ptosis and weakness of orbicularis oculi. Patients have ocular symptoms that worsen as the day progresses and with increased stress on the eye such as reading or watching television. Examination of the eye may elicit signs of weakness of the levator and extraocular muscles.1

Ptosis is often unilateral or asymmetric at presentation. The pattern of ptosis is usually the alternating type from one side to the other. Enhancement of ptosis either during prolonged up gaze or upon return to primary gaze suggests fatigability. Rapid fatigue after rest is another sign.12 The patient is asked to sustain down gaze briefly and then make a fast eye movement (or saccade) to primary gaze. An affected

eyelid will quickly rise and then fall (by as little as 1 mm or more) such that the lid appears to twitch. Eyelid "curtaining" occurs when the more ptotic eyelid is passively lifted above the iris by the examiner and the contralateral eyelid becomes more ptotic by slowly drooping or "curtaining." This phenomenon results because of equal innervation to both levator palpebrae superioris muscles13.

Differential diagnosis

The differential diagnosis of signs and symptoms associated with ocular myasthenia gravis depends on the specific symptoms clusters 1,8 which includes isolated ptosis, isolated ophthalmoparesis and other signs or symptoms of bulbar weakness.

Thyroid ophthalmopathy- Grave's disease produces abnormal eye movements due to a constrictive ophthalmopathy. It can usually be differentiated from MG by the lack of ptosis and the presence of proptosis, lid retraction, lid lag, and periorbital oedema.

Chronic progressive external ophthalmoplegia (CPEO) and Kearns-Sayre syndrome (KSS) are mitochondrial disorders that produce progressive, generally symmetric ophthalmoparesis and ptosis. These patients frequently have slow saccades, an early sign that may suggest CPEO rather than MG, where saccades are normal.

Myotonic dystrophy and oculopharyngeal dystrophy may produce ptosis and ophthalmoparesis. Myotonic dystrophy is an autosomal dominant disorder characterized by variable ptosis and weakness of the face, jaw, and neck as well as weakness of the extremities. Oculopharyngeal dystrophy is muscular dystrophy characterized by slowly progressive ptosis and dysphagia with onset in the fourth or fifth decade of life. Weakness of the proximal muscles is commonly present upon initial presentation, but ophthalmoparesis typically develops after the onset of ptosis and dysphagia.

Brainstem and motor cranial nerve pathology - Structural disease of the brainstem can cause isolated ocular symptoms. Parasellar tumors and aneurysms can impair function of the third, fourth, and sixth cranial nerves, leading to symptoms similar to ocular myasthenia.14,15 The presence of trigeminal dysfunction and/or pupillary abnormalities is inconsistent with OMG and may point to a structural lesion.

Multiple motor cranial neuropathies, such as those produced by carcinomatous or lymphomatous meningitis, may also produce eye movement abnormalities that may be confused with OMG. If the

diagnosis of OMG is not firmly established in cases of possible multiple cranial nerve abnormalities, examination of the cerebrospinal fluid for abnormal cells and cytology is usually necessary.

Bell's palsy is a form of facial paralysis resulting from a dysfunction of the cranial nerve VII (the facial nerve) causing an inability to control facial muscles on the affected side. Bell's palsy is the most common acute mononeuropathy.

Diagnostic tests

The diagnosis of OMG can often be made on a clinical basis when the history and examination findings are classic. However, confirmation by diagnostic testing is usually desired. The sensitivity and specificity of tests are different for generalized versus OMG.

Tensilon test is used for diagnosis. This test is usually done using Edrophonium chloride but in its absence Neostigmine can be used. Edrophonium chloride (Tensilon) and Neostigmine inhibits acetylcholinesterase and can transiently reverse signs of weakness due to OMG, such as ptosis and extraocular muscle paresis. Neostigmine was used for our patient. The test is positive if there is significant improvement in ptosis or ophthalmoparesis. The sensitivity of the Tensilon test for OMG is similar to that for GMG, 85 – 95% but it is associated with false-negative and false-positive results. 16,17

Ice pack test - This test can be used in patients with ptosis, particularly those in whom the Tensilon test is considered too risky. It is not helpful for those with extraocular muscle weakness. It is based on the physiologic principle of improved neuromuscular transmission at lower muscle temperatures. In this test, a bag is filled with ice and placed on the closed lid for one minute. The ice is then removed and the extent of ptosis is assessed immediately; the duration of improvement is short (less than one minute). The sensitivity appears to be about 80% in those with prominent ptosis. 18,19

Prognosis

The case presented in this study has been on regular follow up and has not had any change in the progression of his illness. However, two-thirds of patients presenting with ocular myasthenia gravis will go on to develop signs and symptoms of extremity weakness and other bulbar muscle weakness, while one-third will develop persistent OMG.20 Most (78 %) of those who will develop generalized MG (GMG) do so within the first year, and virtually all (94 %) will do so by three years. Neither age nor sex alters the course of the disease.

Treatment

Treatment considerations include symptomatic and immunomodulatory treatment of myasthenia, thymectomy, and corrective treatments of ptosis and strabismus. For the symptomatic management of ptosis and diplopia, the use of lubricating drops is critical to prevent corneal dryness and exposure keratopathy.21, 22 An eye patch, opaque contact lens, or occlusion of an eyeglass lens are simple ways to eliminate diplopia. An anticholinesterase agent such as Pyridostigmine (Mestinon) is most commonly used for treatment of myasthenia. Neostigmine which is an effective and readily available anticholinesterase can be used as an alternative.23 Our patient was treated with Neostigmine with good response.

The commonly used immunosuppressive agent for the treatment of myasthenia is prednisone. Starting with lower doses and gradually increasing over three to four weeks is recommended. Maximum daily dose of 0.5 to 1 mg/kg of prednisone is often needed for several weeks to months in order to maintain benefit. Steroid sparing agents -Azathioprine, mycophenolate mofetil, and cyclosporine are second line immunosuppressants for patients who do not respond to or tolerate prednisone. 24, 25, 26 Imunosuppressive agent is usually reserved for patients with more severe disease than that manifested by pure OMG.27

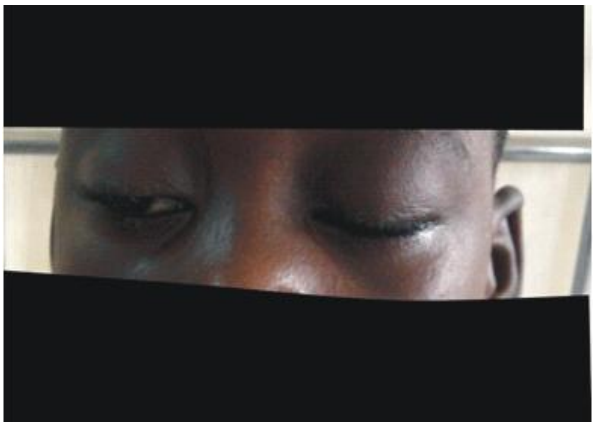
Plasmapheresis and intravenous immune globulin are used for the short-term management of severe GMG and have no role in patients with OMG.28

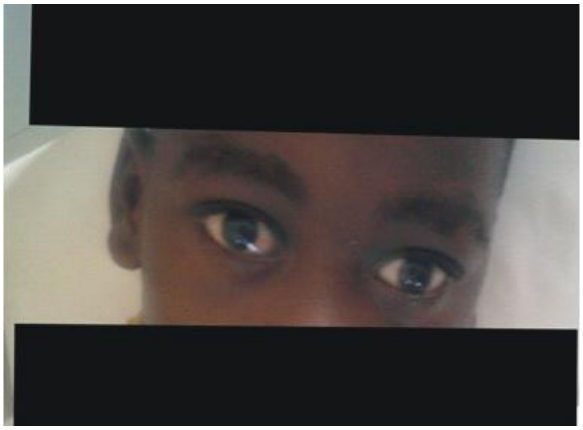
Surgical correction can be performed on patients with stable ptosis. Extraocular muscle resection and recession can be performed on patients with stable ophthalmoparesis.28

Thymectomy for all patients with thymoma and myasthenia is recommended. Evidence-based review concluded that thymectomy is also beneficial in GMG patients without tumor.29-31

Conclusion:

Ocular myasthenia gravis is a rare, autoimmune disorder that requires a high index of suspicion for proper diagnosis and prompt management.





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