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Case Note

Early onset myasthenia gravis with atypical features

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Abstract

A 14 year old boy with atypical myasthenia gravis is reported. The interesting features of the case were the onset in first decade with progressive weakness of limb muscles simulating limb girdle myopathy, presence of bilateral symmetrical non fluctuating external ophthalmoplegia with ptosis and the absence of diplopia. Differential response to choline esterase inhibitors was clinically apparent. In contrast to excellent improvement in limb weakness with choline esterase inhibitors, there was no improvement in external ophthalmoplegia or ptosis. The possibilities are discussed and literature is reviewed.

Key words: Myasthenia gravis (MG), External ophthalmoplegia, Acetylcholine receptor (Ach-R), Acetylcholine receptor antibodies, (Ach-R ab), Ragged red fibers, Muscular dystrophy, Congenital myasthenia gravis, Choline esterase inhibitors, Overlap syndrome

Myasthenia gravis (MG) is a disorder of neuromuscular transmission resulting from decrease in number of acetylcholine receptors due to antibody mediated T cell dependant immunological response. Asymmetrical ptosis and binocular diplopia is the commonest initial presentation of MG ocular muscles involvement. Onset with weakness of bulbar and limb muscles are less common. Maximum disease severity is reached within first year of disease in 75% of cases[1]. Fluctuating motor weakness and its tendency to increase after exercise are the characteristic diagnostic features of the disease. It can present at any age with average age of onset 26 and 31 years in males and females respectively. Early onset MG was reported by Erb[2]. The early onset MG especially the congenital origin differs in clinical presentations and in response to treatment with choline esterase inhibitors. Often the symptoms of MG are masked by associated endocrinal and immunological disorders. A case of MG with atypical features is presented where initial presentation simulated limb girdle myopathy. The additional interesting feature was the presence of symmetrical external ophthalmoplegia with ptosis which was non fluctuating and the symptom of diplopia was absent.

Case report

A 14 years old boy presented with neurological illness manifesting with gradually progressing generalised weakness of 8-9 years duration. Due to weakness he was not able to get up from squatting posture and felt difficulty in raising the limbs above the head. There were no ocular, bulbar or respiratory symptoms. He denied history of fever, arthralgia or muscle pains. Family history for similar illness was negative. At admission clinical examination revealed a thin built boy with marphanoid features i.e. arm span (160 cms) more than the height (156 cms), high arch palate and sclerodactyly. Other features of Marphan's syndrome i.e. lenticular dislocation and cardiac abnormality were lacking. Neurological examination revealed bilateral ptosis with symmetrical external ophthalmoplegia. (Fig-1). He could move his eyes only to a little degree in either direction. Pupils, fundoscopy and other cranial nerves were normal. He had generalised symmetrical muscle wasting which was more marked in the proximal group of muscles. Limbs were hypotonic. No trophic changes, fasciculations or muscle tenderness was noted. Power was Grade-4. Deep tendon reflexes were normal and plantar response flexor on both sides. Gowers' sign was positive. Other systems, spine and joints were normal. During examination he was noted to fatigue early. However, there was no change in voice on prolonged conversation or change in ptosis on sustained upward gaze.

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Investigations done i.e. hemogram, urine analysis, metabolic and renal parameters, serum electrolytes, ECG, echocardiography, X-ray chest and thyroid functions were normal. C-reactive proteins, Rheumatoid factor and ANF were negative. Neostigmine test for MG was positive. The patient noted marked improvement in his muscle power and could repeatedly get up from squatting posture without support. Also, he could raise the arm above his shoulders. However, no improvement noted in ocular movements or in ptosis. EMG & repetitive stimulation tests could not be done due to lack of facilities.

He was treated with Pyridostigmine 30 mg x 6 hourly and steroid (prednisolone 1mg/kg/d) was added latter on. Clinical examination after 4 weeks revealed marked improvement in muscle power but there was no improvement in ocular movements or in ptosis.

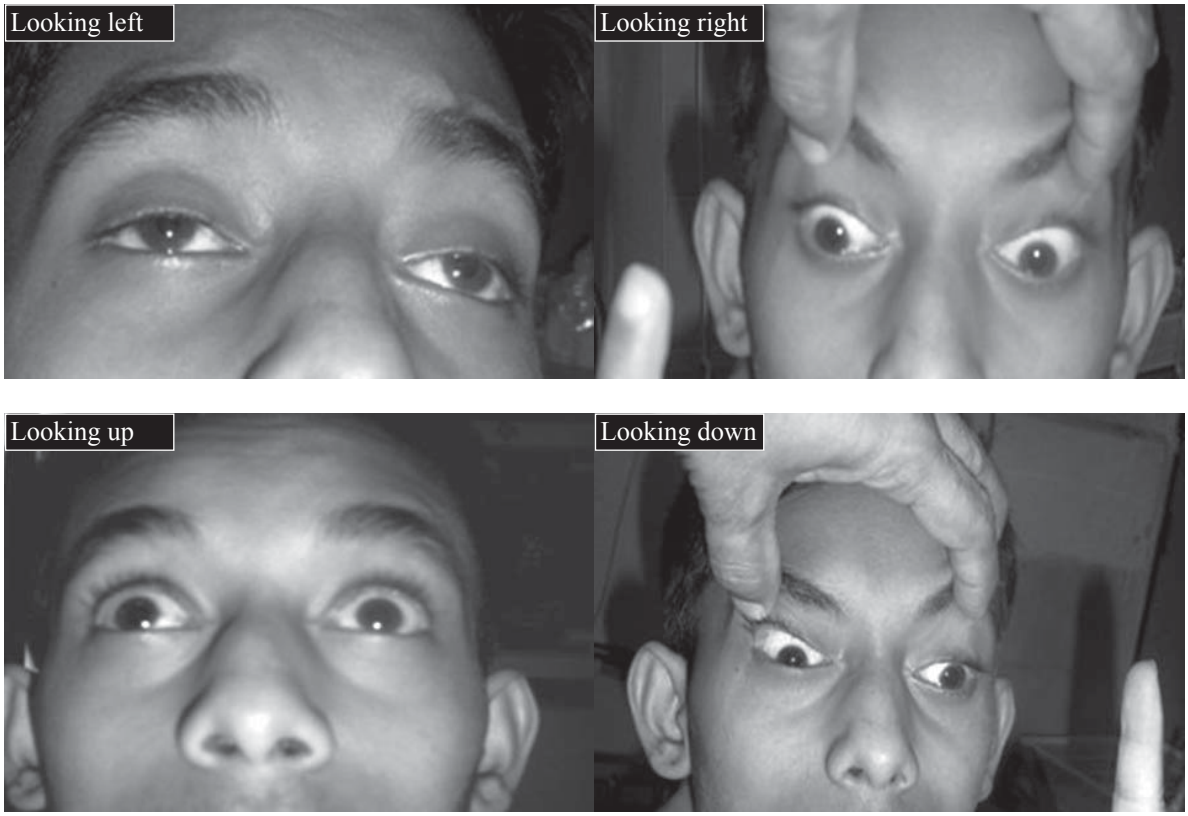

Fig 1: External Ophthalmoplegia with Ptosis

Discussion

Patient under discussion had bilateral symmetrical ptosis with external ophthalmoplegia starting in early childhood. He had progressively increasing muscular weakness, resembling limb girdle muscular dystrophy. Marked improvement in limb power on neostigmine test and therapeutic response to choline esterase inhibitors confirmed the diagnosis of MG. A normal CPK excluded associated limb girdle myopathy. Absence of diplopia and fluctuating diurnal variation of ocular muscle weakness and its unresponsiveness to choline esterase inhibitors was the interesting feature of the case.

Progressive external ophthalmoplegia and ptosis with absence of diplopia, is the characteristic presentation of DNA mutation syndrome with "ragged red fibers", myotonic dystrophy and muscular dystrophy affecting ocular muscles. As ocular muscle weakness is symmetrical, diplopia is absent in these cases. Patients of DNA mutation syndrome with ragged muscle red fibers have characteristics clinical features[2]. Kearns-Sayre syndrome[3] manifest before the age of 20 years. In addition to external ophthalmoplegia, patients have retinal pigmentary changes, cardiac conduction abnormalities, raised proteins (more than 100 mg/dl) in CSF or cerebellar ataxia with varying degree of muscular weakness and easy fatiguability. An autosomal dominant progressive external ophthalmoplegia due to nuclear DNA mutations also present before puberty. These cases have symptoms of exercise intolerance, weakness of neck flexors and proximal muscles with

normal CSF. CPK may be normal or increased. Serum lactate, which is normal or slightly elevated at rest, increases excessively after exercise. Another autosomal recessive disorder of DNA mutation manifests with external ophthalmoplegia, cardiomyopathy and weaknesss and wasting of facial, neck and proximal limb muscles with raised CPK levels. Myotonic dystrophy, an autosomal dominant disorder, also has similar ocular findings. Siblings of the affected parent may develop disease at early stage. Patients of myotonic dystrophy have frontal baldness, pigmentary retinopathy, cataract, and wasting of temporalis, masseter, facial, neck and distal muscles. However, proximal muscles are spared. Myotonia is the characteristic finding in these cases. The above diseases can be excluded as the present case lacked these features.

Ptosis and progressive ophthalmoplegia is also a feature of muscular dystrophy variant confined to ocular muscles. Oculopharyngeal muscular dystrophy patients in addition to progressive symmetrical opthalmoplegia and ptosis, have pharyngeal and limb muscles weakness as well. Raised CPK, myopathic EMG pattern and muscle biopsy is diagnostic. Later, revealing characteristic vacuoles in muscle fibers and tubular filaments in muscle cells nuclei. However, unlike present case, they manifests in 5th and 6th decade.

Several rare cases of genetically determined MG have been reported. The characteristic features are onset at birth or in infancy, fatiguable weakness, an decremental response to repetitive nerve stimulation, absence of acetylcholine receptor antibodies and an inconstant response to choline esterase inhibitors.[4] An autosomal recessive congenital MG, predominantly effecting male child and presenting at birth or shortly afterwards with ophthalmoplegia and ptosis has been reported. Later, like case under discussion, mild generalized weakness may develop. Choline esterase inhibitors have little or no effect on ophthalmoplegia. Plasmapharesis and thymectomy are also ineffective[5] though some improvement may occur in facial and other muscles.

MG is defined in clinical, immunological, pharmacological and neurophysiological terms and there is little difficulty in distinguishing MG from other diseases and syndromes. However, there are some diseases which may share certain clinical, pharmacological or neurophysiologic features of MG and are grouped under overlap syndrome. One such feature is the sensitivity to curare group of drugs. These drugs block acetylcholine receptors (Ach-R). This effect further aggravates the already reduced safety margin in MG cases. An increased sensitivity to curare form drugs may be expected in MG. Bannett and Cash (1943)[6] suggested that sensitivity to curare may be used as a diagnostic test for MG. The generalized curare test did not enjoy a widespread use due to possibility of life threatening aggravation of myasthenic weakness. This lead to its modification to regional curare test[7] and its use in combination with repetitive stimulation for diagnosing MG[8]. Use of this test lead to diagnosis of MG in 15% cases where other tests were negative. In another study of 14 cases with clinically documented ocular MG, seven had abnormal regional curare test although repetitive stimulation test was normal. Decremental response following curare was reversed by edrophonium. Three patients with abnormal curare test underwent thymectomy and showed improvement or normalization of regional curare test after thymectomy.

Ross[9,10] described a case where patient had ocular myopathy with ptosis unresponsive to edrophonium but showed MG like sensitivity to curare. Horowitz and Siwak[8] studied 224 patients of MG with regional curare test where response to repetitive stimulation was normal. A diagnostic decremental repetitive response, after regional curare test, was noted in 29% of cases. The lowest return rate was in cases of ocular MG. The authors suggested that these cases might have neurological disorder other than MG. In contrast to these cases, some patients with MG fail to respond to edrophonium or neostigmine but are sensitive to curare[11]. Black et al[12] reported a case of ocular and bulbar MG and thymoma without response to any of the electrical or pharmacological test. This patient was later found to have high level of antibody to acetylcholine receptors.

The case under discussion had ptosis with ophthalmoplegia unresponsive to neostigmine, similar to the cases described earlier[8, 9, 10]. In addition, he had typical neostigmine responsive myasthenic weaknes of limb girdle muscles which showed excellent clinical respone to choline esterase inhibitors This differential response to neostigmine in limb and ocular muscles was the most interesting feature of the disease. The regional curare test, estimation of acetylcholine receptor antibodies and histopathological examination, especially electron microscopy, of ocular and limb muscles would have clarified the doubt whether the disease was MG or was an overlap syndrome of MG in limb muscles and neuromuscular disorder of different nature in ocular muscles. He has been advised to go neurological center where these facilities exists.

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