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Chronic Progressive External Ophthalmoplegia(CPEO): A not so rare mitochondrial myopathy

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Abstract

Mitochondria myopathies have a variable clinical presentation and CPEO(chronic progressive external ophthalmoplegia) is the hallmark which should alert the clinician to this diagnosis. Herein we report a-40-year old lady with progressive ptosis without diplopia and without any similar family history who was diagnosed as having a mitochondrial myopathy and given supportive therapy.

Keywords: Mitochondrial myopathies, Ptosis, Ophthalmoplegia, Diplopia, Family history.

Introduction

Chronic progressive external ophthalmoplegia (CPEO) is a common manifestation of patients with mitochondrial diseases and it is often the defining clinical feature, overshadowing other skeletal muscle or neurologic involvement. It is a progressive disorder in which all extraocular muscles (EOMs)are affected, characterized by bilateral, generalized restriction of eye movements (ophthalmoplegia) and drooping of the upper eyelids (ptosis).[(1)]

Case History

A-forty-year old female, resident of Seoni, Madhya Pradesh, presented to us with bilateral ptosis since three years, gradual painless visual loss since 1 year and dysphagia since one month. Patient was alright three years back, and then developed bilateral ptosis insidiously without any diurnal variation. Visual loss was painless and gradually progressive since one year. Dysphagia since one month was to both solids and liquids. There was no history of any diurnal variation in ptosis, no h/o any weakness, breathlessness, weight loss, no family h/o similar complaints, no h/o night blindness and no h/o snakebite (Fig. 1).

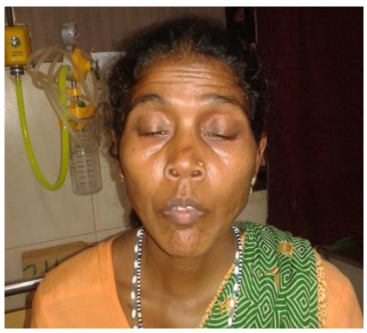

Fig. 1: Bilateral ptosis in a middle-aged female

On examination, her vitals were normal and fundus (Fig. 2) showed bilateral partial optic atrophy. On neurologic examination, apart from the obvious bilateral ptosis, her higher functions were normal, gag was weak and there was mild neck muscle weakness. There was no proximal muscle weakness and rest of the neurologic findings were normal. Hervisual acuity was 6 /9 in both eyes. On ENT examination, there was no evidence of sensori-neural hearing loss.

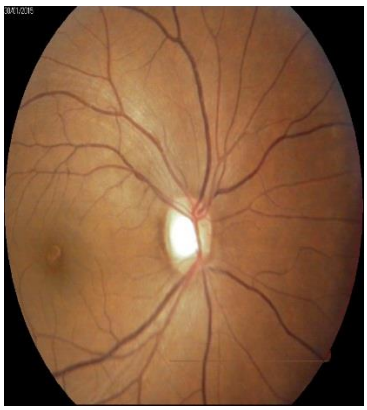

Fig. 2: Fundus showing bilateral partial optic atrophy

On the basis of history and examination, we had kept a differential diagnosis of chronic progressive external ophthalmoplegia(CPEO), oculopharyngeal muscular dystrophy, thyroid associated ophthalmopathy and ocular myaesthenia gravis. On investigations, her CBC,ESR, RBS and ECG were normal. Tensilon test was negative for Myasthenia gravis. Serum TSH, CPK were normal. EMG and NCV(to rule out associated neuropathy) was normal. MRI Orbit (Fig. 3) showed atrophy of extraocular muscles and MRI Brain was normal. Muscle biopsy was not done, referred to higher centre for the same.

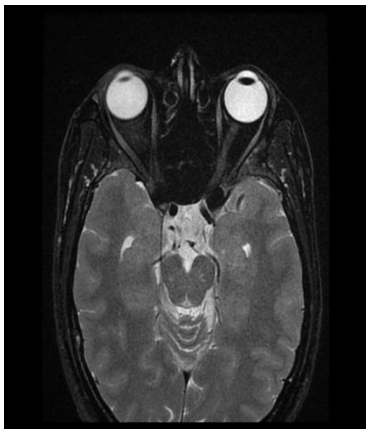

Fig. 3: MRI Orbit showing atrophy of extraocular muscles

Ophthalmology consultation was done which advised that operative intervention was not possible due to poor Bell's phenomenon. Corrective Krutch glasses were given for ptosis (Fig. 4).

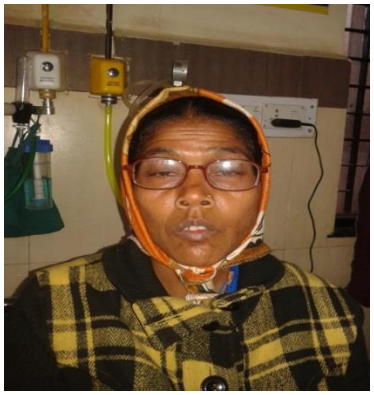

Fig. 4: Patient seen wearing the corrective crutch glass

Discussion

Although once considered rare, accumulating evidence suggests that mitochondrial disorders are relatively common. Organ systems relying most on aerobic metabolism are preferentially affected and involvement of the nervous system in general (referred to as mitochondrial encephalomyopathy) is common. When skeletal muscle is affected, either alone or with central nervous system disease, the term mitochondrial myopathy is used. The clinical expression of mitochondrial myopathies is extremely variable. Myopathy may be the sole or main sign, or merely an incidental finding associated with a multi-systemic illness.

Myopathies are ubiquitous in mitochondrial disorders, and even asymptomatic patients will typically have significant muscle pathology on biopsy. Skeletal limb muscle biopsy typically reveals cytochrome c oxidase (COX)-deficient fibers, some of which demonstrate characteristic subsarcolemmal accumulation of abnormal mitochondria, the classic ragged-red fiber.[2] On Gomoritrichome staining, the mitochondria appear as bright red masses against the blue background of the myofibers, which led to the term "ragged red fibers" (RRF). Although COX-deficient muscle fibers accumulate in EOMs during normal aging[3-4] the levelsof COX deficiency in both skeletal muscle(vastus lateralis-quadriceps) and EOM of patients with CPEO are significantly higher[5] thus highlighting the pathogenic load of genetic defects in these patients.

The following groups illustrate the different ways mitochondrial myopathies can present clinically:

- As chronic progressive external ophthalmoplegia (with or without mild proximal muscle weakness) or Kearns-Sayre syndrome.
- As an isolated myopathy with or without exercise intolerance and/or myalgia.
- As a severe myopathy or encephalomyopathy of infancy and childhood.
- As a predominantly multisystem disease with myopathy (e.g. MELAS and MERRF).

A certain degree of overlap exists between all these entities.[6]Kearns-Sayre syndrome (KSS) refers to the combination of CPEO with pigmentary retinopathy and onset before age 20. Other abnormalities have been described, including short stature, cerebellar ataxia, raised CSF protein (>100 mg/dL), cardiac conduction defects or cognitive deficits/mental retardation.

Familial CPEO can be either autosomal dominant or autosomal recessive and is due to nuclear DNA mutations. It seems to have a higher percentage of associated abnormalities than sporadic CPEO, such as bulbar symptoms (dysphagia, dysphonia, hearing impairment), severe depression, cataracts or neuropathy. The diagnosis of the primary mitochondrial disorders can be challenging. One of the major clues to mitochondrial disease is a clear family history of the same disorder, particularly in cases of maternal transmission only. A detailed extended family history is therefore essential. In particular, a history of neonatal or childhood death, deafness, diabetes, cardiac symptoms, visual impairment and developmental delay should be sought. However, up to 62 percent of cases of primary mitochondrial disorders do NOT show maternal transmission. In many of these cases, the mitochondrial phenotype arises from nuclear DNA mutations, and inheritance follows Mendelian genetics.[6]

Potential therapeutic strategies could involve increasing the level of wild-type mtDNA by recruiting EOM satellite cells, which are thought to harbor lower levels of mutant mtDNA, to differentiate into mature myofibres.[7-8] EOMs are easily accessible, and the proliferation of satellite cells may be induced by injection of specific myotoxic stimuli such as bupivacaine.[9]

Conclusion

Mitochondrial disorders are not a rare clinical entity in adults and high index of suspicion is needed for diagnosis. Muscle biopsy(electron microscopy) would have been conclusive in our middle aged female patient but was not possible in our set up. Genetic testing is not feasible in our country at present. However, awareness about classical clinical presentation will lead to more data about true prevalence and evolution of therapeutic strategies in our country.

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