Chronic Progressive External Ophthalmoplegia
A Rare Case Report

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ABSTRACT
Chronic progressive external ophthalmoplegia (CPEO), also known as progressive external ophthalmoplegia (PEO), is a type of eye disorder characterized by slowly progressive inability to move the eyes and eyebrows. [1] It is often the only feature of mitochondrial disease, in which case the term CPEO may be given as the diagnosis. In other people suffering from mitochondrial disease, CPEO occurs as part of a syndrome involving more than one part of the body, such as Kearns-Sayre syndrome. Occasionally CPEO may be caused by conditions other than mitochondrial diseases.

A woman aged 20 years presented with history of drooping of both eyelids started 07 years back. No history of fatiguability, fluctuations in drooping of eyelids. No history of ptosis, diplopia, or motor weakness. No history of consanguinity. Neurological examination showed moderate bilateral ptosis and marked limitation of conjugate gaze in all directions. Serum acetylcholine receptor antibody was negative. Neostigmine test was negative. MRI brain normal. Repetitive nerve stimulation test showed no decremental response both at rest and post exercise. Histopathological examination of biopsy specimen from left quadriceps revealed Ragged red fibres on Modified Gomari Trichome (MGT) stain, suggestive of mitochondrial myopathy - CPEO.

KEYWORDS
Chronic Progressive External Ophthalmoplegia, Ragged Red Fibers, mitochondrial DNA.

Introduction:
CPEO is a slowly progressive myopathy primarily involving and often limited to extraocular muscles. CPEO was described in 1868 by von Graefe. Initially, it was believed to represent a neuronal origin, but muscle biopsies have supported a myopathic origin. Men and women are equally affected. Ptosis beginning in childhood and sometimes in adolescence is followed by ophthalmoparesis. Ciliary and iris muscles are not involved. Pattern of inheritance is mainly autosomal dominant, rare recessive or uncertain. Some nuclear gene mutations have been implicated. POLG1, TWINKLE, and ANT1. Some cases of CPEO transmitted by mendelian manner, are not of mitochondrial origin. Muscle biopsy is still the definitive test for diagnosis.

Case report:
A woman aged 20 years presented with history of drooping of both eyelids started 07 years back. No history of fatiguability, fluctuations in drooping of eyelids. No H/O diplopia, Drooping of eyelids are slowly progressive. No motor weakness. No H/O consanguinity. Neurological examination showed moderate bilateral ptosis and marked limitation of conjugate gaze in all direction (fig 1). Her visual acuity was normal and visual fields were restricted. Neither retinal pigmentary degeneration nor optic atrophy was found. Other neurological examination was unremarkable.

Laboratory studies revealed normal blood counts, serum electrolytes, thyroid and liver functions. Serum acetylcholine receptor antibody was negative. Neostigmine test for myasthenia gravis is negative. Repetitive nerve stimulation test from right nasalis and trapezius muscles showed no decremental response both at rest and post exercise. MRI brain was normal. Histopathological examination of biopsy specimen from left quadriceps showed normal fascicular architecture with mild variation in the fibre size. There is no necrosis, degeneration and inflammation. ATPase shows type 1 predominance. There are granular fibres on H & E which were Ragged red on Modified Gomari Trichome (MGT) stain, suggestive of mitochondrial myopathy - CPEO.
ative with cox and blue ragged fibres on SDH and COX SDH suggestive of Mitochondrial myopathy.

Discussion:
CPEO is a slowly progressing disease. It may begin at any age and progresses over a period of 5–15 years.[1] The first presenting symptom of ptosis is often unnoticed by the patient until the lids droop to the point of producing a visual field defect. Often, patients will tilt the head backwards to adjust for the slowly progressing ptosis of the lids. In addition, as the ptosis becomes complete, the patients will use the frontalis (forehead) muscle to help elevate the lids. The ptosis is typically bilateral, but may be unilateral for a period of months to years before the fellow lid becomes involved.

Ophthalmoplegia is usually symmetrical. As such, double vision is sometimes a complaint of these patients. In fact, the progressive ophthalmoplegia is often unnoticed till decreased ocular motility limits peripheral vision. Often someone else will point out the ocular disturbance to the patient. Patients will move their heads to adjust for the lost of peripheral vision. Often, patients will tilt the head backwards to adduct the eye. All directions of gaze are affected, however, downward gaze appears to be best spared. This is in contrast to Progressive Supranuclear Palsy (PSP) which typically affects vertical gaze and spares horizontal gaze.

Other causes of ocular myopathies like thyroid associated ophthalmopathy ,ocular myasthenia gravis , oculo - pharyngeal muscular dystrophy , myotonic dystrophy type 1,(or) congenital cranial disinnervation disorders of external ocular muscles are ruled out based on historical and objective data. Kearns - sayre syndrome was ruled out because of lack of pigmentary retinopathy.

This classical manifestation of mitochondrial diseases can develop either in isolation (or) in association with other neurological features referred to as CPEO-plus. This include additional signs and symptoms hearing loss, neuropathy, ataxia, parkinsonism and depression.

It is important to differentiate CPEO from other pathologies that may cause an ophthalmoplegia. There are specific therapies used for these pathologies.CPEO is diagnosed by muscle biopsy. On examination of muscle fibers stained with Gomori-trichrome stain, one can see an accumulation of enlarged mitochondria. This produces a dark red staining of the muscle fibers given the name “ragged red fibers”. While ragged red fibers are seen in normal aging, amounts in excess of normal aging give a diagnosis of a mitochondrial myopathy.

Polymerase Chain Reaction (PCR), from a sample of blood or muscle tissue can determine a mutation of the mtDNA.

Elevated acetylcholine receptor antibody level which is typically seen in myasthenia gravis has been seen in certain patients of mitochondrial associated Ophthalmoplegia.[7]

There is currently no defined treatment to ameliorate the muscle weakness of CPEO. Treatments used to treat other pathologies causing Ophthalmoplegia has not been shown to be effective.

Experimental treatment with tetracycline has been used to improve ocular motility in one patient.[9] Coenzyme Q10 has also been used to treat this condition.[10] However, most neuroophthalmologists do not ascribe to any treatment.

Genetics :
Mitochondrial DNA which is transmitted from the mother, encodes proteins that are critical to the respiratory chain required to produce adenosine triphosphate (ATP). Deletions or mutations to segments of mtDNA lead to defective function of oxidative phosphorylation. This may be made evident in highly oxidative tissues like skeletal muscle and heart tissue. However, extraocular muscles contain a volume of mitochondria that is several times greater than any other muscle group. As such, this results in the preferential ocular symptoms of CPEO.

Multiple mtDNA abnormalities exist which cause CPEO. One mutation is located in a conserved region of mitochondrial tRNA at nucleotide 3243 in which there is an A to G nucleotide transition. This mutation is associated with both CPEO and Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). [3]

A common deletion found in one-third of CPEO patients is a 4,977 base pair segment found between a 13 base pair repeat.

The mtDNA that is affected maybe a single or multiple point deletion, with associated nuclear DNA deletions. One study showed that mitDNA deletion seen in CPEO patients also had a associated nuclear DNA deletion of the Twinkle gene which encodes specific mitochondrial protein; Twinkle.[4]

Whether a tissue is affected is correlated with the amount of oxidative demands in relation to the amount of mtDNA deletion.

In most cases, PEO occurs due to a sporadic deletion or duplication within the mitochondrial DNA.[12] However, transmission from the mother to the progeny appears only in few cases. Both autosomal dominant and autosomal recessive inheritance can occur, autosomal recessive inheritance being more severe. Dominant and recessive forms of PEO can be caused by genetic mutations in the ANT1, POLG, POLG2 and PEO1 genes.

Conclusion:
CPEO is a slowly progressive myopathy primarily involving and often limited to extra ocular muscles. CPEO is diagnosed and confirmed by muscle biopsy showing ragged red fibres.
REFERENCES