Chronic Progressive External Ophthalmoplegia A case series

[1]Dr Neebha Anand, [2]Dr Kiranmai Garg, [3]Dr Urmil Chawla, [4]Dr Reena Gupta

[1]Professor, [2]Resident, [3]Professor, [4]Professor
[1]Regional Institute of Ophthalmology,
[1]Pt. B.D. Sharma PGIMS, Rohtak, India

Abstract: Background: Progressive External Ophthalmoplegia is a descriptive term for a group of hereditary myopathies affecting extraocular muscles. Minimum prevalence of CPEO is about 1 in 30,000 of general population. It can occur with isolated oculomotor symptoms or in conjunction with other systemic findings. Purpose: To report a case series of Progressive External Ophthalmoplegia with varied presentations and associations. Method: Retrospective case series of five cases diagnosed with Progressive External Ophthalmoplegia with review of clinical aspects of each of the cases. Results: While there is no definitive cure for CPEO, control of symptoms can markedly improve patient's quality of life. Referral for management of concomitant neurologic or cardiac disease is indicated.

Index Terms— CPEO, Diffuse ophthalmoplegia, Red ragged fibres, Gomori trichrome stain

I. INTRODUCTION

Progressive External Ophthalmoplegia (PEO) is a term that describes an array of clinical findings associated with mitochondrial myopathy rather than a true diagnosis. PEO spectrum disorders include CPEO (Chronic Progressive External Ophthalmoplegia), CPEO plus syndrome or PEO with associated systemic disorders. When PEO occurs in isolation, it is termed as CPEO. CPEO plus syndrome may be defined as co-occurrence of PEO with other symptoms of mitochondrial dysfunction like Kearns-Sayre syndrome, oculopharyngeal dystrophy and myotonic dystrophy [1]. The term PEO was first described in 1868 by Von Graefe and has considerably evolved since then [2]. Researchers have documented its systemic association, histopathological characteristics and genetic level associations in their studies suggesting that PEO represents only a portion of the systemic disorder. Minimum prevalence of CPEO is about 1 in 30,000 of general population [3]. PEO is a genetically heterogenous disorder with 50% of the cases being sporadic and remaining 50% being inherited (autosomal dominant, autosomal recessive or maternal transmission) [4]. PEO can present at any age with varied presentations, most common being, ptosis and diffuse ophthalmoplegia. Myasthenia gravis, Thyroid associated ophthalmopathy are some of the clinical entities that can be confused with presentations of PEO.

Although PEO is a clinical diagnosis but specific investigations are needed in ruling out alternative disorders and confirming the diagnosis in early and atypical cases. Early and accurate diagnosis of PEO is of paramount importance as it can herald many serious disorders and can prevent associated mortality and morbidity. This paper reports a case series of five patients of PEO showing variable clinical presentations and its associations.

II. CASES

Case 1: 29-year-old male patient presented with gradual and progressive drooping of Right eye (RE) Upperlid since 20 years followed by sudden drooping of Left eye (LE) Upperlid since 4 years associated with restricted bilateral ocular movements. There was no History of (H/O) diminution of vision, diplopia or diurnal variation. Patient also reported hoarseness of voice with no H/O fatigue while speaking, difficulty in swallowing, regurgitation of water or choking while eating. No H/O fever, headache, facial deviation, facial numbness, difficulty in opening or closing jaw, limb or truncal weakness was reported. There was no significant medical, surgical or family history. There was no history of preceeding trauma. Ocular examination revealed bilateral severe ptosis, ophthalmoplegia and exotropia (Fig. 1) with normal pupillary reactions. LPS (Levator palpebrae superioris) action was 1mm in right eye and 3mm in left eye. Best Corrected Visual Acuity (BCVA) of patient was found to be 6/18 in both eyes with bilateral immature senile cataract. Fundoscopy was within normal limits bilaterally. Ice pack test revealed no improvement in any of the clinical features. Systemic and neurological examination of patient was within normal limits. Laboratory investigations revealed elevated serum creatine phosphokinase and lactate dehydrogenase (LDH) levels. Serum acetylcholine receptor binding antibodies and thyroid antibodies were found to be negative. MRI revealed no significant abnormality. With clinical suspicion of mitochondrial myopathy, the patient underwent biopsy of deltoid muscle which showed Ragged red fibers with Gomori trichrome stain pointing towards diagnosis of CPEO (Fig. 2)

Figure 1showing Bilateral severe ptosis (Left) with ophthalmoplegia and exotropia (Right)

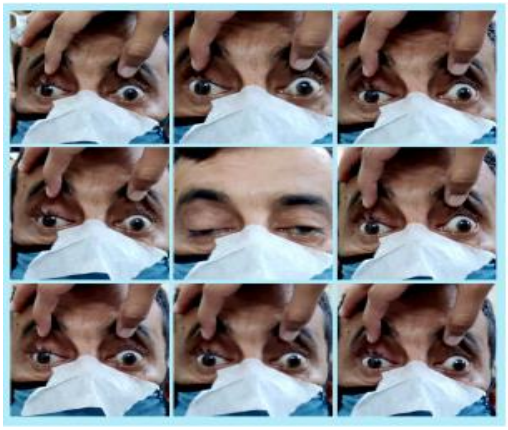
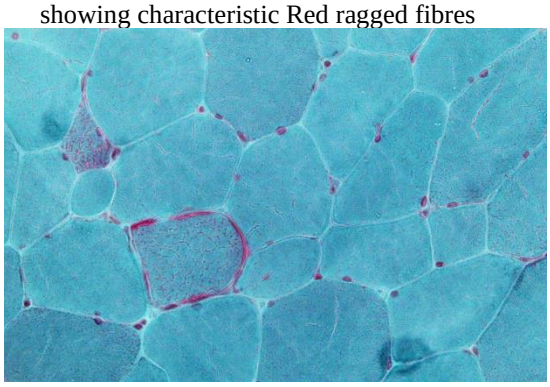
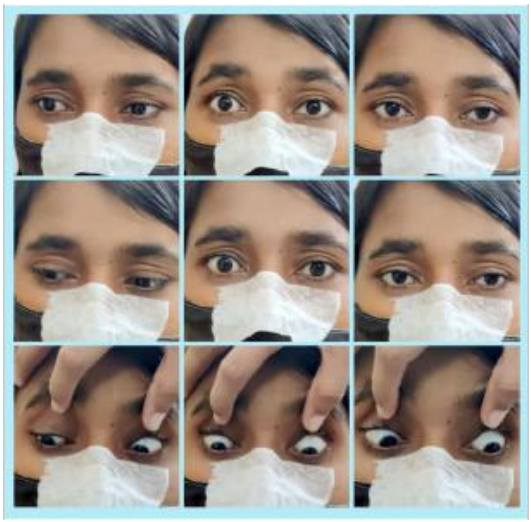


Figure 2 showing Gomori trichrome stained muscle biopsy showing characteristic Red ragged fibres



Case 2: 20-year-old female presented with complaint of drooping of bilateral upperlid (Left >Right) since 2 months. There was associated H/O weakness of both upper and lower limbs since then. No H/O ocular pain, periorbital swelling, diminution of vision, diplopia or diurnal variation was reported. Patient had no complaints of difficulty in swallowing or talking, regurgitation of water, facial deviation or any other systemic ailments. There was no relevant medical, surgical or familial history. No H/O trauma was found. On examination, patient was found to have 6/6 vision in both eyes. Patient had bilateral ophthalmoplegia less so in inferior gaze with Mild ptosis in right eye and Moderate ptosis in left eye (Fig. 3). LPS action was 12mm in Right eye and 8mm in left eye. Anterior and posterior segment examination was within normal limits bilaterally. Neurological examination revealed mild proximal weakness of lower & upper limb. Thyroid associated ophthalmopathy and myasthenia gravis were ruled out using clinical (negative fatigue test and ice pack test) and laboratory tests (absence of acetylcholine receptor binding antibodies and thyroid antibodies in serum). Radiological investigations were unrevealing. Creatine phosphokinase and LDH levels in serum were raised. In order to confirm the diagnosis of PEO, muscle biopsy was carried out which showed red ragged fibres with gomori trichrome stain similar to the one seen in case 1 (Fig. 2).

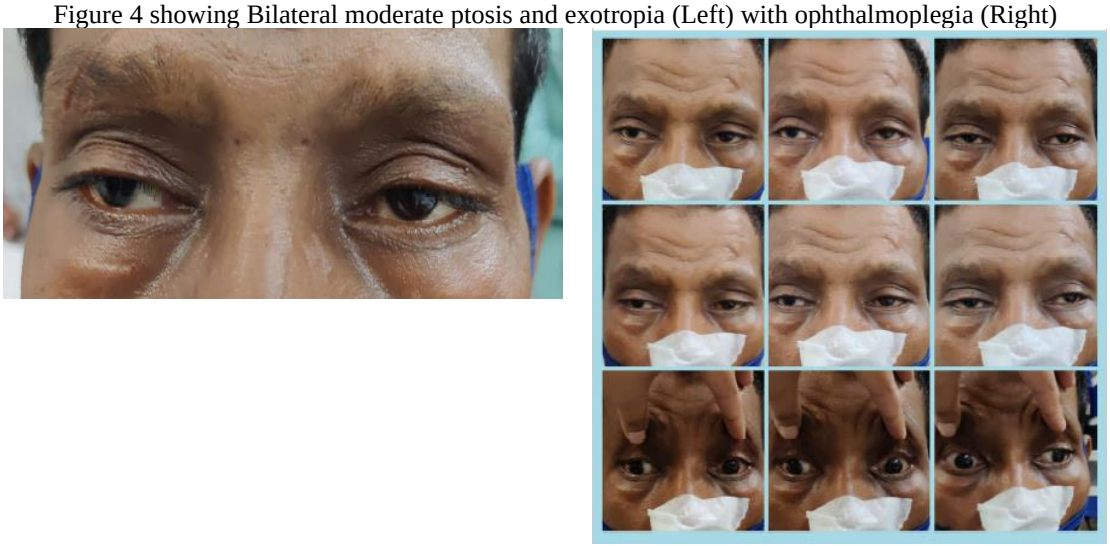
Figure 3 showing RE mild ptosis & LE severe ptosis (Left) with bilateral ophthalmoplegia (Right)



Case 3: 51-year-old male presented with H/O double vision in all gazes since 2 years associated with drooping of both eye upperlid and decreased ocular movements. There was no H/O ocular pain or diurnal variation. To rule out myasthenia gravis, history of difficulty in swallowing, regurgitation of water, difficulty in opening or closing jaw, limb or truncal weakness was elicited. There was no significant medical, surgical or family history. There was no history of preceeding trauma. Ocular examination showed bilateral moderate ptosis, right eye exotropia and restricted ocular motility less so in dextroversion and levoversion (Fig. 4). BCVA

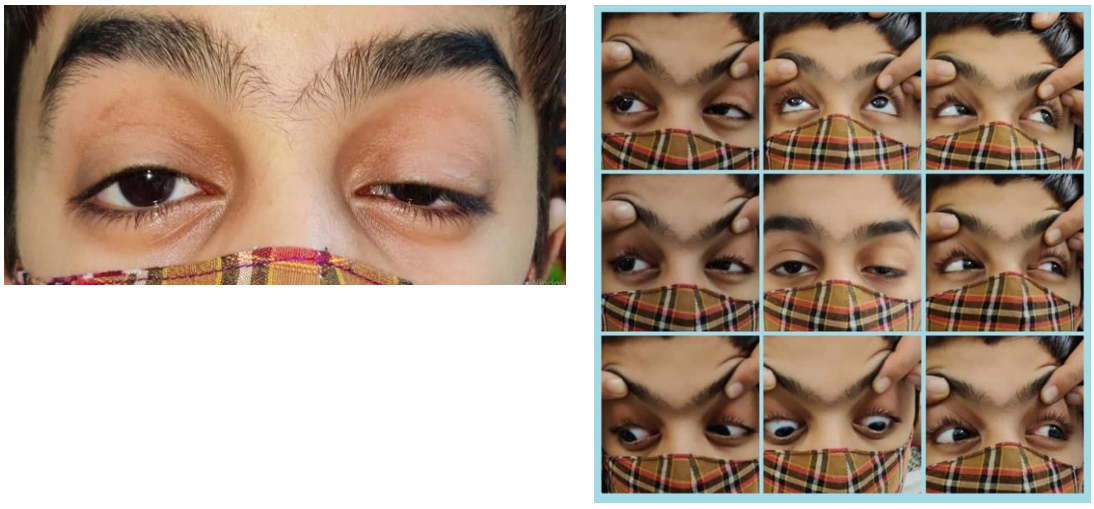
was 6/36 in right eye and 6/9 in left eye. LPS action was 3mm in Right eye and 4mm in left eye. Anterior segment examination showed iris coloboma in right eye with normal pupillary reactions. Fundoscopy revealed right eye type 3 uveal coloboma as per Ida Mann classification. To rule out disorders like myasthenia and thyroid eye disease, tests like ice pack test, fatigue test, serum acetylcholine receptor binding antibodies and thyroid antibodies were performed which were unremarkable. MRI ruled out possible suspicion of third and fourth nerve palsy. Elevated serum creatine phosphokinase and LDH levels were found during laboratory analysis. The patient underwent biopsy of deltoid muscle which showed Ragged red fibers with Gomori trichrome stain thus confirming the diagnosis of PEO (Fig. 2).

Figure 4 showing Bilateral moderate ptosis and exotropia (Left) with ophthalmoplegia (Right)



Case 4: 12-year-old male presented with H/O gradually progressive drooping of Left eye upperlid since 2 years associated with H/O diminution of vision. There was no H/O diplopia or diurnal variation. No H/O difficulty in swallowing, fever, headache, facial deviation, facial numbness, difficulty in opening or closing jaw, limb or truncal weakness was reported. There was no significant medical or surgical history or any history of trauma. There was no H/O any similar or related complaints in the siblings. Ocular examination revealed Chin lift with RE moderate ptosis and LE severe ptosis, restricted ocular movements in all gazes and esotropia (Fig. 5) with normal pupillary reactions. LPS action was 6mm in right eye and 3mm in left eye. BCVA was 6/9 in right eye and 6/24 in left eye. No significant abnormality was detected on anterior and posterior segment examination bilaterally. Neuromuscular and thyroid disorders were ruled out. Systemic and neurological examination was unremarkable. Radiological investigations were within normal limits. Diagnosis of CPEO was confirmed using lab investigations and findings of muscle biopsy (Fig. 2).

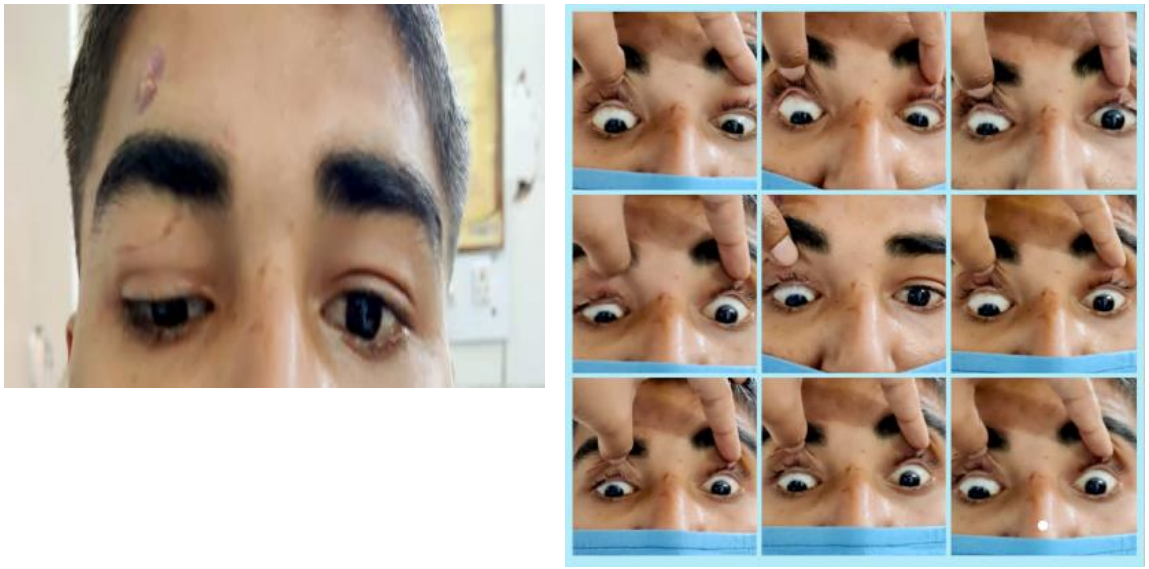
Figure 5 showing RE moderate ptosis and LE severe ptosis severe ptosis (Left) with restricted ocular movements and esotropia (Right)



Case 5: 21-year-old male patient who was operated case of RE sling surgery 15 years back, presented with C/O gradually progressive drooping of RE upperlid since 13 years associated with H/O diminution of vision. There was no H/O diplopia or diurnal variation. No H/O difficulty in swallowing or muscle weakness was reported. There was no significant medical, surgical or family history. There was no history of preceeding trauma. Ocular examination showed RE severe ptosis with poor LPS action and hypotropia with markedly restricted ocular motility in all directions of gaze in both eyes. Patient was found to have protruded and infected sling knot on the forehead (Fig. 6). BCVA of patient was 6/60 in RE and 6/6 in LE with normal pupillary reactions. Rest of the ocular examination was unremarkable. Forced duction test was negative. Diagnosis of PEO was confirmed by elevated serum creatine kinase and LDH levels with positive findings of muscle biopsy (Fig. 2). Absence of clinical improvement on application

of ice pack and negative serology for anti- acetylcholine receptor antibodies ruled out Myasthenic disorder. Lab investigations helped to ruled out presence of any thyroid disorder.

Figure 6 showing RE severe ptosis with hypotropia (Left) with restricted ocular movements (Right)



III. DISCUSSION

PEO is clinically and genetically heterogenous group of disorders and not a specific diagnosis. PEO can present at any age with bilateral ptosis and diffuse ophthalmoplegia [5]. PEO related ptosis is usually symmetrical, gradually progressive with poor LPS action [6-8]. Other clinical findings that can present variably are Strabismus (Exotropia> Esotropia), Diplopia and Amblyopia [5,9,10]. Pigmentary retinopathy is characteristic of Kearns-Sayre Syndrome (KSS) [2]. Optic atrophy can present as an association of PEO in patients with OPA 1 gene mutation[11]. Cardiac conduction defects, neuropathies, endocrinopathies, sensorineural hearing loss, dysphagia etc constitue systemic associations of PEO [4]. Cardiac conduction defects can be fatal [12].

PEO can masquerade ocular/generalized myasthenia gravis (MG), Thyroid associated Ophthalmopathy (TAO), Wernicke's encephalopathy, Progressive supranuclear palsy (PSP), Miller-Fisher syndrome and Congenital fibrosis of extraocular muscles (CFEOMs) [1]. PEO can be associated with other syndromes of mitochondrial dysfunction including Kearns-Sayre Syndrome (KSS), Oculopharyngeal muscular dystrophy, Myotonic dystrophy, MELAS (Mitochondrial encephalopathy, Lactic acidosis and stroke like episode), SANDO (Sensory ataxic neuropathy with dysarthria and ophthalmoparesis), MNGIE (Mitochondrial neurogastrointestinal encephalopathy disease) [1]. Hence, the patient should undergo thorough ocular and systemic examination to confirm the diagnosis and rule out the alternative diagnosis. Orbital CT/MRI, blood/ CSF (Cerebrospinal fluid) lactate levels, creatine kinase levels, muscle biopsy and electromyography are the targeted investigations that aid in diagnosis of PEO [13-18]. Extensive screening should be done due to clinical heterogeneity of PEO as it can affect any organ of body with inclination towards metabolically active organs. Early diagnosis aids in counselling of the patient and timely management as well as screening of the family members for similar disorder.

All the five cases presented in different decades of age but with similar complaint i.e. gradually progressive ptosis. Although PEO related ptosis is usually thought to be symmetrical, it was bilaterally asymmetrical in all the cases. Ophthalmoparesis to varied extent was present in all the cases. In addition to clinical presentation, laboratory investigations like raised blood levels of lactate and creatine kinase and histological findings of muscle biopsy confirmed the diagnosis of PEO. None of the cases showed any significant fundoscopic findings or any cardiac abnormalities thus ruling out possibility of KSS.

CONFLICTS OF INTEREST: NIL

FINANCIAL DISCLOSURE: NONE

REFERENCES

1. McClelland C, Manousakis G, Lee MS. Progressive External Ophthalmoplegia. Curr Neurol Neurosci Rep. 2016;16(6):53.
2. Kearns TP, Say re GP. Retinitis pigmentosa, exte rnal ophthalmophegia, and complete heart block: unusual syndrome with histologic study in one of two cases. AMA Arch Ophthalmol. 1958;60(2):280–9.
3. Patrick Yu-Wai-Man, Anna l Clements, Victoria Nesbitt, Philip G Griffiths, Grainne S Gorman, Andrew M Schaefer, et al. A national epidemiological study of chronic progressive external ophthalmoplegia in the United Kingdom - molecular genetic features and neurological burden. *Invest. Ophthalmol. Vis. Sci.* 2014;55(13):5109.
4. Moraes CT, DiMauro S, Zeviani M, et al. Mitochondrial DNA deletions in progressive external ophthalmoplegia and KearnsSayre syndrome. N Engl J Med.1989;320(20):12939.
5. Miller NR, Walsh FB, Hoyt WF. Walsh and Hoyt's clinical neuroophthalmology. Philadelphia, Pa; London: Lippincott Williams & Wilkins. 2005;6(1).
6. Wabbels B, Ali N, Kunz WS, Roggenkamper P, Kornblum C. Chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome: interdisciplinary diagnosis and therapy. Ophthalmologe. 2008;105(6):550–6.

7. Ahn J, Kim NJ, Choung HK, et al. Frontalis sling operation using silicone rod for the correction of ptosis in chronic progressive external ophthalmoplegia. Br J Ophthalmol. 2008;92(12):1685–8.
8. Shorr N, Christenbury JD, Goldberg RA. Management of ptosis in chronic progressive external ophthalmoplegia. Ophthal Plast Reconstr Surg. 1987;3(3):141–5.
9. Tinley C, Dawson E, Lee J. The management of strabismus in patients with chronic progressive external ophthalmoplegia. Strabismus. 2010;18(2):41–7.
10. Richardson C, Smith T, Schaefer A, Turnbull D, Griffiths P. Ocular motility findings in chronic progressive external ophthalmoplegia. Eye (Lond). 2005;19(3):258–63.
11. Yu-Wai-Man P, Griffiths PG, Gorman GS, et al. Multi-system neurological disease is common in patients with OPA1 mutations. Brain. 2010;133(Pt 3):771–86.
12. Young TJ, Shah AK, Lee MH, Hayes DL. Kearns-Sayre syndrome: a case report and review of cardiovascular complications. Pacing Clin Electrophysiol. 2005;28(5):454–7.
13. Okamoto K, Ito J, Tokiguchi S, Furusawa T. Atrophy of bilateral extraocular muscles—CT and clinical features of seven patients. J Neuro-Ophthalmol. 1996;16(4):286–8.
14. Ortube MC, Bhola R, Demer JL. Orbital magnetic resonance imaging of extraocular muscles in chronic progressive external ophthalmoplegia: specific diagnostic findings. J aapos. 2006;10(5):414–8.
15. Mitochondrial Medicine Society's Committee on D, Haas RH, Parikh S, et al. The in-depth evaluation of suspected mitochondrial disease. Mol Genet Metab. 2008;94(1):16–37.
16. Pfeffer G, Chinnery PF. Diagnosis and treatment of mitochondrial myopathies. Ann Med. 2013;45(1):4-16.
17. Milone M, Wong LJ. Diagnosis of mitochondrial myopathies. Mol Genet Metab. 2013;110(1–2):35–41.
18. Sundaram C, Meena sAK, Uppin MS, et al. Contribution of muscle biopsy and genetics to the diagnosis of chronic progressive external opthalmoplegia of mitochondrial origin. J Clin Neurosci. 2011;18(4):535–8.