Case Report

Chronic progressive external ophthalmoplegia plus

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Abstract

Chronic progressive external ophthalmoplegia (CPEO) is an uncommon mitochondrial myopathy that advances gradually, characterized by ophthalmoplegia and ptosis. CPEO can emerge as an isolated condition or as part of a syndrome involving additional neurological impairments, termed CPEO plus (CPEO+). CPEO+ requires comprehensive evaluation, where a multidisciplinary approach, encompassing neurological assessments of both central and peripheral systems, along with examinations of musculoskeletal and cardiac functions is recommended. Essential diagnostic tools include muscle biopsy, biochemical analysis of muscles, neuroradiological or orbital computed tomography/magnetic resonance imaging evaluation, and molecular genetic testing. Due to the scarcity of diagnostic facilities in sub-Saharan Africa, including Tanzania, diagnosis of CPEO+ is delayed leading to patient suffering, however, its management remains intricate and noncurative. This article presents a rare case study of a 23-year-old male. He exhibits clinical, histological, and radiological characteristics consistent with CPEO+.

Keywords: Blepharoptosis, chronic progressive external ophthalmoplegia plus, extraocular muscles, magnetic resonance imaging, mitochondrial disease, ptosis

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INTRODUCTION

Mitochondrial diseases result from damage to the electron transport chain within cell mitochondria. Diseases can vary from isolated muscle-related disorders to more comprehensive multisystem disorders. Primarily affecting the eyes, skeletal muscles, and the nervous system.[1-3] Chronic progressive external ophthalmoplegia (CPEO) is a slowly advancing hereditary disease of extra-ocular muscles. It is the most prevalent form of mitochondrial myopathy. CPEO is rare, with around one to three cases per 100,000 people in the general population.[4]

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CPEO plus (CPEO+) is an extremely rare variant of CPEO, which includes additional features of neurological deficits. It typically emerges in the third or fourth decade of life, but it can affect anyone of any age or gender equally.[3,5]

CASE REPORT

Case history

A 23-year-old male petty trader presented with gradually progressing painless left eyelid drooping (ptosis) [Figure 1] and bilateral limb weakness. Weakness is more pronounced on the left, persisting for 9 months. Left eyelid droop correlated with double vision and impaired ocular

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movement, prompting compensatory head tilting. There was no history of headaches, seizures, head, or eye trauma. The review of systems, along with the medical and family history, is unremarkable.

Physical examination

The patient had a stable clinical status. Evident left eyelid ptosis with normal pupillary functions. There was no enophthalmos. Cognitive functions were intact. Cranial nerve assessments highlighted left superior rectus ophthalmoplegia demonstrated by poor upward gaze in the left eye [Figure 2]. Motor examination revealed bilateral limb weakness, more pronounced on the left side. Abnormal Trendelenburg gait was noted. Other systems were essentially normal.

Investigations

Electromyography was done and indicated myogenic pathology in sampled limb muscle groups. Nerve conduction tests showed mild multiple mononeuropathies in bilateral upper and lower limbs. Skeletal muscle biopsy revealed focal degeneration and minimal lymphocytes/eosinophils indicative of myopathy [Figure 3]. Other tests (ophthalmoscopy, electrocardiogram, echocardiogram, and blood and urine workout) were unremarkable.

Figure 1: A 23-year-old male with chronic progressive external ophthalmoplegia plus presenting with ptosis of the left eyelid seen during the physical examination

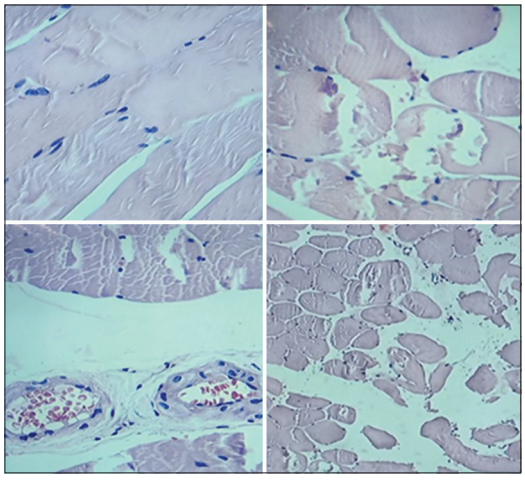

Figure 3: Biopsy of a skeletal muscle sample of a 23-year-old male with chronic progressive external ophthalmoplegia plus. Shows, focal area of degeneration and very scant lymphocytes and eosinophil suggestive of myopathy

Imaging findings

Magnetic resonance imaging (MRI) of the orbits was done and revealed atrophy of the left superior rectus

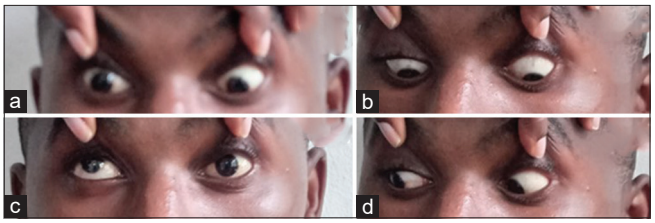

Figure 2: Eyes movement test of a 23-year-old male with chronic progressive external ophthalmoplegia plus. Marked limitation of maintenance of left eye horizontal gaze (a). Limited eye movement in upward gaze of the left eye (c). Normal horizontal and upward gaze of the right eye (a and c). Normal downward, and oblique movements of both eyes were noted (b and d)

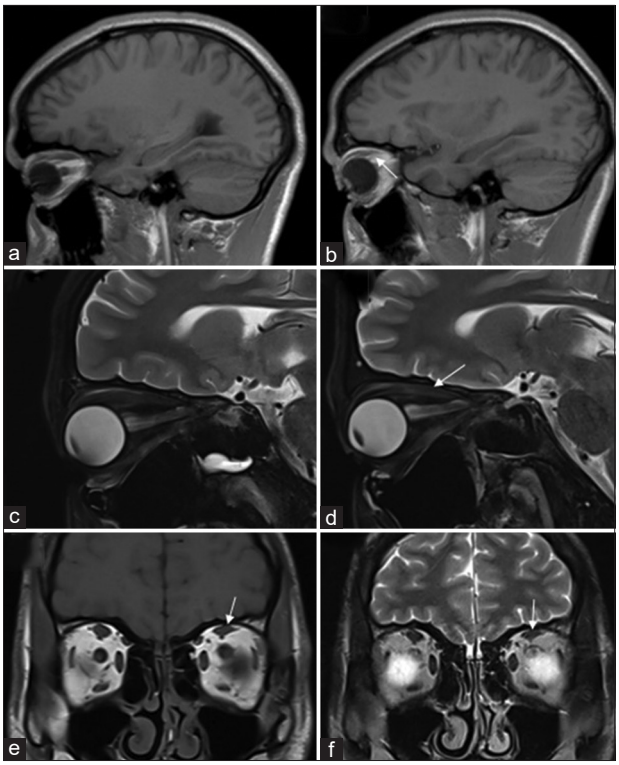

Figure 4: Magnetic resonance imaging images of orbits of a 23-year-old male with chronic progressive external ophthalmoplegia plus: (a), Right orbit, T1W1 contrasted sagittal plane. (b) Left orbit T1W1 contrasted sagittal plane. (c) Right orbit, T2WI FAT SAT, sagittal plane. (d): Left orbit, T2WI, FAT SAT, sagittal plane. (e), T1W1 noncontrasted, coronal plane. (f) T2WI coronal plane. Findings: Asymmetrical thinning and reduced muscle volume of the left superior rectus muscle (white arrows) compared to the right side. Areas of the left superior rectus with increased T2W FAT SAT signal intensity are also noted. No abnormal enhancement was present. Bilateral globes were normal in size. Lens were standard in position. No mass lesion was noted within orbits. Bilateral retina and optic nerves were normal along their course

muscle [Figure 4]. Atrophy is evident by asymmetrical thinning and decreased muscle volume of left superior rectus muscle [Figure 4b-f] compared to the right side [Figure 4a-f]. Areas of the left superior rectus with increased T2W Fat Saturation (FAT-SAT) signal intensity are also noted [Figure 4d]. No abnormal enhancement was present.

Brain MRI also showed non-enhancing, multifocal sub-centimeter T2W and fluid-attenuated inversion recovery (FLAIR) hyperintense lesions in the subcortical and deep white matter of bifrontal and right insular lobes as well as the right basal ganglia. No abnormal diffusion [Figure 5a-k]. The impression of nonspecific white matter lesions was reached, which may be interpreted as "unidentified bright objects" (UBOs).

A total spine MRI was done to rule out spinal canal pathology that could result in abnormal gait and upper or lower limb weakness. The results showed features of cervical muscle spasms without any other significant findings [Figure 6].

DISCUSSION

CPEO is a slowly advancing hereditary disorder of extraocular muscles, representing the most common form of mitochondrial myopathies.[4] CPEO can emerge on its own or present as a syndrome accompanied by additional neurological impairments. CPEO concomitant with neurological deficits is termed CPEO+. CPEO+ is exceptionally rare, often appearing in the third or fourth decade, but can affect any age or gender.[3,5] In this case, a 23-year-old male lacking familial genetic link, highlights its sporadic occurrence.

CPEO+ is mostly identified by ophthalmoplegia (abnormal eye movements), caused by the paralysis of one or more of the six extraocular muscles. Ophthalmoplegia often leads to double vision (diplopia).

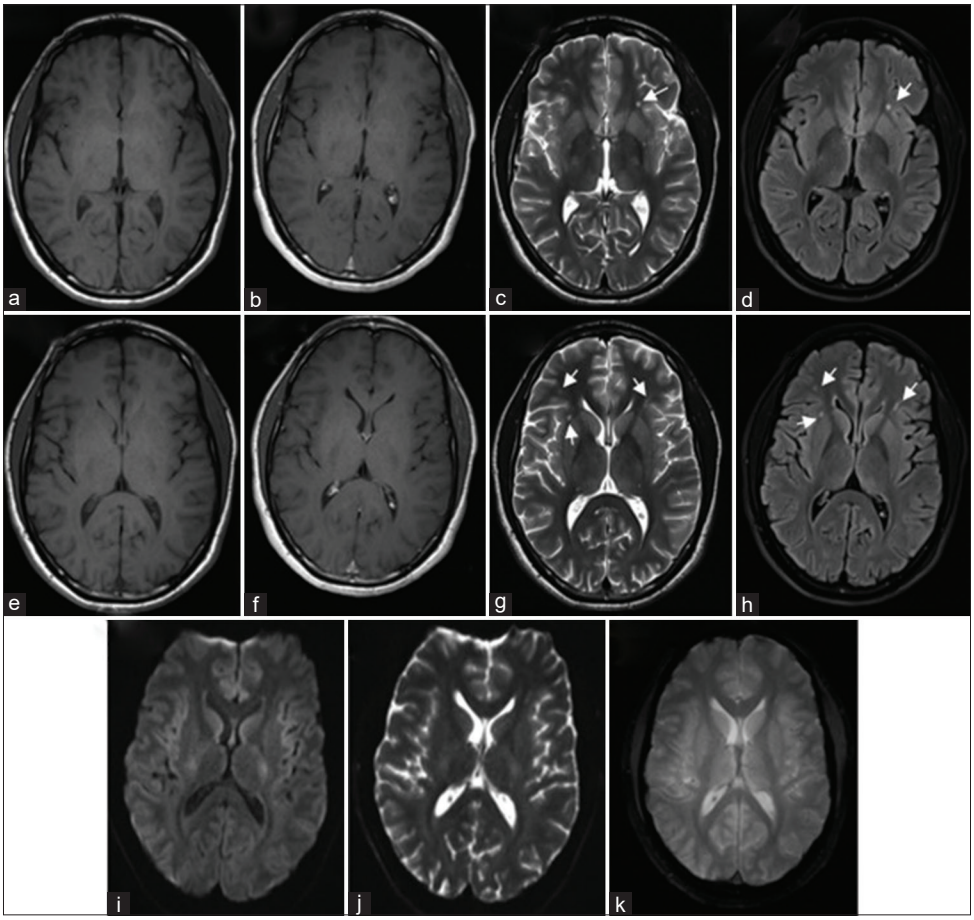

Figure 5: Magnetic resonance imaging images of the brain of a 23-year-old male with chronic progressive external ophthalmoplegia plus. All are axial planes: (a and e) T1WI noncontrasted, (b and f) T1WI postcontrast, (c and g) T2WI, (d and h) Fluid-attenuated inversion recovery (FLAIR), (i) Diffusion-weighted imaging (DWI), (j) Apparent diffusion coefficient (ADC) and (k) Enhanced susceptibility weighted imaging (eSWAN). Findings: Presence of asymmetrical multifocal sub-centimeter lesions of high-signal intensity on the T2W/FLAIR images in subcortical and deep white matter of bilateral frontal lobes and right insula cortex (white arrows). On T1WI lesions are isointense to white matter without enhancement following contrast administration. No abnormal diffusion on DWI/ADC. And no blooming artifacts on eSWAN. Lesions can be described as "unidentified bright objects." No definite lesions are seen in the basal ganglia or thalami. Ventricular system, cisterns, sulci, and other structures were unremarkable

Figure 6: A 23-year-old male with chronic progressive external ophthalmoplegia plus. Findings: There is a loss of normal cervical lordosis. The brainstem, spinal cord, vertebral height, disc height, alignment, and bone marrow signal are within normal limits. The canal and neural exit foramina are capacious at all levels. The conus terminates at the T12/L1 level and is normal in appearance. Techniques: Total spine magnetic resonance imaging images, all are sagittal planes: (a) T1W noncontrasted, (b) T2W, and (c) Short tau inversion recovery

In addition, it involves bilateral, often symmetrical ptosis (drooping of eyelid).[6] This specific case notes the left ophthalmoplegia alongside ipsilateral ptosis. Other common features of CPEO+ encompass retinal pigment changes, hearing loss, balance problems, fatigue, muscle weakness, nerve damage, and cognitive decline. [1] In comparison, our index case displays symptoms such as bilateral limb weakness (proximal-dominant) and abnormal gait, strongly supporting a diagnosis of CPEO+.

Diagnosing CPEO+ involves nervous (central and peripheral) systems, musculoskeletal, and cardiac and ophthalmological assessments.[7] Ocular tests cover visual acuity, peripheral vision, eye movement, fundoscopy, and electroretinography.[7] In our case, ophthalmological assessments revealed left-sided superior rectus ophthalmoplegia. Fundoscopy and optical coherence tomography (OCT) were essentially normal. Examinations of the nervous and musculoskeletal system detected abnormal (Trendelenburg) gait and limb paraesthesia. Cardiac assessment was unremarkable.

A notable laboratory marker for mitochondrial diseases such as CPEO is an elevated serum lactate level, though it is not consistently present.[7,8] This case did not undergo lactate-level testing. Muscle biopsy is another crucial histological approach for mitochondrial myopathy, which typically displays "ragged-red" fibers using the Gomori trichrome stain. This histopathological morphology indicates abnormal mitochondrial accumulation under the muscle cell membrane.[7,8] Despite being confirmed in this case, the histological findings alone does not definitively signify a mitochondrial disorder. Molecular genetic testing might confirm the diagnosis of mitochondrial disease by detecting different mutations in mitochondrial DNA.[7-9] Genetic testing was not pursued due to the patient's financial constraints.

Imaging findings

Orbital computed tomography and MRI of individuals with CPEO+ demonstrate varying degrees of mild-to-moderate atrophy in one or more extraocular muscles. Volume reduction of extraocular muscles by 25%–60% when compared to individuals without the CPEO+ is a common finding.[10] Typically, these findings should be symmetrical and manifest bilaterally. Some affected individuals may display abnormalities in the signal of extraocular muscles, including increased T1 signal intensity and, on rare occasions, increased signal on short tau inversion recovery images.[10,11] In our case, orbital MRI revealed atrophy and T2W FAT-SAT hyperintensity in the left superior rectus muscle.

Furthermore, brain MRI scans of patients with CPEO+ might reveal symmetrically or asymmetrically leukoencephalopathy (temporal or occipital predominantly) and basal ganglia calcifications.[12] As evidence in our case, the presence of nonenhancing subcortical and deep white matter lesions in the right insular cortex and both frontal lobes. The lesions can be described as "UBO."

Differential diagnoses

Possible alternative diagnoses for CPEO+ encompass various primary mitochondrial disorders, commonly Kearns–Sayre syndrome. Other differentials are myasthenia gravis and polymyositis.[13]

Treatment and prognosis

Currently, no definitive cure exists for CPEO+. Emphasis is on education, genetic counseling, symptom management, and supportive care. Medical treatment by coenzyme Q, vitamin supplements creatine monohydrate, and ketogenic diet may be initiated, but lacks scientific confirmation. Fresnel prisms can aid to correct diplopia, while surgical intervention of affected extraocular muscles should be cautious due to disease progression.[1,14,15] Addressing ptosis involves surgical correction and eyelid taping.[14,15] In our case, the patient currently receives only education and supportive care for neurological deficits without improving on follow-up.

CONCLUSION

CPEO+ is an exceptionally rare hereditary condition. For developing countries such as Tanzania, its rarity poses several challenges leading to delays in diagnosis and appropriate management, adversely affecting patient outcomes. Challenges include nonspecific overlapping symptoms, limited number of specialized health expertise, lack of readily availability of advanced diagnostic facilities (for instance genetic testing and MRI), patients' financial constraints, lack of established treatment protocols, and limited treatment options.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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