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SHORT REPORT

A Family With Chronic Progressive External Ophthalmoplegia

A. Filiz KOÇ[1], Suzan ZORLUDEMİR[2], Hacer BOZDEMİR[1]
[1]Department of Neurology, Faculty of Medicine, Çukurova University, Adana - Turkey
[2]Department of Pathology, Faculty of Medicine, Çukurova University, Adana - Turkey

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The mitochondrion is a cellular organelle of energy production by multiple biochemical reactions (1-4). Mitochondrial disorders are heterogeneous based on biochemical abnormalities, patterns of genetic inheritance, and clinical phenotypes. Neurological syndromes are the most frequent presentations of mitochondrial disorders, since the brain and muscles are the organs with the highest aerobic energy needs (1,2,5).

Chronic progressive external ophthalmolplegia (CPEO) is primarily caused by multiple mitochondrial DNA (mtDNA) deletions. The most frequently seen one is common deletion, which is defined by accumulation of truncated mtDNA molecules (delta-mtDNA) lacking a specific 4977-bp fragment. This deletion leads to Pearson's syndrome, Kearn-Sayre syndrome and CPEO (6). Besides mtDNA deletions, point mutations may cause CPEO. Mendelian inheritance autosomal dominant and recessive may be seen in this disease (7-9). Some sporadic cases have been reported in the literature (10).

The onset of CPEO is at any time between the first and seventh decade. The clinical course is slowly progressive. In these patients, conjugate gazes in all directions are limited and slow. These findings are accompanied by bilateral ptosis without diplopia and pain. Furthermore, symptoms due to the involvement of other neuroanatomic structures such as the bulbus (e.g., dysarthria, dysphagia, dysphonia) and the extrapyramidal system (e.g., dystonia, tremor, rigidity) may be seen. Additionally, dementia, sensorineural deafness, degenerative stigmata, and endocrinopathies may be found.

Case

A 53-year-old male presented with drooping of the eyelids starting 30-35 years before. Its course was slowly progressive. He had no diplopia, and pain in his eyes. Weakness in facial and skeletal muscles was absent. In his past history, there were type II diabetes mellitus (DM) for 5 years and blurred vision due to glaucoma for 2 years. He had been taking medicines for DM and glaucoma since then. His parents were non consanguineous. His father and brother had similar clinical features as shown in his pedigree (Figure 1).

In the neurological examination, atherosclerotic changes in the retinal vessels, traumatic anisocoria (right > left), asymmetric ptosis (right > left), partial

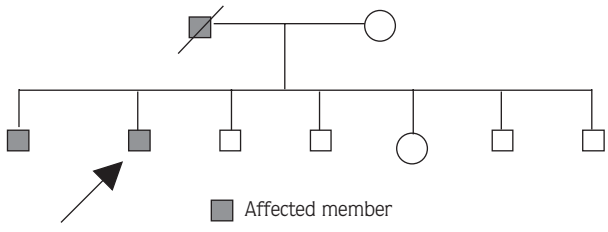

Figure 1. Pedigree

opthalmoplegia (gaze limited in all directions by 85-90%) (Figure 2), and hypoactive deep tendon reflexes were seen.

Routine hematological screening, including serum creatine phosphokinase (CPK), liver function tests, lactic/pyruvic acid levels, and thyroid function tests was normal except for fasting blood glucose, which was mildly elevated (148 mg/dl, normal range: 70-110 mg/dl). Electrocardiography (ECG) and echocardiography (EchoCG) were normal. Electromyography (EMG) displayed myopathic changes in orbicularis oculi and frontal muscles bilaterally, but was normal in extremity muscles. A muscle biopsy from the right biceps revealed ragged red fibers (RRFs) with a modified Gomori trichrome stain (Figure 3). The electronmicrographic examination showed subsarcolemmal mitochondrial aggregates, increased and distended mitochondria, giant abnormal mitochondria, paracrystalline inclusions and osmophilic and electrodense structures (Figure 4). The common deletion was positive in mtDNA.

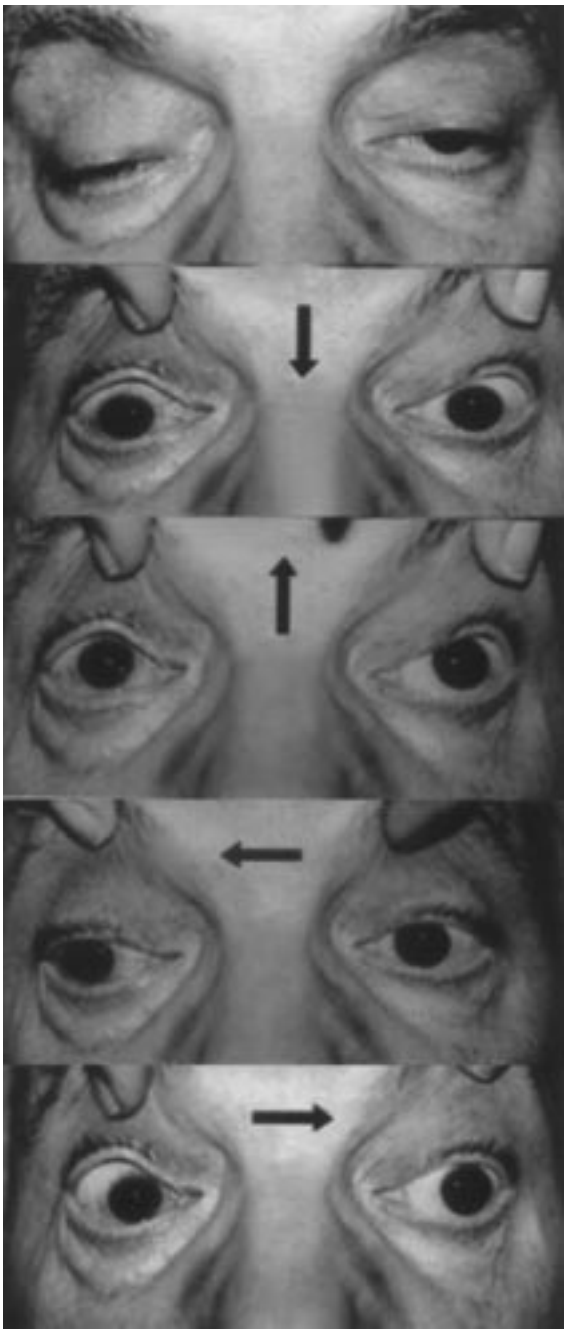

Figure 2. Conjugate eye movements (partial opthalmoplegia).

With all these findings, a CPEO diagnosis was made in our case. We also thought the same disease was in 2 affected members of the family after taking their history and examining their pictures.

Neuromuscular disorders due to mitochondrial diseases are quite rare and CPEO is one subgroup of this large group (11). Most patients have mtDNA deletions, although some have point mutations (12). Clinical findings may start between the first and seventh decade. Eyes are affected in all cases but diplopia and strabismus are rarely seen (13). Ophthalmoplegia may often be accompanied by weakness in proximal muscle groups. If muscle weakness is severe, muscle atrophy may occur. Patients may also complain of cramps and muscle pains. Additionally, facial diplegia, dysphagia, dysphonia, and dysarthric speech may be seen in this clinical picture. Respiratory failure can develop in some cases as a result of respiratory muscles' involvement. For this reason, these patients are susceptible to anesthetic complications; therefore, physicians should be careful during general anesthesia (14).

Spinocerebellar and dorsal column degenerations and ataxic gait rarely occur due to sensorial polyneuropathy. Findings of extrapyramidal syndrome may be observed especially in autosomal recessively inherited cases. Mental changes, cardiomyopathy, rhabdomyolysis, sensorineural deafness, cataracts and endocrinopathies (e.g., DM, hypogonadism) are relatively rare conditions (15). Psychiatric problems such as depression and characteristics of avoidant personality disorder may also be seen. In laboratory examinations, serum CPK and lactic acid may be normal or elevated. RRFs are seen in muscle biopsy (16-20). MtDNA deletions and point mutations are demonstrated in CPEO. The common deletion, which

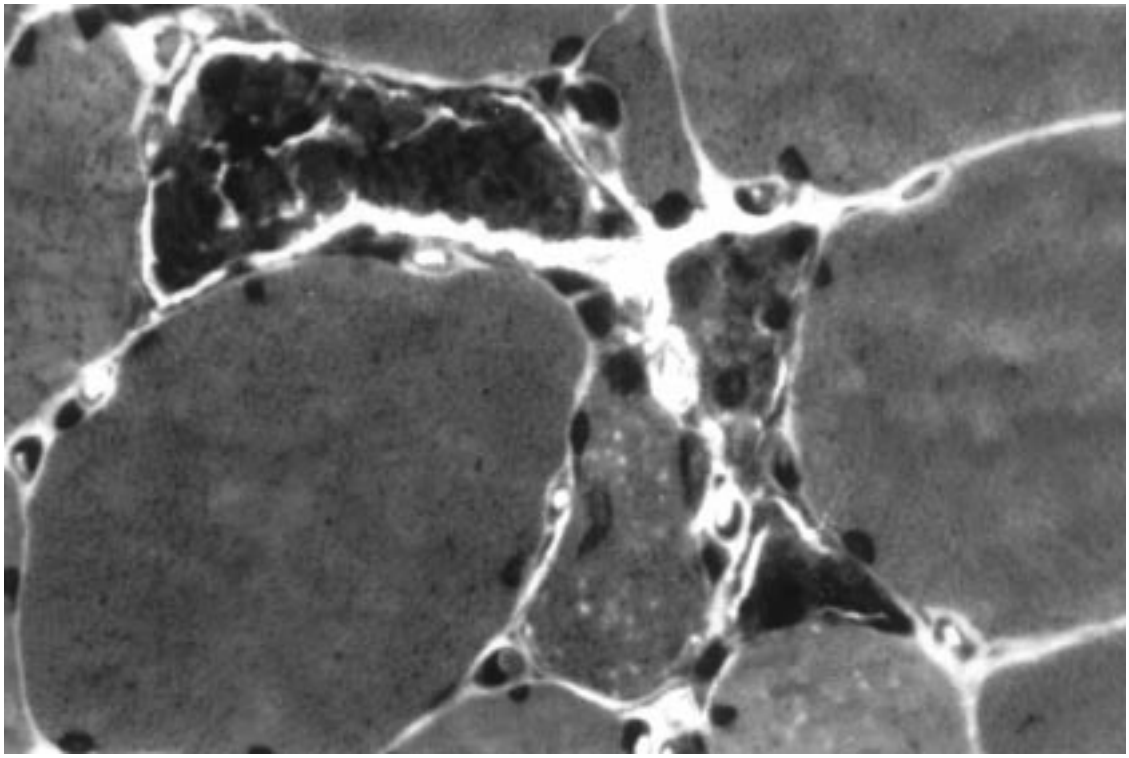

Figure 3. Ragged red fibers in modified Gomori trichrome stain.

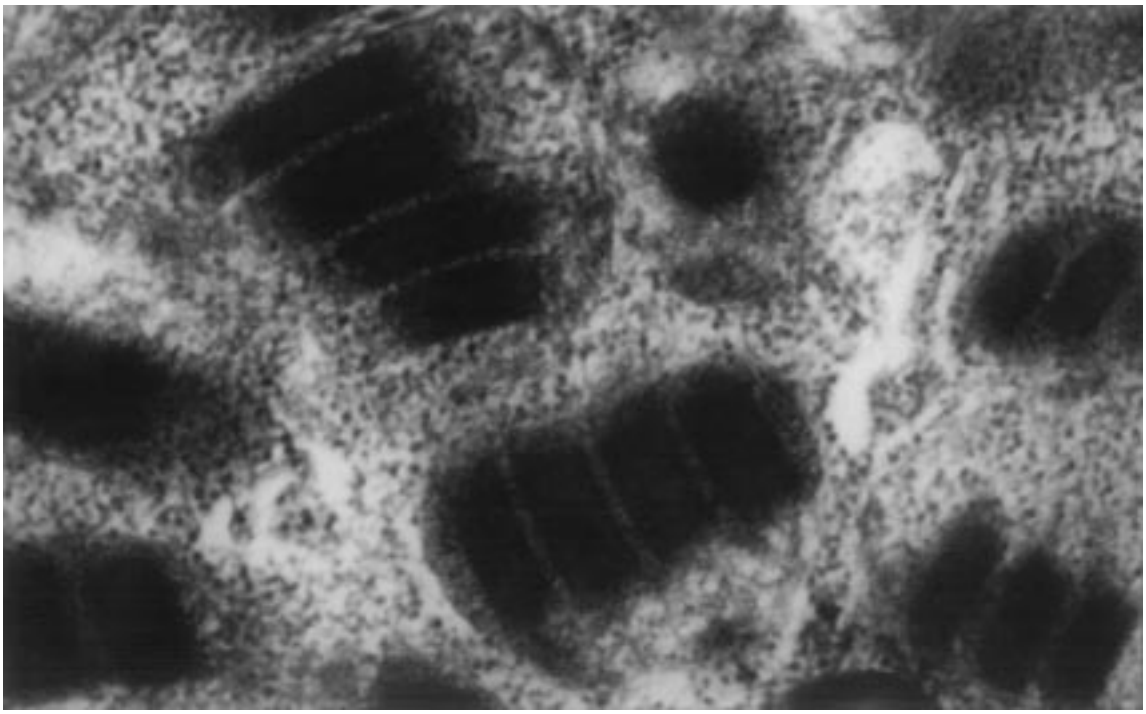

Figure 4. Mitochondrial paracrystalline inclusions, osmophilic inclusions and electrodense structures in electron micrograph (x 40,000)

lacks a specific 4977-bp, is the mostly commonly seen one. As a result, truncated mtDNA (delta-mtDNA) molecules accumulate. This affects genes encoding polypeptide components of the mitochondrial respiratory chain, 5 of the 22 tRNAs neccessary for mitochondrial protein synthesis (6).

In our case, type II diabetes mellitus and glaucoma were associated with the picture of ophthalmoplegia and no signs of facial and skeletal muscles' involvement were found clinically and electrophysiologically. RRFs were seen in the muscle biopsy by modified Gomori trichrome stain. In the electron micrographic examination, there were subsarcolemmal mitochondrial aggregates, increased and distended mitochondria, giant abnormal mitochondria, paracrystalline inclusions, and osmophilic and electrodense structures (Figure 4). The common deletion was positive.

The genetic inheritance pattern in mitochondrial diseases is similar to that of autosomal dominant. This is also true for our family. In the pedigree, there were 2 affected members whose clinical symptoms were similar to those of the proband, namely the father and brother. His parents were unconsanguineous. The father, who had died, and the brother, who was living far away, could not be evaluated. Based on both the family history taken from the patient and family pictures, we thought a diagnosis of CPEO was appropriate for his father and brother 3 years older. He reported that his father and elder brother had had similar problems with the eyes. These complaints had started after the third decade and they had had similar slowly progressive clinical courses. However, no history of either DM or glaucoma could be obtained.

In this paper, a family whose diagnosis was confirmed as CPEO based on clinical, histopathological, and genetic characteristics was presented.

Corresponding author:

A. Filiz KOÇ

Çukurova University School of Medicine,

Department of Neurology,

Adana - Turkey

e-mail:zaferkoc@superonline.com

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