CHRONIC PROGRESSIVE EXTERNAL OPHTALMOPLEGIA (CPEO) – CASE PRESENTATION

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ABSTRACT

We present the case of a patient aged 38 years with Chronic Progressive External Ophtalmoplegia (CPEO), a slowly progressive myopathy primarily involving and often limited to the extraocular muscles. Medical history, clinical examination and laboratory studies are revealed. The implicated gene mutations and differential diagnosis are approached.

Keywords: chronic Progressive External Ophtalmoplegia, mitochondrial DNA, Kearns-Sayre syndrome

INTRODUCTION

Chronic Progressive External Ophthalmoplegia (CPEO) is a slowly progressive myopathy primarily involving and often limited to the extraocular muscles. CPEO was described in 1868 by Von Graefe. Initially, it was believed to represent neuronal degeneration, but muscle biopsies have supported a myopathic origin. Males and females are equally affected. Ptosis begining in childhood, and sometimes in adolescence, is followed by ophtalmoparesis. 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. Imaging studies show thin symmetrical extraocular muscles. Muscle biopsy is still the definitive test for diagnosis. Polymerase chain reaction (PCR) has been shown to be also conclusive.

CASE REPORT

A woman aged 36 years with onset of the disease in childhood with left palpebral ptosis (six year old – Fig. 1) was admitted in our department. Her medical history include progressive course of left eyelid ptosis since childhood. Because an abnormal somatic development was admitted at endocrinology clinic for more investigations (9 years old). Insidiously, right eyelid ptosis was installed too, later on she revealed external ophthalmoplegia.

Ten years later, the left eye was deviated to the left, with divergent strabismus and limitations of extraocular movements with relative sparing of downgaze. Neurologic examination revealed moderate bilateral ptosis and marked limitation of conjugate gaze in all directions (Fig. 2). Nystagmus was absent. Her visual acuity and field were normal. Neither retinal pigmentary degeneration nor optic atrophy was found. Pupils were round and regular, equal in size, and promptly reacted to light. Because very slowly progression, diplopia was not noticed. Other neurological examination was unremarkable. Laboratory studies revealed normal blood counts, serum electrolytes, thyroid and liver functions. Serum levels of prolactin and growth hormone were normal.

Tumor markers, antinuclear antibody, and cryoglobulin were normal. The study of serum acetyl-

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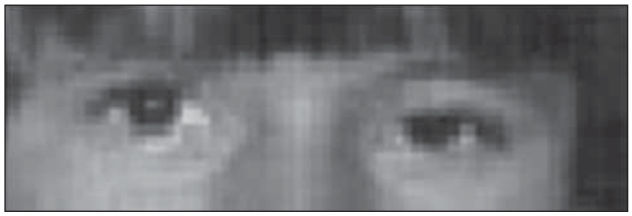

FIGURE 1

FIGURE 2

choline receptor antibody was negative. Neostigmin test for myasthenia gravis was negative. The CSF was under normal pressure, without cells, and with 48 mg of protein per deciliter. Brain and orbits CT scans emphasize different degree of extraocular muscles atrophy (Table 1).

TABLE 1

Extraocular muscles	Year 2007	Year 2010
Muscles	Measurements 2007	Measurements 2010
Medial rectus right eye (RE)	2.2 mm	1.8 mm
Medial rectus left eye (LE)	2.5 mm	2.0 mm
Lateral rectus RE	1.5 mm	1.9 mm
Lateral rectus LE	1.2 mm	1.3 mm
Inferior rectus RE	1.8 mm	–
Inferior rectus LE	2.0 mm	–
Superior rectus RE	2.0 mm	2.0 mm
Superior rectus LE	2.2 mm	2.1 mm

EEG and nerve conduction velocity tests were within normal limits. EMG showed normal motor units without spontaneous activities. The electrocardiogram showed a sinus rhythm and transthoracic echocardiography demonstrated a normal left ventricular chamber size and contractility. No muscle histopathology studies and neither molecular genetic analysis were done. We performed ophthalmology exam, pulmonary respiratory tests, with good results.

DISCUSSIONS

An ocular myositis was ruled out because of lack of painful eyes. We have not historical or objective data for others causes of ocular myopathies like: thyroid associated ophthalmopathy, ocular myasthenia gravis, Tolosa-Hunt syndrome, oculopharyngeaal muscular dystrophy, myotonic dystrophy type I, or congenital cranial dysinnervation disordesrs of extraocular muscles. Kearns-Sayre syndrome, was ruled out because of lack of pigmentary retinopathy. We conclude that our patient have a CPEO.

This entity is caracterised by slowly ptosis and weakness of extraocular muscles with limitation of ocular movement months to years later. The onset is in childhood, but olders can be affected too (range between 11-82 years). Rarely transient diplopia may occur, and ptosis is often asymmetric. CPEO is the most frequent manifestation of mitochondrial myopathies (1).

Extraocular muscle have smaller motor unit sizes, higher motor neuron discharge rate, higher blood flow, and higher mitochondrial volume fractions compared with skeletal muscle. They are especially dependent on oxidative phosphorylation for energy. Histochemical analysis of the orbicularis oculi muscle revealed pathological hallmarks with ragged red fibres and isolated clusters of cytochrome c oxidase (COX)-deficient fibres (2). Mutations in mtDNA can exist as point mutations, duplications, deletions or depletions. Some mtDNA mutations are the result of nuclear DNA mutations. CPEO can be classified into two distinct genetic subgroups depending on whether patients harbour single, large-scale mitochondrial DNA (mtDNA) deletions or multiple mtDNA deletions secondary to a nuclear mutation disrupting mtDNA replication or repair. TWINKLE gene mutations results in multiple mtDNA deletions (if heterozygous) and mtDNA depletions (if homozygous) while DNA polymerase gamma (POLG) mutations cause multiple mtDNA deletions and depletions (3,4,5).

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 caused by nerve damage in the inner ear, neuropathy, ataxia, parkinsonism, or depression.

A variable decrease in N-acetyl-aspartate (NAA) has previously been reported in the brain of patients with the Kearns-Sayre syndrome – a particularly severe clinical phenotype characterised by the development of CPEO and pigmentary retinopathy before the age of twenty years, often in association with progressive cardiac conduction block.

Patients with CPEO did not have significantly reduced brainstem volumes compared with controls and no brainstem metabolite abnormalities were detected with proton MRS. We could find white

matter lesions and cortical atrophy (6). A significant reduction of extraocular muscle size was seen in CPEO patients. Patients with CPEO-plus had significantly reduced total grey matter and cerebellar volumes compared with controls.

CONCLUSIONS

Mitochondrial myopathy, chronic progressive external ophthalmoplegia (CPEO), CPEO-plus, and the Kearns-Sayre syndrome are caused by mutations of mitochondrial DNA and probably reflect a clinical continuum.

CPEO can occur as an isolated phenomenon of ophthalmoplegia or as a variable constellation of associated disorders (skeletal muscle myopathy, cardiac and ophthalmic disease, hyperacusis and deafness, peripheral neuropathy, pyramidal, extrapyramidal, and cerebellar signs and symptoms, endocrine and other systemic disease and dementia. Progressive external ophthalmoplegia is a striking but nonspecific clinical sign that occurs in a variety of disease states such as myasthenia gravis, thyrotoxicosis, Guillain-Barre syndrome, Refsum's disease. Approximately 1500 nuclear genes can affect mitochondrial structure and function and the targeting of such genes may be necessary to reach the diagnosis. The identification of causative molecular defects in nuclear or mitochondrial genome leads to the definite diagnosis of mitochondrial myopathy (7).An analytical clinical study must be performed in this cases for an accurate diagnosis.

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