Mitochondrial Ophthalmoplegia With Fatigable Weakness and Elevated Acetylcholine Receptor Antibody

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Abstract: A 25-year-old man with chronically progressive ptosis and bilateral ophthalmoplegia displayed fatigability and fluctuation of ptosis, an abnormal single-fiber electromyogram, and a markedly elevated acetylcholine receptor antibody level. Yet a muscle biopsy showed clear evidence of a mitochondrial cytopathy, and the clinical features did not improve after treatment with prednisone. This case emphasizes the difficulty in differentiating mitochondrial cytopathy from myasthenia gravis and points out that elevated acetylcholine receptor antibody levels may occur in nonmyasthenic conditions.


Chronic progressive external ophthalmoplegia (CPEO) and ptosis are common manifestations of mitochondrial cytopathy. However, these features can also occur in myasthenia gravis, Graves disease, and brainstem lesions. Distinguishing ophthalmoplegia due to mitochondrial cytopathy from these other conditions, particularly ocular myasthenia gravis, can be difficult. We present a case of CPEO due to mitochondrial cytopathy with a diagnostically misleading combination of fatigability and an elevated acetylcholine receptor antibody level.

CASE REPORT

A 25-year-old man presented with progressive bilateral ptosis for 6 years. He denied double vision, difficulty breathing or swallowing, or other symptoms of muscle weakness. He reported that his ptosis improved with sleep and rest and with “rubbing his eyes and then blinking quickly.” He had had decreased vision in the left eye since childhood. He was otherwise in good health and using no medications. His family history was negative for myasthenia gravis.

Visual acuity was 20/30 in the right eye and 20/400 in the left eye. He recognized all of the pseudoisochromatic color plates with the right eye but none with the left eye. The pupils were of normal size and equally reactive to light with no relative afferent defect. Intraocular pressures were 12 mm Hg in both eyes. Bilateral ptosis was present, which was fatigable on sustained up gaze (Fig. 1A). The degree of ptosis varied during the examination; blinking reduced it for 1–2 minutes (Fig. 1B). There was moderate orbicularis oculi weakness on attempted forced eyelid closure bilaterally. Ocular ductions were reduced in all gaze directions (Fig. 2). He had a comitant left exotropia of 10 prism-diopters (PD) and right hypertropia of 16 PD in upgaze and 14 PD in downgaze. Dilated fundus examination was normal. Automated perimetry was normal in the right eye and showed a central scotoma in the left eye.

MRI of the brain and orbit was normal. The acetylcholine receptor antibody level was markedly elevated at 16.7 nmol/L (normal <0.2 nmol/L). Repetitive nerve stimulation electromyography (EMG) was normal. However, single-fiber EMG of the orbicularis oculi showed a mean value of consecutive differences (MCD) of 53.1 μs, 3/22 blocks, and 12/22 abnormal end plates. These findings were interpreted as indicating a neuromuscular transmission defect. CT scanning of the upper mediastinum did not identify any thymic masses. Needle EMG of the deltoid and the orbicularis oris muscles showed some polyphasic potentials, considered a myopathic pattern. An electroretinogram (ERG) showed low amplitude photopic and scotopic responses and a diminished response to a 30 Hz flicker in both eyes.

The patient was treated with 60 mg pyridostigmine three times per day and 10 mg prednisone every other day for 2 weeks, which was then increased to 40 mg daily for 4 weeks. This treatment did not lead to objective improvement in either the ptosis or ocular motility abnormality.
Electron microscopical examination of a deltoid muscle biopsy showed widespread subsarcolemmal and sarcoplasmic deposition of lipid droplets and vacuolar degeneration in some muscle spindles. These changes were interpreted as indicating a myopathy with dystrophic features. Histopathologic and electron microscopical examination of an orbicularis oculi specimen showed focal myofibrillary degeneration with associated loss of the Z-discs and I-bands. The main abnormality was in the mitochondria, which showed subsarcolemmal and sarcoplasmic aggregation in large numbers. There was variation in the size and shape of the mitochondria with distortion of cristae, the latter assuming a “fingerprint” pattern in many areas. These findings were interpreted as being consistent with a mitochondria cytopathy (Fig. 3).

The patient was followed for 2 weeks after the surgery. Eventually he discontinued all medications as they appeared to be ineffective. He was then lost to follow-up.

DISCUSSION

We present a diagnostically confusing case of ophthalmoplegia and ptosis due to mitochondrial cytopathy with concurrent features of myasthenia, namely fatigable and fluctuating ptosis and high acetylcholine receptor antibody levels. There were many features suggestive of mitochondrial cytopathy, such as a long-standing course of ptosis, initial absence of diplopia, cone-rod dysfunction, and a lack of response to corticosteroid treatment. Although our patient’s ERG was consistent with cone-rod dysfunction, he did not have the pigmentary retinal findings seen in...
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FIG. 3. Orbicularis oculi biopsy. A. Electron micrograph (10,000×) shows subsarcolemmal and sarcoplasmic aggregation of mitochondria of different shapes and sizes (arrowhead). B. Magnification (30,000×) shows an aggregate of distended mitochondria with complex cristae in a "fingerprint" pattern. These findings are consistent with mitochondrial cytopathy.

Kearns-Sayre syndrome. The degree of retinal dysfunction was unusually asymmetric but supportive of the diagnosis of mitochondrial cytopathy. He eventually developed diplopia and exotropia, but this has been reported in mitochondrial cytopathy (1).

In our patient, the abnormal single-fiber EMG further suggested a diagnosis of myasthenia gravis. However, it should be emphasized that although single-fiber EMG is a very sensitive test for myasthenia gravis, it is not specific for that condition (2,3). Increased jitter and/or blocking have been reported in mitochondrial cytopathy (4,5). It has been postulated that a primary defect in neuromuscular transmission may be present in mitochondrial cytopathy (4).

Perhaps the most diagnostically confusing feature of our patient is the presence of a markedly elevated acetylcholine receptor antibody level. It is unclear whether this elevation represents an epiphenomenon or whether he has mitochondrial cytopathy and myasthenia gravis. A trial of pyridostigmine and corticosteroids did not produce any significant therapeutic effect. Suzuki et al (6) reported a 59-year-old patient with mitochondrial diabetes, facial palsy, ophthalmoplegia, and hearing loss in association with mildly elevated acetylcholine receptor antibodies. The patient had negative results for repetitive nerve stimulation and a negative edrophonium chloride (Tensilon) test. The acetylcholine receptor antibody level in this patient was only marginally elevated at 0.6 nmol/L (normal is <0.2 nmol/L). Mitsikostas et al (7) reported an elevated acetylcholine receptor antibody titer in two elderly women with external ophthalmoplegia, elevated lactic acid, and ragged red fibers. Elevated acetylcholine receptor antibody levels can also be detected in autoimmune conditions such as primary biliary cirrhosis, Eaton Lambert syndrome, and Graves ophthalmopathy (8-12). Jacobson et al (8) found that 4 of 50 (8%) consecutive patients with Graves ophthalmopathy had elevated acetylcholine receptor antibodies. No obvious differences existed between the seropositive and seronegative groups. None of the four seropositive patients developed signs of myasthenia gravis during the median follow-up period of 4.5 years. It is possible in our patient that the very high acetylcholine receptor antibody level is caused by mitochondrial damage in the skeletal muscles triggered by an autoimmune response to the acetylcholine receptor, or that he has an autoimmune condition that we did not recognize.

REFERENCES