Tetracycline delays ocular motility decline in chronic progressive external ophthalmoplegia

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Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial cytopathy characterized by bilateral ptosis during adolescence, followed later by limitation of extraocular muscle movement and diplopia. The biochemical defect consists of mutations or deletions of mitochondrial DNA genes that encode respiratory chain enzymes involved in adenosine triphosphate (ATP) generation and its subsequent translocation from the mitochondria. To date, there is no definitive treatment that reverses or halts the progression of the muscle weakness. Herein, we report improvement in ocular motility in a patient with CPEO following treatment with tetracycline. The retrospective review was approved by the institutional review board.

Case report. A 47-year-old woman, with bilateral upper eyelid ptosis since childhood, underwent ptosis repair in 1987, at age 28. There was a gradual return of the ptosis over the ensuing years. By age 33, she began experiencing diplopia. She had otherwise enjoyed excellent health. Her family history was significant for six brothers and three sisters with ptosis.

We initially evaluated her in October 1997, at age 38, for diplopia and ptosis. Her visual acuity was 20/20 for both eyes. There was 6- to 7-mm bilateral upper eyelid ptosis and decreased levator excursion to 14 mm bilaterally. All ocular motility measurements were obtained by the same examiner, and maximal effort from the patient was encouraged at each visit. On the initial examination, the total horizontal range of ocular motility (combined abduction and adduction) was reduced in the right eye to 120% of a possible maximum 200% and reduced to 145% for the left eye. The total vertical range of ocular motility (combined elevation and depression) was reduced in the right eye to 150% of a possible maximum 200% and reduced to 160% for the left eye. The remainder of the neuro-ophthalmologic examination was normal. Retinal pigmented degeneration was absent.

The patient underwent a second bilateral ptosis repair with muscle biopsy. Histologic examination of the muscle biopsy specimens confirmed the diagnosis of CPEO, with the findings of ragged red fibers on trichrome stain, representing accumulation of abnormal mitochondria within muscle fibers. She was observed for 4 years with continued gradual decline of horizontal and vertical eye movements. In October 2001 (figure), the left eye moved horizontally 80% and vertically 130%, while the right eye moved horizontally 80% and vertically 140%. Tetracycline 500 mg daily was initiated in October 2001 for the possibility of stabilizing the eye movement. One year later, in October 2002, the horizontal eye movements improved above the pretetracycline baseline level. A similar finding of improvement above the pretetracycline baseline level occurred for the right eye, but only for approximately 2 years (figure). In comparison with the projected decline in eye movement (based on a linear regression of the pretetracycline data from October 1997 to October 2001), the horizontal and vertical eye movements initially improved and were associated with a delay in the progressive worsening of the ophthalmoplegia. The degree of upper lid ptosis remained approximately 4 mm for both eyes during the 4 years. Tetracycline therapy was well tolerated at the dose given and over the duration of therapy.

Discussion. To our knowledge, our report is the first to demonstrate that tetracycline may play a role in improving ocular motility in CPEO. Previous studies have documented that tetracycline and its second-generation semisynthetic derivatives, minocycline and doxycycline, exert neuroprotective and myoprotective effects, particularly in animal models of Huntington disease and Parkinson disease. Reports have shown that mutation of adenine nucleotide translocase (ANT1), important in the translocation of ATP from the mitochondria into the cell cytoplasm, may result in CPEO. ANT1 mutation can result in the opening of the membrane permeability transition pore and release of cytochrome c, a trigger of apoptosis. Recent evidence suggests that cytochrome c release occurs more readily from cells harboring mutant mitochondria when exposed to a pro-apoptotic signal. Furthermore, apoptotic cell death was found to be mediated through both increased cytochrome c release and caspase-3 activation. The improvement in ocular motility that we documented could have occurred from tetracycline blocking apoptosis through the inhibition of cytochrome c and caspase-3 release in the mitochondria.

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Figure. The progressive decline in horizontal and vertical eye movements over 4 years (pretetracycline treatment) from October 1997 to October 2001, as demonstrated in our case of chronic progressive external ophthalmoplegia. Maximum horizontal (combined abduction and adduction) or vertical (combined elevation and depression) eye movement is 200%. The linear bold and then dashed black lines represent the linear regression decay in eye movement as projected from horizontal and vertical eye movement decline over 4 years from October 1997 to October 2001. Following treatment with tetracycline 500 mg daily that began in October 2001, there was an initial improvement of ocular motility and then gradual decrease in ocular motility to baseline October 2001 level, with a delay in progression by 4 years for the left eye and by 2 years in the right eye.
References