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MR of Extraocular Muscles in Chronic Progressive External Ophthalmoplegia

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PURPOSE: Our goal was to determine whether the extraocular muscles in patients with chronic progressive external ophthalmoplegia (CPEO) could be distinguished from those of age-matched control subjects by MR imaging.

METHODS: Nine patients with CPEO and eight age-matched healthy control subjects were studied. The extraocular muscles of eight of the patients (16 eyes) and all the control subjects (16 eyes) were measured digitally. Images consisted of 1.5-mm contiguous sections acquired using a volume (three-dimensional) gradient-echo acquisition. In all, measurements were performed on 11 interpolated 1.0-mm coronal sections, five on each side of the muscle center. Only the medial, inferior, and lateral rectus muscles were evaluated. The superior rectus was omitted to avoid averaging problems with the superior orbitalic vein and levator palpebrae muscle. The 11 sections were summed to obtain a volume measurement of the central portion of each muscle.

RESULTS: The digitally measured extraocular muscles in the patients with CPEO had statistically significantly smaller volumes than those of the control subjects. The average muscle volumes for the patients with CPEO were 215 mm³ for the medial rectus, 202 mm³ for the inferior rectus, and 269 mm³ for the lateral rectus. The average extraocular muscle volumes for the control subjects were 366 mm³ for the medial rectus, 365 mm³ for the inferior rectus, and 425 mm³ for the lateral rectus.

CONCLUSION: MR imaging can show small extraocular muscles in patients with CPEO, which may help to distinguish this disorder from other entities. Since denervated extraocular muscles do not readily atrophy, this MR sign would support a myogenic pathologic substrate for CPEO. Variation in the degree of extraocular muscle atrophy may simply reflect the length of time the mitochondrial defect and ophthalmoplegia have been present.

Chronic progressive external ophthalmoplegia (CPEO) is not a specific disorder or single disease entity but a clinical sign. Typically, patients present with blepharoptosis followed by a decrease in horizontal then vertical gaze. Most CPEO is considered

myopathic, but neurologic, inflammatory, and autoimmune disease must also be considered in the differential diagnosis. Duchenne muscular dystrophy, facioscapulohumeral dystrophy, and most metabolic, inflammatory, and congenital myopathies do not show evidence of extraocular muscle involvement (1).

We observed that some CPEO patients, referred for magnetic resonance (MR) imaging, had extremely small extraocular muscles. As a consequence, we reviewed the MR findings and obtained measurements of extraocular muscle volumes in nine patients with CPEO.

Methods

We reviewed the MR studies and quantitative data regarding extraocular muscle volume in eight patients with the clinical diagnosis of CPEO (one additional patient had only conventional images available for review) (Table 1). Eight healthy subjects with a similar age and sex distribution had MR imaging to determine control values for extraocular muscle volume (Table 2). All patients and control subjects signed a consent form.

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TABLE 1: Findings in patients with chronic progressive external ophthalmoplegia (CPEO)

| Case | Age, y/Sex | Duration of Symptoms | Extraocular Muscle Volume, mm ³ (P)* | | |
|--------------------------------|------------|----------------------------------|---|-----------------|----------------|
| | | | Medial Rectus | Inferior Rectus | Lateral Rectus |
| 1 | 57/M | 15-year history of CPEO | 223 (.0001) | 278 (.0007) | 321 (.099) |
| 2 | 55/F | 25-year history of CPEO | 147 (.0001) | 145 (<.0001) | 215 (<.0001) |
| 3 | 73/M | 20-year history of CPEO | 185 (<.0001) | 187 (<.0001) | 269 (<.0001) |
| 4 | 18/F | 10-year history of KSS with CPEO | 213 (<.0001) | 231 (<.0001) | 270 (<.0001) |
| 5 | 21/F | 9-year history of CPEO | 249 (.036) | 213 (.003) | 288 (.186) |
| 6 | 50/M | 20-year history of CPEO | 245 (<.0001) | 206 (<.0001) | 309 (<.0001) |
| 7 | 30/M | 23-year history of KSS with CPEO | 164 (.005) | 116 (<.001) | 187 (.0006) |
| 8 | 63/M | 17-year history of CPEO | 298 (.099) | 240 (<.0001) | 293 (.042) |
| 9 | 52/M | 20-year history of CPEO | No quantitative data available; extraocular muscles appeared threadlike on MR | | |
| Average measurements (16 eyes) | | | 215 | 202 | 269 |

Note.—CPEO patients are compared with healthy control subjects. KSS indicates Kearns-Sayre syndrome.

* Measurements represent an average of both eyes for each patient. P value is derived from Student's *t* test.

TABLE 2: Extraocular muscle volume in control subjects

| Case | Age, y/Sex | Volume, mm ³ | | |
|--------------------------------|------------|-------------------------|-----------------|----------------|
| | | Medial Rectus | Inferior Rectus | Lateral Rectus |
| 1 | 52/M | 296 | 284 | 298 |
| 2 | 59/M | 497 | 435 | 569 |
| 3 | 50/M | 356 | 430 | 443 |
| 4 | 21/F | 272 | 274 | 342 |
| 5 | 73/M | 363 | 359 | 423 |
| 6 | 60/F | 394 | 466 | 462 |
| 7 | 63/M | 432 | 414 | 448 |
| 8 | 55/F | 323 | 263 | 417 |
| Average measurements (16 eyes) | | 366 | 365 | 425 |

Note.—Measurements represent an average of both eyes for each patient.

Both groups were asked to fixate straight ahead; each lens was subsequently monitored on the axial MR sections to assure compliance and to nullify any asymmetry from extraocular muscle contraction. Axial and coronal spin-echo intermediate and T2-weighted images of the brain were obtained. Our imaging protocol also included a three-dimensional gradient-recalled echo sequence of the orbits and brain. This permitted the reconstruction of contiguous images in any desired plane. Imaging techniques for extraocular muscle measurement consisted of 3-D magnetization-prepared rapid gradient echo (MP-RAGE) sequences with parameters of 10/4/1 (repetition time/echo time/excitations) and a 10° flip angle (obtained on a Siemens Magnetom at 1.5 T); field echo 3-D sequences with parameters of 30/10 and a 35° flip angle (obtained on a Picker Outlook at 0.23 T); or radio frequency fast steady-state sequences with parameters of 15/4.4 and a 25° flip angle (obtained on a Picker Edge at 1.5 T), which yielded volumetric T1-weighted 1.5-mm contiguous sagittal source images. Data were transferred to a Sparc 20 (Sun Microsystems, Mountain View, Calif) independent workstation and reformatted to produce 1.0-mm contiguous coronal images of the orbits. Bilateral measurements of the medial, inferior, and lateral rectus muscles were obtained. The superior rectus was excluded to avoid volume-averaging with the levator palpebrae muscle and superior ophthalmic vein. Digital measurements of the images were made by using a Power Macintosh 7200 with NIH Image Software, version 1.58.

Volume measurements of each extraocular muscle were obtained by first identifying the center of each muscle belly.

Each extraocular muscle was considered to be a spindle-shaped structure. The single section through the muscle in the coronal plane with the largest area, corresponding to the center of the muscle, was identified. The area of this central section and of 10 additional section areas, five anterior to and five posterior to this central section, were calculated. Each section was 1 mm thick and contiguous with adjacent sections; areas were measured in square millimeters, and the 11 resulting section areas were summed, permitting calculation of the volume in cubic millimeters of the central portion of each extraocular muscle. Normal extraocular muscle volumes (16 eyes) were then compared with the extraocular muscle volumes in eight of our patients with CPEO (16 eyes). This method excluded complications associated with determining extraocular muscle insertions and tendon-muscle boundaries. We thought that measuring the volume of a portion of the extraocular muscle would better assess differences among extraocular muscle size than would single measurements of height and width or a single measurement of a cross-sectional area. The same digital extraocular muscle volume analysis was performed in the eight control subjects. All measurements were performed by a single author. Lateral rectus volumes, in general, were higher owing to this muscle's oblique course through the orbit in the coronal plane. We chose to measure this muscle directly from coronal images rather than introduce the additional condition of estimating the orientation of the long axis of the muscle to obtain images directly coronal to the long axis of this muscle. Statistical analyses (Student's *t* test) were performed using Microsoft Excel, version 5.0a.

Results

Coronal images of patients with CPEO (Fig 1) regularly showed small extraocular muscles as compared with the images from the control group (Fig 2); several patients had extremely small or threadlike extraocular muscles. The 11 separate images used to determine inferior rectus muscle volume in one of the control subjects are shown in Figure 3; those for one of the patients with severe CPEO appear in Figure 4. Muscle volume measurements for the patients with CPEO and for the control subjects are given in Tables 1 and 2.

As a group, patients with CPEO had smaller extraocular muscle volumes than did the control group. Average volumes for medial, inferior, and lateral rectus muscles in the patients were 215 mm³, 202 mm³,

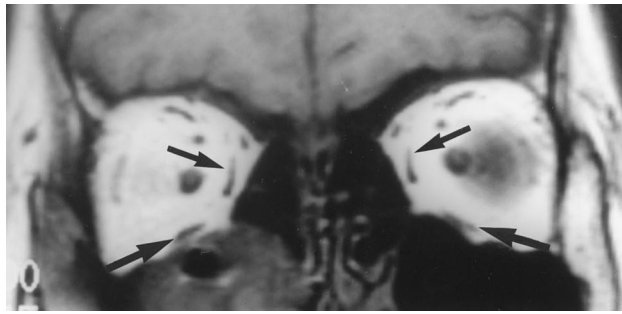


FIG 1. Patient with CPEO. Coronal T1-weighted MP-RAGE (10/4/1, 10° flip angle) orbital image, reconstructed from sagittal source images. Note the small, threadlike extraocular muscles bilaterally (*small arrows* indicate medial recti; *large arrows*, inferior recti).

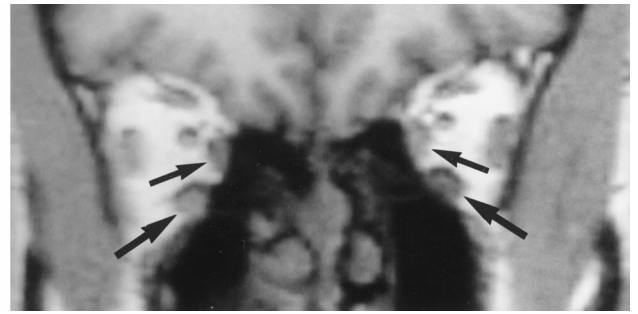


FIG 2. Healthy control subject. Coronal T1-weighted MP-RAGE (10/4/1, 10° flip angle) orbital image. Note the normal extraocular muscles (*small arrows* indicate, medial recti; *large arrows*, inferior recti).

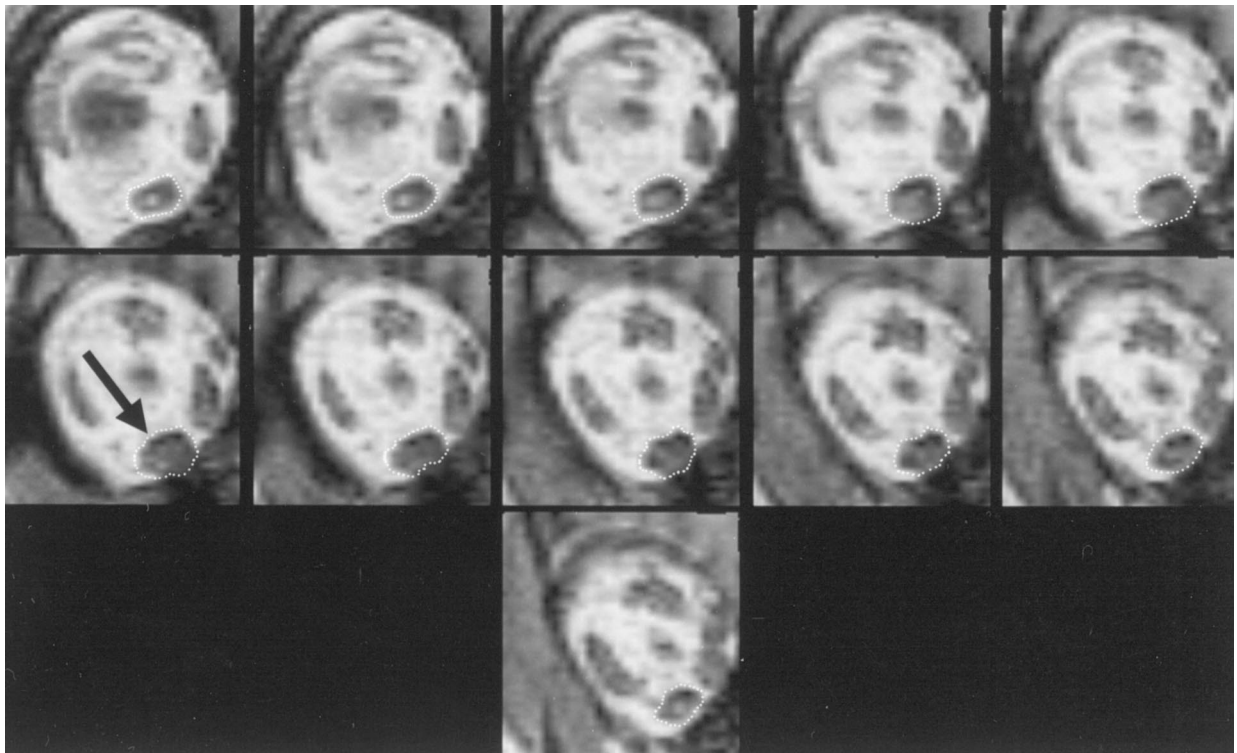


FIG 3. Sample images show the volume measurement of a normal inferior rectus muscle in a control subject. The MP-RAGE (10/4/1, 10° flip angle) images were reprocessed to yield individual 1-mm orbital sections in the coronal plane. After the midportion of the inferior rectus was identified (*arrow*), five additional sections on each side of the center were measured for a total of 11. The normal inferior rectus is outlined.

and 269 mm³, respectively. In the control subjects, average muscle volumes were 366 mm³, 365 mm³, and 425 mm³ for the medial, inferior, and lateral rectus muscles, respectively.

Six patients (cases 1 through 3 and 6 through 8) with histories of CPEO of 15 years or longer had very small extraocular muscle volumes, which were statistically significantly different from those of control subjects. Two patients (cases 4 and 5), with 9- and 10-year histories of CPEO, had somewhat smaller but definitely decreased extraocular muscle volumes relative to those of the control subjects.

MR signs of a mitochondrial encephalopathy and cerebellar atrophy were seen in only one patient with Kearns-Sayre syndrome (KSS) (case 4). Another pa-

tient with KSS (case 7) and a patient with CPEO (case 2), who did not completely fulfill the criteria for KSS because of late age of onset, had small extraocular muscles but otherwise normal brain MR findings. All other patients with CPEO had either normal findings or mild, age-related cerebellar atrophy on MR images of the brain (cases 1, 3, 8, and 9). Mild cortical atrophy was documented in three patients (cases 2, 8, and 9) that was considered consistent with their ages. One patient (case 3) had unrelated areas of posttraumatic encephalomalacia and a small lacunar infarct.

We compared the cross-sectional areas of the largest individual extraocular muscles on coronal sections in our control subjects with published measurements of the extraocular muscle area obtained in autopsy

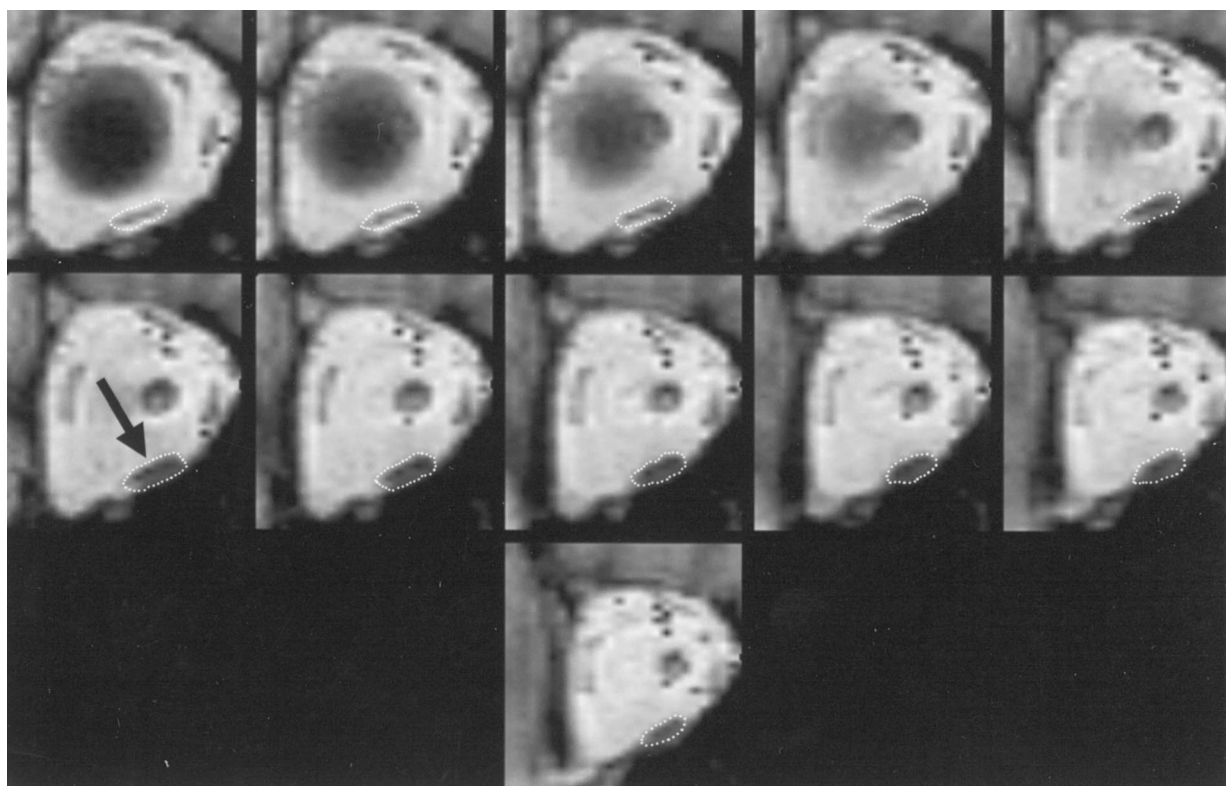


FIG 4. Sample images show the volume measurement of an inferior rectus muscle in a patient with CPEO. The MP-RAGE (10/4/1, 10° flip angle) images were reprocessed to yield individual 1-mm orbital sections in the coronal plane. After the midportion of the inferior rectus was identified (arrow), five additional sections on each side of the center were measured for a total of 11. The abnormal inferior rectus is outlined.

specimens (2, 3) and found them to be consistently larger than the cadaveric extraocular muscles.

Discussion

CPEO can occur at any age, presenting with blepharoptosis followed by slowly progressive loss of extraocular muscle function. Typically, as observed in our series, downward gaze is relatively preserved as compared with horizontal and upward gaze (4). It is important to exclude other causes of ocular motility abnormalities, such as brain stem lesions, bilateral cavernous sinus disorders, neuromuscular junction disorders (including myasthenia gravis, congenital myopathies, ocular fibrosis, thyroid ophthalmopathy, and other orbital lesions), and the Miller-Fisher variant of Guillain-Barré syndrome. Systemic myositis usually does not involve the oculofacial muscles, but myositis presenting as external ophthalmoplegia has been reported (5). None of our patients had evidence of any systemic disorder other than CPEO or KSS at the time of their MR examinations.

CPEO was described in 1868 by Von Graefe (6). Initially, it was believed to represent neuronal degeneration; however, findings at subsequent extraocular muscle biopsies have supported a myopathic origin. Myopathic changes found in normal extraocular muscle, when evaluated by the same criteria used for limb-muscle biopsy specimens, and the discovery of myopathic changes produced by ocular muscle den-

ervation (7) have complicated and confused the pathophysiology of CPEO. Recent developments in cellular biology and muscle mitochondrial genetics support a myopathic origin for CPEO (8). Further verification of a myopathic origin comes from the observation that extraocular muscle denervation does not produce widespread atrophy as it typically does with limb muscles. Extraocular muscles have a unique morphology with six distinct fiber types (9) when denervated atrophy is limited to the orbital, singly innervated fibers (9).

CPEO can occur as an isolated phenomenon of ophthalmoplegia or as a variable constellation of associated disorders, including skeletal muscle myopathy; cardiac and ocular disease; hyperacusis and deafness; peripheral neuropathy; pyramidal, extrapyramidal, and cerebellar signs and symptoms; endocrine and other systemic disease; and dementia (10). KSS is a restricted or limited form of CPEO delineated by a combination of CPEO, pigmentary retinopathy, onset before age 15, and one of the following: elevated cerebrospinal fluid protein (above 100 mg/dL), heart block, or cerebellar dysfunction (11).

There is considerable overlap in the clinical and radiological signs of CPEO and KSS. Neuroradiologic findings include normal brain, cortical and cerebellar atrophy (12), and increased T2 signal intensity in the subcortical cerebral white matter, cerebellar white matter, globi palladi, thalami, and substantia nigra (13). In general, patients with CPEO or KSS uncon-

plicated by significant neurologic abnormalities beyond ophthalmoplegia have normal brain MR findings or atrophy of the cerebral cortex or cerebellum. The white matter, basal ganglia, and thalami abnormalities typical of mitochondrial encephalopathy are usually found in patients with additional neurologic signs or symptoms (12). Findings in our patients displayed this spectrum of imaging findings; only one patient (case 4) with KSS and multiple neurologic deficits had widespread T2 abnormalities.

Cerebellar atrophy was observed in our series in both CPEO and KSS; in no case was the atrophy severe. One patient (case 5), a 21-year-old woman with CPEO and atypical retinopathy, did not meet the criteria for the clinical diagnosis of KSS. Interestingly, both she and an additional patient with severe KSS (case 4), while exhibiting smaller extraocular muscle volumes than control subjects, did not have nearly as prominent extraocular muscle volume loss as the older patients, who all had at least 15-year histories of CPEO. This suggests that the full expression of severe extraocular muscle volume loss in CPEO and KSS may require a decade or more to become manifest by MR imaging.

Our study had several limitations. Comparison with autopsy measurements is unreliable owing to hydration and fixation changes, and cannot take into account changes in muscle volume and shape caused by contractions that occur in life. These factors may account for the differences in muscle measurements observed between our subjects and the autopsy data. We did not attempt to determine rigorously the reproducibility of our measurement technique or to compare it with other measurement techniques, including computed tomography. Our patients only underwent MR imaging as part of their examination. Three independent observers reviewed the images and considered the findings obvious. In addition, we performed an analysis of the muscles to objectify their observations.

Both CPEO and KSS are mitochondrial disorders, and a significant percentage of patients have a so-called common deletion of mitochondrial DNA measuring 4.9 kb (8, 14). This section of the mitochondrial genome encodes for enzymes of the oxidative phosphorylation chain and, if defective, the metabolic demands (supply of adenosine triphosphate) of active cells may not be met. Other mitochondrial defects affecting the synthesis of oxidative phosphorylation chain enzymes have been found in CPEO, including variable length deletions and a single point mutation that encodes for mitochondrial tRNA needed in protein synthesis (15). Ocular muscles have high metabolic demands (14), a mitochondrial function three to

four times higher than limb muscle (16), extraordinary high discharge rates (17), and even at rest produce at least 10 g of tension (17). Mitochondrial mutations reduce energy production (18), which could, over a period of years, account for the muscle atrophy seen in our patients with CPEO. Patients with identical deletions can have different clinical phenotypes, suggesting that CPEO and KSS may be incomplete and complete expressions of the same mitochondrial defect (14). Given the clinical and molecular similarities of CPEO and KSS, a separation into two syndromes is probably artificial. It is important that the person performing the neuroimaging studies in these patients be alert to the possibility of a loss in extraocular muscle volume.

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