

VCU Department of Neurology Case Studies

Fleming's Steakhouse
May 17, 2006

Ryan Drake, D.O.

Case Presentation

- 21 y/o Asian female without significant past medical history presented for neuro-ophthalmologic consultation regarding a “droopy left eyelid”
- The patient experienced a droopy eyelid since childhood undergoing lid surgery at age 12, initially with improvement, however the ptosis continued to progress eventually involving her right eye
- She also reported difficulty with eye movements and must turn her head to look in a specific direction, noting minimal horizontal diplopia on extreme lateral gaze

Case Presentation

- Her visual acuity had gradually worsened over the years, and was unable to see 20/20 even with correction
OS>OD
- She reported previous negative muscle bx. prior to lid surgery
- She denied any specific pattern to her ptosis; speech or swallowing difficulty, weakness or sensory loss
- She was on no medication, denied tobacco or substance abuse and admitted to being a “social” drinker
- There was no family history of ocular or neurological disease

Exam

- General examination was normal
- Mentation and cranial nerve exam 5, 7-12 were normal
- The motor exam showed 5/5 strength, without fatigable weakness
- Normal muscle tone, without myotonia
- Sensory exam was normal and deep tendon reflexes were 1+ throughout with down-going toes
- Coordination and gait were also normal

Neuro-ophthalmologic exam

- OD 20/25 (ph NI) OS 20/100 (ph 20/50)
- Color plates OD 14/14 OS 13/14
- normal visual fields and funduscopic exam
- bilateral ptosis with frontalis compensation



Neuro-ophthalmologic exam

- EOM: complete upgaze impairment and only minimal movement with adduction, abduction and down gaze
- Doll's maneuver was attempted but inconclusive
- Forced duction testing was performed by anesthetizing the eyes and applying gentle traction to the sclera with a cotton swab, however there was no additional movement in all directions of gaze



Labs/Imaging

- normal CBC, BMP, ANA, lactate, thyroid, and myasthenia gravis antibody panel
- 12 lead EKG and transthoracic echocardiogram were normal
- MRI of brain/orbits revealed significant atrophy of all extraocular muscles
- deltoid punch biopsy from 1994 revealed normal microscopic and electron microscopy, without evidence of ragged red fibers or dystrophin

1.5T MRC25144

A

VCUMC

Ex: 33003

T1_se_AX-POST

021Y r 033032r

C: OMNISCAN

Acc: 01901699

Se: 12/16

2006 Mar 17

Im: 7/3

Acq Tm: 18:00:27.005003

Ax: 11.4 (COI)

256 x 192

T1-Axial



ET: 1

TR: 500.0

TE: 7.8

5.0thk/1.5sp

W:1216 L:586

P

DFOV: 16.5 x 22.0cm

1.5T MRC25144

A

VCUMC

Ex: 33003

T1_se_AX-POST

021Y F 6398527

C: OMNISCAN

Acc: 01901699

Se: 12/16

2006 Mar 17

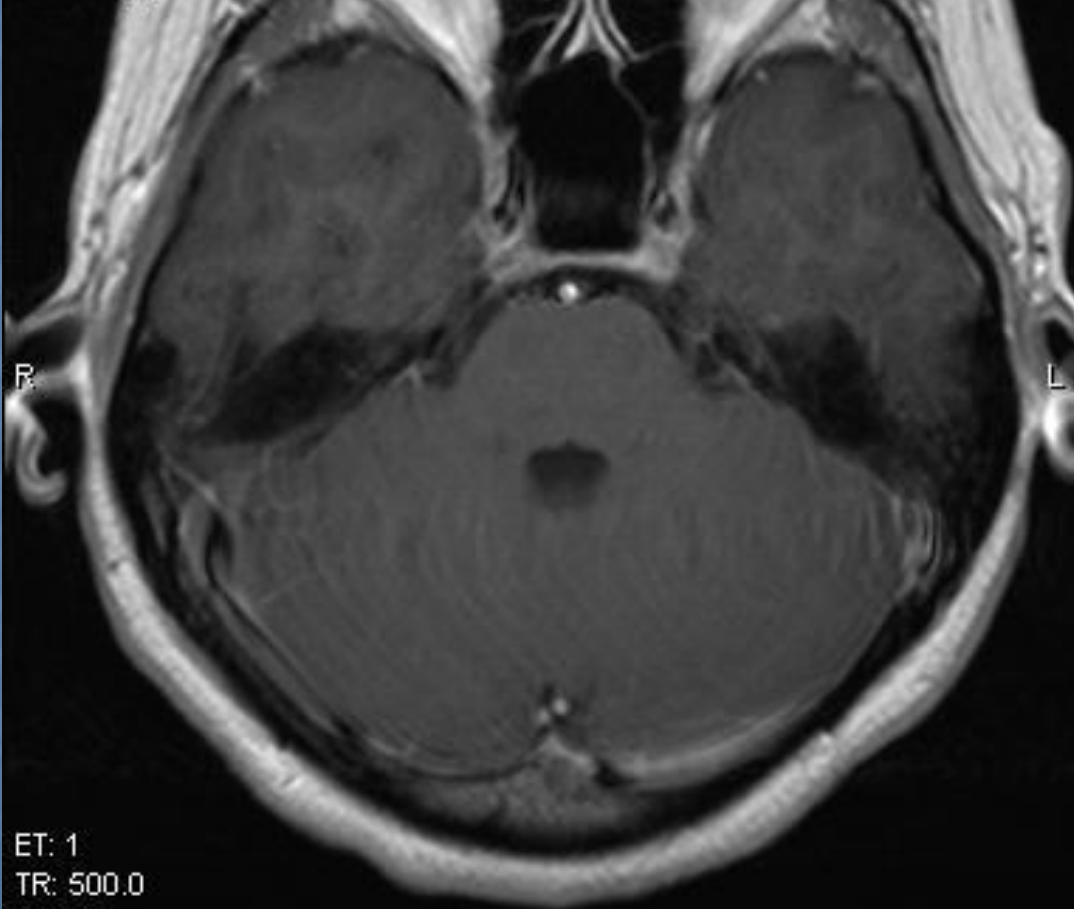
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Acq Tm: 18:00:26.730010

Ax: 17.9 (COI)

256 x 192

T1-Axial



ET: 1

TR: 500.0

TE: 7.8

5.0thk/1.5sp

W:1231 L:589

P

DFOV: 16.5 x 22.0cm

Differential Diagnosis

- CPEO
- Kearnes-Sayers Syndrome
- Myasthenic syndromes
- Oculopharyngeal muscular dystrophy
- Myotonic dystrophy
- Sarcoidosis of the extraocular muscles
- Amyloidosis with bilateral orbital infiltration
- Thyroid eye disease (Graves' disease)
- Centronuclear myopathy
- Congenital cranial dysinnervation diseases (CCDD)
- Miller-Fisher variant of Guillain-Barré syndrome
- Vitamin E deficiency: abetalipoproteinemia

Working Diagnosis

- mitochondrial cytopathy, specifically Chronic Progressive External Ophthalmoplegia (CPEO) based on history, exam and current studies
- CPEO is a rare mitochondrial disease first described by Von Graefe in 1868 with the clinical hallmarks of progressive ptosis and impaired ocular motility
- CPEO can occur as an isolated disease or as a symptom in a variety of mitochondrial diseases (e.g. CPEO plus, Kearns-Sayer Syndrome, MELAS)
- CPEO is most commonly a sporadic condition caused by a single deletion in mitochondrial DNA (mDNA)
- autosomal dominant and recessively transmitted CPEO secondary to nuclear DNA defects is reported in a number of families
- Currently there is commercially available genetic testing analyzing muscle for the most common mDNA mutations

- on exam she had bilateral ptosis and near complete ophthalmoplegia which is seen in CPEO
- She had no evidence of other cranial nerve involvement, generalized or fatigable weakness, evidence of neuropathy or cerebellar dysfunction which would help eliminate other diagnoses
- Decreased visual acuity can be a sign of retinal disease, which is typically seen in Kearns-Sayre Syndrome
 - (CPEO, onset <20, pigmentary retinopathy + one of three: cardiac conduction abnormalities or CSF protein >100mg/dl or cerebellar dysfunction)
- Although electroretinography was still pending, funduscopic examination was normal, so retinopathy is less likely. A positive forced duction test eliminated a neuropathic etiology of the ophthalmoplegia.

- Laboratory studies in this case were all negative including acetylcholine antibodies and thyroid function
- normal EKG and TTE further supported CPEO as opposed to Kearns-Sayre Syndrome
- Our patient's brain MRI revealed symmetrically thin atrophic extraocular muscles indicative of a progressive myopathic disease
- One study looked at MRI findings of ocular muscles in patients with CPEO vs. age-match controls and showed statistically significant decreased extraocular muscle volumes as was seen in our patient, which further supported CPEO versus an infiltrative myopathy or neurogenic etiology
- White matter changes and cortical atrophy on MRI can also be seen in patients with mitochondrial cytopathies, however this was not the case in our patient

- previous muscle biopsy was negative, specifically noting absence of ragged red fibers or dystrophin
- While ragged red fibers are the hallmark pathological finding on muscle biopsy in mitochondrial cytopathies, they are not always seen
- Multiple case reports support the need for genetic testing of the muscle rather than tissue analysis only, especially when an etiology is not found
- In one case report ragged red fibers were not present, but even when histochemical analysis and spectrophotometry of the muscle was done, there was still no evidence of mitochondrial disease, further supporting the need for genetic testing
- Currently the patient is considering a second biopsy with mDNA analysis to confirm the diagnosis

Can chemodenervation with botulinum toxin safely be used in patients with mitochondrial cytopathy?

- The use of botulinum toxin is becoming more prevalent to treat various disorders including dystonia, spasticity, hemifacial spasm, blepharospasm, sialorrhea, hyperhidrosis and headache
- Patients with mitochondrial disease can be affected by drooling, spasticity, complex migraine and oftentimes dystonia. Although other treatments are available, there is sometimes the need to use a chemodenervating agent, particularly in cases of dystonia or spasticity
- One report of a Chinese girl with Leigh syndrome required botulinum for significant spasmodic dysphonia without adverse effects

- Another concern is the unmasking of subclinical mitochondrial disease as has been reported in a few case reports
- One case report in particular noted significant dysphagia and ptosis despite multiple attempts at various injection sites, with subsequent diagnosis of a mitochondrial disease
- There is speculation that patients with mitochondrial disease are more susceptible to the effects of botulinum toxin. The mechanism to increased susceptibility is possibly secondary to abnormal neuromuscular transmission supported by increased jitter seen on single fiber EMG
- With the limited amount of data available on the use of botulinum toxin, many authors recommend much lower doses and caution its use in patients with mitochondrial disease

Therapeutic Options

Creatine Monohydrate

- Randomized, placebo-controlled studies for mitochondrial cytopathies are limited, but do show increased isometric strength, aerobic and anaerobic power and improvement in ADLs
- A recent placebo-controlled trial involving mostly patients with CPEO, there was no improvement in exercise performance, eye movements, or activities of daily life
- Creatine monohydrate theoretically works to increase intracellular ATP and decrease the demand on the oxidative phosphorylation system

Co-Enzyme Q10

- One case report indicated significant improvement in ductions in a patient with CPEO
- There have been case reports showing benefit in other mitochondrial disease, but the only double blinded placebo control study revealed only minimal benefit
- Coenzyme Q10 mechanism is via bypassing defective electron chain transport complexes to maximize ATP production

Idebenone

- Synthetic analogue of coenzyme Q10 shown to be of modest benefit in mitochondrial disease, specifically Leber's and MELAS
- One case report revealed reversal of mitochondrial cardiomyopathy

Succinate

- Substrate to electron transport providing additional energy was shown in a case report to improve symptoms in KSS

Thiamine

- Stimulates pyruvate decarboxylase to potentially decrease lactate production and was felt to be effective in treating a case of Leigh's disease
- Normalization of lactate has been seen in KSS

Ophthalmologic Treatment

- Fresnel prisms work to correct ocular alignment for patients with diplopia
- Eyelid crutches act as a physical mechanism to hold ptotic lids open
- Lid surgery, commonly via frontalis sling procedure, to correct ptosis is sometimes necessary, although patients are at risk for exposure keratopathy if lids do not approximate following surgery

- **Pacemaker:** Per 2002 ACA/AHA guidelines, there was a consensus recommendation for pacing in patients with KSS with or without symptoms, however not in isolated CPEO

Patient Support and Information

- Muscular Dystrophy Association
<http://www.mdausa.org>
- United Mitochondrial Disease Foundation,
PO Box 1151, Monroeville, PA, 15146-
1151
<http://www.umdf.org>

Outcomes

- Limited data on outcomes regarding CPEO
- One case series in Germany looked at the age and etiology of death in patients with mitochondrial diseases
 - average age of death was 32 y/o with most common cause being cardiopulmonary failure
 - In the patients with CPEO, the average age of death was 56 y/o and cause of death was reported to be cardiopulmonary failure, aspiration pneumonia from myopathic dysphagia and pulmonary embolism
 - Correlation of percentage of abnormal mDNA and age of death was not seen

Board Style Questions

- 1) A patient with newly diagnosed Chronic Progressive External Ophthalmoplegia presents to your office to be established. What testing is indicated to screen for the risk of sudden death?
 - a) CTA of head and neck
 - b) Abdominal ultrasound
 - c) EKG
 - d) Spiral CT of chest
 - e) EEG

Answer

- c) EKG
- Patients with CPEO may actually have Kearns-Sayre Syndrome and be at risk for sudden death secondary to cardiac disease
- The incidence of sudden death in KSS is near 20%.
- Approximately 57% of patients with KSS have cardiac disease, most notably conduction abnormalities which include atrioventricular (AV) block or His-ventricular interval prolongation
- Patients with CPEO should undergo screening EKG and if found to have conduction abnormalities are recommended to have prophylactic cardiac pacemaker insertion
- Echocardiogram is also indicated to screen for cardiomyopathy

Board Style Questions

- A 20 y/o female presents with bilateral ptosis and ophthalmoparesis. All of the choices should be considered in the differential diagnosis except?
 - a) Oculopharyngeal muscular dystrophy
 - b) Thyroid eye disease
 - c) Myasthenia gravis
 - d) Hypokalemic periodic paralysis
 - e) Mitochondrial cytopathies

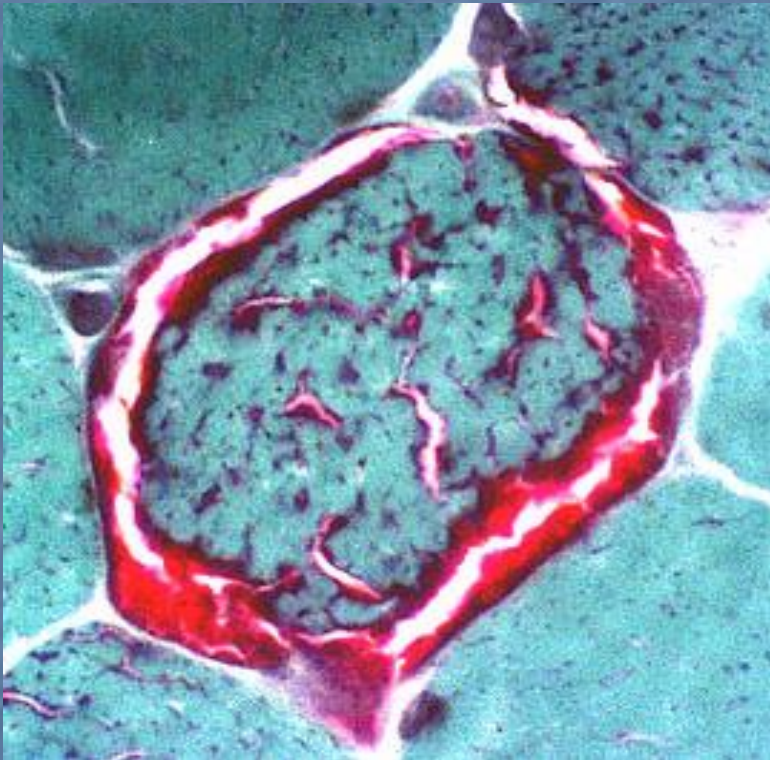
Answer

d) Hypokalemic periodic paralysis

- Extraocular motility is spared in hypokalemic periodic paralysis
- Oculopharyngeal muscular dystrophy can initially present with ocular involvement, most commonly isolated ptosis, presenting in mid 30s or later
- Thyroid eye disease (Graves) can involve eye muscles and commonly presents after age 20
- Myasthenia gravis frequently involves ocular muscles and should be considered in anyone with ocular motility dysfunction
- Mitochondrial cytopathies (e.g. CPEO or KSS) can present with ocular involvement

Board Style Question

What neuropathological finding is seen below?



<http://www.neuro.wustl.edu/neuromuscular/pathol/mitochondrial.htm>

- a) Ragged red fibers
- b) Neuronal plaque
- c) Rimmed vacuoles
- d) Tomaculae
- e) Amyloid

Answer

a) Ragged red fibers

- The Gomori Trichrome stained slide shows ragged red fibers
- These represent the accumulation of mitochondria within the muscle
- They are commonly seen in mitochondrial disease such as CPEO, KSS or MELAS

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After a long day of soccer

