Mitochondrial Myopathy

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Figure 1. Histogram illustrating range of age at onset of symptoms in 66 patients with mitochondrial myopathy.
MITOCHONDRIAL MYOPATHY: SYMPTOMS AT PRESENTATION

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of cases (66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptosis</td>
<td>39</td>
</tr>
<tr>
<td>Aware of restricted eye movements</td>
<td>8</td>
</tr>
<tr>
<td>Diplopia</td>
<td>5</td>
</tr>
<tr>
<td>Visual failure</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>18</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>3</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>4</td>
</tr>
<tr>
<td>Deafness</td>
<td>3</td>
</tr>
<tr>
<td>Ataxia</td>
<td>8</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
</tr>
<tr>
<td>Myoclonic jerks</td>
<td>3</td>
</tr>
<tr>
<td>Short stature</td>
<td>3</td>
</tr>
</tbody>
</table>
Kearns-Sayre Syndrome

Kearns-Sayre Syndrome (KSS) is defined by three criteria that seem invariable:

Onset less than 20 years of age
Progressive external ophthalmoplegia
Pigmentary retinopathy
Children with KSS appear normal at birth
Boys and girls equally affected
The Ophthalmoplegia begins at age 5, can be recognized as early as age 2

Parents notice ptosis or constricted eye movements. Characteristically affects all eye muscles equally and never the pupils.
KSS Secondary Triad

Cardiac conduction defects
CSF protein of 100 mg/dL or more
A cerebellar syndrome

Many other abnormalities have been found in patients with KSS, including mental retardation, Babinski signs, limb weakness, hearing loss, seizures, short stature, delayed puberty, and various endocrine abnormalities.
The Pigmentary Retinopathy (PR) a salt-and-pepper retinopathy, called atypical to distinguish it from typical bone spicules retinitis pigmentosa

Pigmentary retinopathy indicates the retinal pigment epithelium is affected

Histologically shows abnormalities of the retinal pigment epithelium as well as rods and cones

PR accompanied by a mild decrease in vision in half the cases.
Figure 3. Fundus OD atypical retinitis pigmentosa.
Figure 4. Fundus OS atypical retinitis pigmentosa.
Figure 5. Fundus peripheral retina atypical retinitis pigmentosa.
Figure 6. Retinal atrophy
Endocrinologically, KSS patient may have:

- Delayed sexual maturation
- Short stature, detailed studies of growth hormone and somatostatin have not been performed
- Diabetes mellitus appears in approximately 20% of patients with KSS
- Hypoparathyroidism has been described
Brain CT hypodense lesions related to the spongy leukoencephalopathy

Brain MRI data is sparse

Skeletal Muscle Biopsy shows in almost all patients with KSS typical ragged-red fibers

Heart muscle has no ragged-red fibers

There is no histopathological difference between KSS and PEO in muscle biopsy specimens
The Cerebellar Syndrome in KSS can vary from very mild to incapacitating. Onset may be anywhere from childhood to adulthood. Mental Retardation can again vary from mild to frank dementia. Seizures are not a prominent feature of KSS.
Clinical Features PEO

Insidious progressive symmetric immobility of the eyes without diplopia
Fixation of the eyes to oculocephalic or caloric stimulation
Sparing of the pupils
Mechanical resistance to a forced-duction test (long standing PEO)
Clinical Features PEO

Absent Bell’s phenomenon i.e. elevation of the eyes on forced eye closure
A negative response to Tensilon or other cholinergic drugs
Typically associated with bilateral symmetrical ptosis and weakness of the orbicularis oculi
PEO difficult when:

Disease starts in neonatal period/infancy
Ptosis is asymmetric
Patient presents with a slow saccade syndrome
Patient has been diagnosed as Myasthenia Gravis but failed to respond to Mestinon
Valuable Clues in PEO

Dilated fundus exam
Bell’s phenomenon
Tensilon test
Forced duction test
Thyroid function tests including if euthyroid, intravenous TRH test
JJ, facial jerk, tendon reflexes and percussion myotonia
PEO is the cardinal sign of a group of disorders caused by several different defects in respiratory chain function. Some of these disorders are associated with deletions in mitochondrial DNA and “ragged-red” fibers which describe vividly the appearance of mitochondria-filled muscle fibers when stained with Gomori Trichrome. Morphology alone cannot determine if a myopathy is due to a mitochondrial defect.
Differential Diagnosis

Although not always an easy task, it is usually possible to clinically distinguish PEO from:

- Graves ophthalmology
- Ocular myasthenia gravis
- Lambert-Eaton myasthenic syndrome
- Oculopharyngeal dystrophy
Conclusion

In its fully developed form Chronic Progressive External Ophthalmoplegia is unmistakable.

Patients sharing the feature of PEO with or without ptosis may differ widely in the severity of symptoms and the resulting disability.
Diagnosis of a Mitochondrial Myopathy

Laboratory studies are directed towards demonstrating widespread clinical abnormalities that require treatment and mitochondrial dysfunction.
Clinical Abnormalities

EKG and cardiac evaluation
Retina consult plus electroretinogram
Neurological consultation plus spinal tap for elevated CSF protein,
EEG for seizures
Endocrine evaluation, essential in child with stunted growth for ? diabetes mellitus and other endocrine abnormalities
Mitochondrial Dysfunction

Serum lactate level pre and post exercise
Brain CT or MRI for spongy leukoencephalopathy
Skeletal muscle biopsy for histochemistry, electromicroscopy for detection of ragged-red fibers
Skeletal muscle biopsy or blood for examination for mtDNA deletions
Table 1. Clinical and laboratory features of seven patients with KSS

<table>
<thead>
<tr>
<th>Clinical &amp; laboratory features</th>
<th>Patients</th>
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<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
</tr>
<tr>
<td>Age at biopsy</td>
<td>15</td>
</tr>
<tr>
<td>Age at onset</td>
<td>8</td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>+</td>
</tr>
<tr>
<td>Pigmentary retinopathy</td>
<td>+</td>
</tr>
<tr>
<td>Heart block</td>
<td>+</td>
</tr>
<tr>
<td>CSF protein (mg/dl)</td>
<td>121</td>
</tr>
<tr>
<td>Cerebellar syndrome</td>
<td>-</td>
</tr>
<tr>
<td>Mental retardation or dementia</td>
<td>+</td>
</tr>
<tr>
<td>Ragged red fibers in muscle</td>
<td>+</td>
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ND  Not determined.
Figure 11. Skeletal muscle ragged red fibers (Hemotoxylin eosin)
Figure 12. Skeletal muscle ragged red fibers (Gomori trichrome)
Figure 13. Skeletal muscle ragged red fibers (NADH)
Figure 14. Skeletal muscle electronmicroscopy in KSS
Mitochondrial DNA Encodes

Seven subunits of NADH CoQ reductase (Complex I)
Cytochrome B (Complex III)
Subunits I, II, and III of cytochrome oxidase (Complex IV)
Subunits 6 and 8 of mitochondrial ATPase (Complex V)
2 Ribosomal RNAs
22 tRNAs
Oculocraniosomatic Neuromuscular Disease OCND

OCND represents a milder form of KSS, with late onset commencing with slowly progressive slowness of saccadic eye movements, ptosis, then advancing to complete external ophthalmoplegia with fixation of the eyes. Ptosis may be asymmetric and usually precedes the onset of ophthalmoplegia.
In 1968 Drachman coined the term “ophthalmoplegia plus” to indicate the range of abnormalities found in OCND. These abnormalities include the second triad listed under KSS together with one or more of the other systemic and neurological abnormalities listed.
PEO + Mitochondrial DNA Deletions

I. Kearns-Sayre Syndrome

I. Oculocraniosomatic Neuromuscular Disease

Other mitochondrial DNA disorders combine mitochondrial abnormalities in the muscle with central nervous system (CNS) disease. Examples include myoclonic epilepsy and ragged-red fibers (MERRF), and mitochondrial disease associated with lactic acid and stroke like episodes (MELAS).
Poor correlation among biochemical abnormalities, size and location of the deletion and clinical phenotype i.e. KSS vs OCND

KSS and isolated OCND can have molecularly identical mtDNA deletion, making it unlikely that KSS is a specific disorder separate from OCND

The existence of overlap patients and patients with probable KSS is consistent with hypothesis that KSS and OCND are a spectrum of the same disease
Mitochondrial DNA (mtDNA)

Deletions

Clinical phenotypes: Deletions in mtDNA are present in muscle mitochondria of most patients with PEO but not in patients with other mitochondrial encephalomyelopathies.
Mitochondrial DNA (mtDNA) Deletions

KSS patients do not show the same deletion but deletions are concentrated in hot spots

KSS patients without detectable deletions may represent either a nuclear mutation or a deletion too small to detect
<table>
<thead>
<tr>
<th>Site of defect</th>
<th>No. of cases</th>
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<tbody>
<tr>
<td>Complex I (NADH CoQ reductase deficiency)</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>With carnitine deficiency</td>
<td>3</td>
</tr>
<tr>
<td>Complex III (CoQ cytochrome c reductase deficiency)</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>With cytochrome b deficiency</td>
<td>3</td>
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<tr>
<td>Complex III and IV (with cytochrome b and aa$_3$ deficiency)</td>
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<tr>
<td>Complex V (mitochondrial ATPase)</td>
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<tr>
<td>With carnitine deficiency</td>
<td>1</td>
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<tr>
<td>Defect not localized</td>
<td>2</td>
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<tr>
<td>No identifiable defect</td>
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http://www.library.med.utah.edu/NOVEL