Case Series

Kearns–Sayre syndrome: Two case reports and a review for the primary care physician

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Abstract

Kearns-Sayre syndrome (KSS) is a mitochondrial encephalopathic disorder. Because mitochondria are ubiquitous organelles that are present in almost every human tissue, their dysfunction can affect nearly any organ system and give rise to a wide range of clinical characteristics. 1: As is the case with most diseases associated with mitochondrial DNA (mtDNA) mutations, the clinical features of KSS were defined before modern molecular genetic classifications emerged. 2: The exact prevalence of KSS is unknown; however, estimates place it at about 1:100,000 people. Although it is a rather rare syndrome, the ability to recognize or consider KSS as part of a differential diagnosis is crucial. Reported here are two case reports: 1) a 30-year-old Caucasian female patient who presented for evaluation to her primary care physician's office and, and 2) A 57-year-old Caucasian female patient long-term C care resident. Guidelines are listed for management as a primary care physician as well as signs and symptoms that are often associated with Kearns-Sayre syndrome and other mitochondrial disorders.

Keywords: Encephalopathy, Kearns-Sayre syndrome, mitochondrial disease, mitochondrial DNA

Introduction

Kearns–Sayre syndrome (KSS) is a mitochondrial encephalopathic disorder. Because mitochondria are ubiquitous organelles that are present in almost every human tissue, their dysfunction can affect nearly any organ system and give rise to a wide range of clinical characteristics.[1] As is the case with most diseases associated with mitochondrial DNA (mtDNA) mutations, the clinical features of KSS were defined before modern molecular genetic classifications emerged.[2] The exact prevalence of KSS is unknown, but estimates place it at about 1:100,000 people. Although it is a rather rare syndrome, the ability to recognize or consider KSS as part of a differential diagnosis is crucial. Reported here are two case reports: 1) A 30-year-old Caucasian female patient who presented for evaluation to her primary care physician's office and, 2) a 57-year-old Caucasian female patient long-term care resident. Guidelines are listed for management by a primary care physician as well as signs and symptoms that are often associated with KSS and other mitochondrial disorders.

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Case Report# 1: A 30-year-old Caucasian female

A 30-year-old Caucasian female patient presented to her primary care physician complaining of difficulty hearing, "fullness" in her ears, and hearing an echo for approximately 6 months in addition to fatigue and exercise intolerance for the last several years. She further noted weakness in her legs, frequent headaches, decreased peripheral vision, and depression with insomnia. She denied any history of syncope, seizures, or strokes.

This patient was the product of a full-term vaginal delivery from an uncomplicated pregnancy. She was observed to have

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difficulty with ocular motility at the age of 5 years. She developed progressive bilateral ptosis and ophthalmoplegia. She underwent surgical correction of her ptosis at the age of 16 years and again at the age of 27 years. She also previously underwent photocoagulation of her left eye. She had smoked half a pack of cigarettes for 10 years but denied any alcohol or drug use. She denied any known drug allergies. Her medication at the time of presentation included cetirizine and an oral contraceptive. Her family history is notable for a younger sister with early signs of chronic progressive external ophthalmoplegia (CPEO) and a father with mitral valve prolapse.

A physical exam revealed a thin, long-limbed female in no distress. She was awake, alert, and oriented to person, place, and time. Her vital signs showed blood pressure of 100/60, heart rate of 68, respiratory rate of 14 at rest, a height of 64 inches, and weight of 90 pounds. Facial diplegia with muscle wasting was noted, as well as bilateral ptosis and bilateral pigmentary retinopathy. The cardiovascular exam demonstrated a regular heart rate with no murmurs, rubs, or gallops. Lungs were clear to auscultation bilaterally without rales, wheezing, or rhonchi. She was noted to have proximal muscle weakness in both the upper and lower extremities with diffuse soft tissue changes and muscle wasting. There was no evidence of muscle fasciculations. Deep tendon reflexes were depressed (one out of four) throughout. The sensory exam was unremarkable.

Cranial nerve examination revealed deficits in cranial nerves 2, 3, 4, 6, 7, and 8. Extraocular eye movements were nearly absent bilaterally, consistent with ophthalmoplegia. Facial muscle motor function as well as pupillary reflexes were decreased. There was moderate-to-severe bilateral sensorineural hearing loss. The remainder of the physical exam was unremarkable.

A summary of laboratory and diagnostic findings is detailed in Tables 1 and 2.

The patient declined repeat mtDNA analysis or repeat muscle biopsy of another site. Despite the patient's normal lumbar puncture and familial pattern of CPEO in her younger sister, the final diagnosis remains likely KSS or Kearns–Sayre variant.

Coenzyme Q10 and daily multivitamin supplements were initiated. Her concomitant mood disorder was treated with nefazodone (a 5-HT2 antagonist) with minimal improvement.

Table 1: Laboratory studies case #1

Laboratory Study	Result
Creatinine kinase (CK)	Elevated
Aldolase	Normal range
Acetylcholine receptor antibody	Negative
Antinuclear antibody (ANA)	Negative
Lyme titer	Negative
Thyroid studies	Normal range
Erythrocyte sedimentation rate	Normal range
FTA/ABS	Negative
Complete blood count	Normal range
Basic metabolic panel	Normal Range
Lumbar puncture	Normal range
mtDNA analysis (whole blood)	Negative for MERF and NARP mutations Indeterminate for MELAS mutation

Table 2: Diagnostic testing results case #1

Diagnostic Study	Results
Magnetic resonance imaging (MRI) Brain-T2	Bihemispheric cerebral white matter changes, suggestive of a global demyelinating process
EMG	Diffuse myopathy with normal conduction velocities
EKG	Sinus rhythm with non-specific ST-T wave changes.
2D Echocardiogram	Mitral valve prolapse with reduced bilateral systolic ventricular function
Visual evoked responses	Decreased bilaterally with prolongation of P100 component
Orbicularis oculi muscle biopsy	Numerous ragged red fibers with elevated succinate dehydrogenase staining and cytochrome-c oxidase staining in many fibers [Figure 1]. Structurally abnormal mitochondria are present on electron microscopy [Figure 2].

Case Report#2: A 57-year-old Caucasian female long-term care resident

A 57-year-old female patient was admitted to a long-term care facility following multiple in-patient hospitalizations. Hospital records are available for 6 years before admission to the facility and were extensively reviewed. She is an unreliable historian due to her complex medical history. She is noted to have over 50 hospitalizations in 5 years for primarily recurrent seizures and stroke evaluations, as well as other issues per records. She was diagnosed with KSS at age 39 following a right quadriceps muscle biopsy. Unfortunately, the detailed findings of this pathology are not available. She had been having recurrent seizures since the age of 5 years. Electroencephalograms have shown left temporal lobe epilepsy. She has had admissions for expression of suicidal ideation.

Her past medical history is notable, in addition to KSS, for major depressive disorder, hypothyroidism, hyperlipidemia, seizure disorder, schizophrenia, dysphagia with PEG tube placement and removal, bilateral lower extremity fractures, neurogenic bladder, T11–T12 compression fractures, chronic kidney disease stage 3, quadriplegia, right internal carotid artery stenosis, vesicovaginal fistulas/bladder neck closure with diverting urostomy bilateral, and nephrostomy tube placement with recurrent urinary tract infections.

Her past surgical history is remarkable for diverting ileal conduit after laparoscopic gastrocutaneous take down, Percutaneous endoscopic gastrostomy (PEG) tube placement and removal, right hip fracture repair, urostomy stent placement, failed bladder neck closure, appendectomy, cholecystectomy, multiple

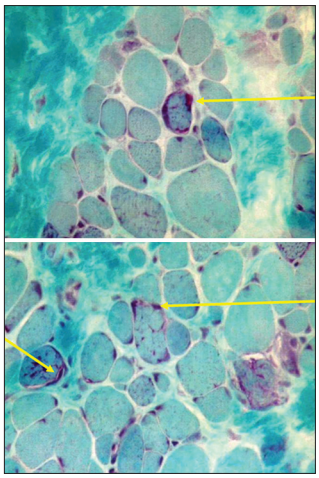

Figure 1: Patient in case #1 showed *ragged red fibers* (shown with arrows) seen on Gomori trichrome stain at 400× magnification. Abnormal mitochondria deposit under the plasma membrane causing this characteristic appearance

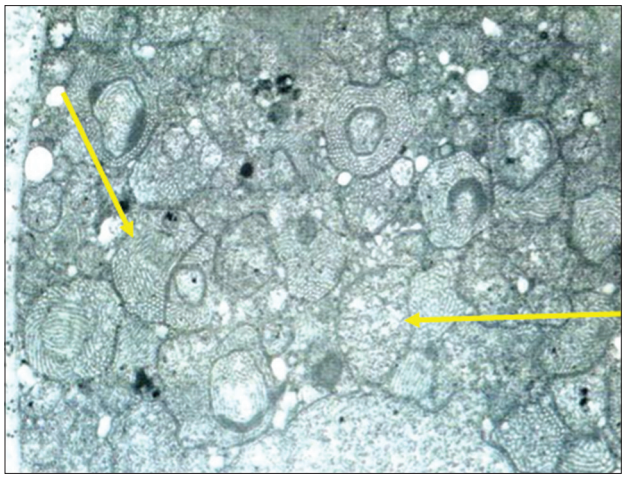

Figure 2: Patient in case #1 had electron microscopy (18,000×) showing structurally abnormal mitochondria (arrows), which are significantly larger and abnormally shaped compared to typical mitochondria

cystoscopies, a quadriceps muscle biopsy, and a left shoulder sebaceous cyst excision.

She has no former or current alcohol, tobacco, or drug use. She previously lived at home with her family. Her daughter also had KSS but passed away at the age of 32 years. Her current medications include oxycodone, temazepam, aripiprazole, aspirin, baclofen, vitamin D, hydralazine, levetiracetam, levothyroxine, metoprolol tartrate, pantoprazole, MiraLAX, senna, and venlafaxine. She has noted allergies to acetazolamide, lamotrigine, pregabalin, and gabapentin.

A physical exam demonstrated an obese female. She was alert, awake, and oriented only to herself, though the nursing staff stated that her mentation waxed and waned depending on her effort. Her vital signs showed a blood pressure of 118/78, a heart rate of 94, a height of 59 inches, and a weight of 177 pounds. A cardiovascular exam showed a regular heart rate with no murmurs, rubs, or gallops. Lungs were clear to auscultation bilaterally with rales, wheezing, or rhonchi.

A neurologic exam revealed deficits in cranial nerves 3, 4, 6, and 7. Extraocular eye movements were nearly absent bilaterally and she demonstrated impaired visual acuity bilaterally as well as decreased upward gaze. Her pupillary reflexes were intact. She showed no sensorineural hearing loss. She showed no ptosis, proptosis, or nystagmus. Sternocleidomastoid and trapezius muscle strength was 4/5 bilaterally. Extremity strength was 2/5 for the bilateral upper extremities and 1/5 for the bilateral lower extremities. Bulk muscle strength was diminished throughout. Her speech was a volitional stuttering speech. She had decreased sensation to light touch to bilateral lower extremities. The psychiatric mental status exam showed tangential thought processes, psychomotor retardation, blunted effect, very limited insight, and judgment. She followed simple commands. The remainders of the physical and mental status exams were unremarkable.

Magnetic Resonance Imaging (MRI) of the brain from available records showed no intracranial abnormality. She had an MRI of the lumbar spine that showed mild-to-moderate chronic anterior compression deformity of the T12 vertebral body with probable large Schmorl's node formation at the inferior endplate. She also demonstrated multilevel degenerative changes.

Discussion

KSS belonged to a group of primary myopathic disorders known as mitochondrial myopathies. One of the reasons why mtDNA mutations are associated with clinical disease is that mitochondrial DNA mutates at least 100 times as frequently as nDNA.[3] The relative amount and distribution of molecular lesions typically correlate with the clinical severity and morphologic features in the patient. However, even small amounts of wild-type genomes can be sufficient to protect tissues from oxidative phosphorylation defects, suggesting that there are still unknown factors influencing how the disease presents itself.[2] Both cases presented show cardinal features of KSS and provide examples of how a patient may present in a variety of settings with this disorder.

Disease presentation

As shown in both cases above, the clinical features of KSS cross many body systems. A comprehensive list of symptoms and features is described in Table 3.

Age of onset is generally before 20 years and family history is usually lacking because most mtDNA deletions are sporadic although sibling pairs with CPEO and KSS have been reported. Family history of features of KSS was noted in both cases presented.

Previous cases in the literature describe features such as pattern of maternal inheritance,[2] abnormally large abundant mitochondria in skeletal muscles,[3] mtDNA deletions,[4] and ragged red fibers on light microscopy with Gomori Trichrome

Table 3: Clinical Features of KSS[4,5]

System	Symptom/Feature
General/ Constitutional	Weakness, Fatigue, Short Stature, Exercise Intolerance
Eye	Progressive external opthalmoplegia, Ptosis, Impaired eye movement, Pigmentary retinopathy
Cardiac	Cardiomyopathy, Heart block
Hepatic	Hepatic Insufficiency
Renal	Renal insufficiency
Musculoskeletal	Myopathy, myoclonus
Neurologic	Ataxia, Neuropathy, Dementia, Migraines
Endocrine	Thyroid dysfunction, Pancreatic dysfunction, Diabetes Mellitus
Psychiatric	Depression, other disorders

Table 4: Diagnostic Studies for KSS[5,6]

Diagnostic Study	Likely Result
MRI Brain (T2 weighted)	Bilateral subcortical demylenating white matter changes (leukoencephalopathy), Cerebral or Cerebellar atrophy, lesions in the basal ganglia
Blood Testing	Elevated lactic acid
Lumbar Puncture	Elevated CSF Protein
EMG with Nerve Conduction Studies	Myopathy, Demyelinating Peripheral Neuropathy
Visual Evoked Response Testing	Delayed response in P100 range
2D Echocardiogram	Cardiomyopathy
Audiogram	Sensorineural Hearing Loss
DNA Testing (Southern blot or PCR analysis)	mtDNA mutations

stain.[7] Large-scale mtDNA mutations are found in up to 40% of adults with mitochondrial disease.[2] Table 4 describes diagnostic and laboratory findings common to KSS, many of which are seen in the preceding cases.

Workup

The initial workup for patients with suspected mitochondrial disorders includes a complete history and physical exam, keeping in mind subtle signs of family history (hearing loss, short stature), or complaints that are seen frequently in the primary care setting (fatigue, weakness, migraines, abdominal pain, depression, cardiac conduction defects, diabetes mellitus, and exercise intolerance). The workup should be complete and include tests listed in Tables 1 and 2. In addition, a Patient Health Questionnaire-2 (PHQ-2), and PHQ-9 if warranted, should be used to evaluate for the presence of depression.

Once the clinical suspicion for KSS or any mitochondrial disorder is raised, and the initial workup is undertaken, an interdisciplinary approach to care is recommended. Specialty referral to at least a neurologist is advised, as well as evaluation by cardiology, Otorhinolaryngology, endocrinology, psychiatry, and genetic counseling. This approach helps provide the appropriate support and treatment recommendations for the patient.

Treatment considerations

Treatment for patients with KSS is primarily supportive based on phenotypic presentation and includes folic acid supplementation, hormone replacement therapy, strabismus surgery, and cochlear implants depending on the affected organ system. Additional experimental therapies include endonuclease and zinc-finger nuclease, which reduces mutation load and coenzyme Q10 as a dietary supplement and mitochondrial antioxidant.[8] KSS has been suggested as an indication for prophylactic implantation of a pacemaker due to the risk of sudden cardiac death from complete heart block.[5] The degree of phenotypic variation and selection of organ system involvement attribute to uncertainty regarding the prognosis and life expectancy.[7]

Conclusions

This case series demonstrates the more common findings of KSS. The ability to identify unique and subtle features is crucial to physician recognition of this syndrome. A multidisciplinary team approach for comprehensive evaluation and treatment should be undertaken. Although there is no effective curative therapy, supportive treatment of end-organ dysfunction may be helpful for the quality of life. Primary care physicians are in the unique position to be able to adequately provide support and coordination of the complex level of care patients with KSS need.

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Conflicts of interest

There are no conflicts of interest.

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