**Retinal Cases and Brief Reports Publish Ahead of Print**
**DOI: 10.1097/ICB.0000000000001397**



# Kearns-Sayre Syndrome Masquerading as Myasthenia Gravis

**Running Title:** Kearns-Sayre Syndrome

Jared T. Sokol MD MBA[1], Sandra Hoyek MD[1], Anne B. Fulton MD[2], Nimesh A. Patel MD[1,2]

[1]Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA

[2]Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, MA

**Patient Consent:** Consent was obtained from the patient before the publication of the case

**Funding:** Patel Research Fund

**Conflicts of interest:** The following authors have no relevant financial disclosures: JTS, SH, NAP

Corresponding author: Nimesh A. Patel, MD, Retina Service, Massachusetts Eye and Ear, 243 Charles St, Boston, MA 02114, USA, E-mail address: nimesh_patel2@meei.harvard.edu

**Summary Statement:** We present a pediatric patient with a presumed diagnosis of myasthenia gravis who was found to have a mitochondrial pigmentary retinopathy and was eventually diagnosed with Kearns-Sayre syndrome after mtDNA sequencing revealed a novel large-scale deletion.

**Abstract:**

*Purpose:* Kearns-Sayre syndrome (KSS) is a mitochondrial DNA (mtDNA) deletion syndrome that is characterized by the triad of onset commonly before age twenty, pigmentary retinopathy, and chronic progressive external ophthalmoplegia. Here we present a case of KSS masquerading as myasthenia gravis (MG).

*Methods:* Case report.

*Results:* A 15-year-old male with a presumed diagnosis of MG presented with blurry vision, ophthalmoplegia, and ptosis. He was found to have a mitochondrial pigmentary retinopathy and was eventually diagnosed with KSS after mtDNA sequencing revealed a novel large-scale deletion of 7.9kb of mtDNA from nucleotides 6578 to 14,460.

*Conclusions:* We report a case of KSS found to have a novel large-scale mtDNA deletion. The presence of a mitochondrial pigmentary retinopathy found on dilated examination led to reconsideration of the previous diagnosis of MG and ultimately led to the correct diagnosis of KSS.

**Key Words:** Kearns-Sayre syndrome, mitochondrial DNA deletion syndrome, myasthenia gravis**,** pigmentary retinopathy, mitochondrial retinopathy

**Introduction:**

KSS is a mitochondrial DNA (mtDNA) deletion syndrome that is characterized by the triad of onset commonly before age 20, mitochondrial pigmentary retinopathy, and chronic progressive external ophthalmoplegia (CPEO). Additional features may include cardiac conduction abnormalities, cerebellar ataxia, endocrinopathies, myopathy (exercise intolerance and delayed muscle weakness), impaired intellect, hearing loss, short stature, renal impairment, and elevated cerebral spinal fluid protein[1]. KSS is caused by large mtDNA deletions and is usually sporadic; all involved tissues in KSS contain the mtDNA deletion, explaining the broad range of possible symptoms. Diagnosis is confirmed with genetic testing of mtDNA for large scale deletions[2]. Cardiac irregularities, especially conduction abnormalities, occur in the majority of KSS patients and can be fatal; a cardiac work-up may be lifesaving and should be performed in all KSS patients[1]. Here we report a pediatric patient who was misdiagnosed with myasthenia gravis (MG) due to symptoms of exotropia and ptosis but was later found to have a mitochondrial pigmentary retinopathy and was eventually diagnosed with KSS caused by a novel mutation.

**Case Report:**

A 15-year-old male with a history of ptosis, exotropia, and a presumed diagnosis of MG presented with blurry vision. Previous MG antibody panel, electromyogram, and chest MRI (evaluating for thymoma) were negative 7 years prior, but the patient's clinical presentation was consistent with MG so he was treated with pyridostigmine with mild temporary benefit. On presentation, the patient endorsed that for 16 months he noticed mild blurry vision in both eyes. He denied flashes, floaters, eye pain, or vision problems in dim light conditions but endorsed that

over the previous 8 years he had progressive limitation of extraocular movements. When performing physical activity, he has easy muscle fatiguability and soreness persisting for multiple days after exertion.

On examination, the patient had short stature and was underweight. Snellen visual acuity was 20/40 OD and 20/30 OS. Pupillary exam and intraocular pressure were normal. Ocular motility was abnormal with -4 limitation of elevation, abduction, and adduction and -3.5 limitation of depression in both eyes. External examination was notable for bilateral ptosis worse on the left. Dilated fundus exam was notable for bilateral widespread granular retinal pigmentary changes throughout the macula and periphery. Autofluorescence imaging showed diffuse granular hypoautofluorescence throughout the posterior pole and retinal periphery (Fig 1 A-B). Optical coherence tomography (OCT) was notable for bilateral scattered reflectivity changes in the ellipsoid and interdigitation zones throughout the macula with overall preservation of macular architecture (Fig 2).

Due to suspicion for a mitochondrial disorder, the patient underwent an extensive work-up including electroretinogram (ERG), mtDNA sequencing, growth differentiation factor 15 (GDF15) measurement, and consultation with a mitochondrial disease specialist. On full field ERG, scotopic sensitivities tested by blue flashes were below the 99% predication interval for normal in the right eye (+0.03 log scotopic seconds) and within the 99% prediction interval for normal in the left eye (-0.81 log scotopic seconds). Photopic function tested by red flashes on a white background and 30 Hz flickering white stimuli was below average in both eyes. Overall, ERG responses to full field scotopic and photopic stimuli were readily detectable but smaller

than average. Plasma GDF15 levels were elevated to 2727 pg/mL (reference value ≤ 750 pg/mL) and mtDNA genetic sequencing from blood revealed a 7.9kb deletion (m.6578_14460del7883) with 15% heteroplasmy, confirming the diagnosis of a mtDNA deletion syndrome. After consultation with a mitochondrial disease specialist, it was concluded that the patient most likely has Kearns-Sayre syndrome (KSS). Electrocardiogram was obtained that revealed abnormal cardiac conduction with a bifascicular block (left anterior hemiblock and complete right bundle branch block).

**Discussion:**

Here we report a case of 15-year-old male with a previously presumed diagnosis of MG who presented with short-stature, muscle fatiguability, ophthalmoplegia, ptosis, blurry vision, and a pigmentary retinopathy that was diagnosed with KSS after mtDNA genetic sequencing revealed a 7.9kb deletion. To our knowledge, this is the first report of the m.6578_14460 mtDNA deletion[3]. Like this patient, 90% of individuals with KSS have a single large-scale mtDNA deletion. A "common deletion" (m.8470_13446del4977) is present in approximately one third of patients with KSS[1]. These deletions are almost always sporadic, occur during oogenesis or early embryogenesis, and are rarely inherited. Similar deletions can cause different phenotypes based on the location of the mutated mtDNA during development; KSS results when the mtDNA deletion is present in all three germ layers[4]. Due to mtDNA heteroplasmy, non-invasive testing of blood, buccal, or urine may be non-diagnostic and skeletal muscle biopsy may be necessary to identify ragged-red fibers[1].

Irregularities of the ophthalmic system are the most common presenting symptom of KSS, with ptosis being the most frequent. The extraocular muscles have a high energy requirement and are particularly sensitive to mitochondrial dysfunction. Over the course of the disease, most patients will develop ptosis, ophthalmoplegia, and a mitochondrial pigmentary retinopathy, with a smaller proportion developing vision loss[5]. The mitochondrial pigmentary retinopathy can range from mild focal pigmentary irregularities to widespread pigmentary changes with chorioretinal atrophy that can involve the fovea[6,7]. The retinal pigment epithelium (RPE) is thought to be the primary affected cell layer, with early changes between the RPE and photoreceptors visible on OCT[7]. Given that the diagnosis of mitochondrial diseases is challenging and patients often undergo significant diagnostic odysseys, there is likely a role for mitochondrial retinal phenotyping as this can serve as an important biomarker to support or even confirm diagnoses of mitochondrial disease[7]. Although retinal changes in mitochondrial diseases have significant heterogeneity, Birtel et al. described three distinct phenotypes of mitochondrial retinopathy: type 1 with mild, focal pigmentary abnormalities; type 2 with multifocal white-yellowish subretinal deposits and pigment changes limited to the posterior pole; and type 3 with widespread granular pigment alterations. Additionally, some patients with type 2 or 3 retinopathy exhibited chorioretinal atrophy that typically started in the peripapillary and paracentral areas with foveal sparing[7]. The patient in this case falls into mild type 3, with widespread granular pigment changes without chorioretinal atrophy. Birtel et al. found that patients with type 1 and mild type 2 and 3 mitochondrial retinopathy had good visual acuity and patients with advanced type 2 and 3 with chorioretinal atrophy reported difficult in dim lights and/or reduced visual acuity[7].

Cardiac manifestations occur in up to 57% of patients with KSS and is the most important prognostic factor. Conduction abnormalities are the most common cardiac signs and can lead to

complete heart block with a mortality rate of 20%[8]. All patients should receive electrocardiogram and echocardiogram initially and at least every year. There should be a low threshold for pacemaker and implantable defibrillator placement[9].

The differential diagnosis of this patient's presentation includes MG, oculopharyngeal muscular dystrophy, myotonic dystrophy, oculopharyngodistal myopathy, congenital fibrosis of the extraocular muscles, thyroid eye disease, and isolated CPEO. Other possible mitochondrial diseases include MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke like episodes), MERRF syndrome (myoclonus epilepsy associated with ragged red fibers), Leigh syndrome, and Pearson marrow-pancreas syndrome.

This patient was incorrectly diagnosed with MG seven years prior to presentation based on his clinical presentation despite negative MG antibody panel, electromyogram, and chest MRI. Although MG can present with ptosis, eye movement abnormalities, and muscle fatiguability, it does not explain the patient's blurry vision and pigmentary retinopathy. To our knowledge, the patient had not had a previous dilated eye examination prior to the MG diagnosis; it is possible that an earlier dilated examination would have identified the pigmentary changes and alternative diagnoses would have been considered.

Given the broad manifestations of KSS, patients require evaluation by a multidisciplinary team including neurology, cardiology, ophthalmology, audiology, endocrinology, genetics, gastroenterology, and nephrology[9]. Although there is no clear evidence to support the use of any specific interventions for the treatment of mitochondrial diseases, many providers offer patients

various vitamins and cofactors, including Coenzyme-Q10, L-carnitine, creatine, α-lipoic acid, and certain B-vitamins[10].

Ophthalmologic management includes regular follow-up with testing and treatment depending on each clinical scenario; this may include electroretinogram, OCT, strabismus surgery, ptosis surgery, and prism glasses. Patients often require subspecialty care with a neuro-ophthalmologist, retinal specialist, and/or oculoplastic surgeon.

In summary, we report a patient with KSS with a novel large-scale deletion of 7.9kb of mtDNA from nucleotides 6578 to 14,460. The presence of a mitochondrial pigmentary retinopathy found on dilated examination led to reconsideration of the previous diagnosis of MG and ultimately led to the correct diagnosis of KSS. Therefore, we propose that all patients with eye movement abnormalities, especially children, undergo dilated fundus examination.

References

1. Goldstein A, Falk MJ. Mitochondrial DNA Deletion Syndromes. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*®. University of Washington, Seattle; 2003. Accessed September 17, 2021. http://www.ncbi.nlm.nih.gov/books/NBK1203/

2. Saldaña-Martínez A, Muñoz M de L, Pérez-Ramírez G, et al. Whole sequence of the mitochondrial DNA genome of Kearns Sayre Syndrome patients: Identification of deletions and variants. *Gene*. 2019;688:171-181. doi:10.1016/j.gene.2018.11.085

3. MITOMAP: A Human Mitochondrial Genome Database. Published 2019. Accessed March 3, 2022. http://www.mitomap.org

4. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. *N Engl J Med*. 2003;348(26):2656-2668. doi:10.1056/NEJMra022567

5. Khambatta S, Nguyen DL, Beckman TJ, Wittich CM. Kearns-Sayre syndrome: a case series of 35 adults and children. *Int J Gen Med*. 2014;7:325-332. doi:10.2147/IJGM.S65560

6. Padhy SK, Kumar V, Mandal S. Pigmentary retinopathy in Kearns-Sayre syndrome. *Case Reports*. 2018;2018:bcr. doi:10.1136/bcr-2018-227394

7. Birtel J, Landenberg C von, Gliem M, et al. Mitochondrial Retinopathy. *Oph Retina*. 2022;6(1):65-79. doi:10.1016/j.oret.2021.02.017

8. Chawla S, Coku J, Forbes T, Kannan S. Kearns-Sayre syndrome presenting as complete heart block. *Pediatr Cardiol*. 2008;29(3):659-662. doi:10.1007/s00246-007-9040-z

9. Parikh S, Goldstein A, Karaa A, et al. Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med*. 2017;19(12). doi:10.1038/gim.2017.107

10. Parikh S, Goldstein A, Koenig MK, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. *Genet Med*. 2015;17(9):689-701. doi:10.1038/gim.2014.177

**Figure Legends:**

Figure 1. Findings on presentation. (A, B) Ultra-widefield pseudocolor and corresponding autofluorescence images of the right eye demonstrating widespread granular retinal pigmentary changes and diffuse granular hypoautofluorescence throughout the posterior pole and periphery. Findings were similar in the left eye.

Figure 2. Spectral domain optical coherence tomography imaging of the right eye showing bilateral scattered reflectivity changes in the ellipsoid and interdigitation zones throughout the macula with overall preservation of macular architecture. Findings were similar in the left eye.