

Ophthalmic manifestations suggesting Kearns-Sayre Syndrome among young adults with cardiac conduction defects (RCD code: III-1A.5a)

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Abstract

Kearns-Sayre Syndrome is a multisystemic mitochondrial cytopathy characterized by specific ophthalmic signs, cardiac conduction disturbances with endocrine, musculoskeletal and central nervous system involvement. As a highly heterogeneous condition, establishing an accurate diagnosis of this disorder can often be seriously delayed. It usually occurs before the age of 20 with ocular symptoms at first. Cardiac manifestations include progressive degeneration of the conduction tissue, leading to different types of conduction disturbances, which in many cases are responsible for significant decrease of life expectancy. There is currently no causative therapy available for Kearns-Sayre Syndrome patients. Several interventions including ophthalmic or neurological may be necessary in order to improve the quality of life, however improving prognosis in this group of patients impose prompt recognitions of those, who require early pacemaker implantation. Therefore, the aim of this article is to review the current knowledge about Kearns-Sayre Syndrome in light of the most typical ophthalmic findings, which can handily be detected by cardiologists and applied to accelerate accurate diagnosis and elaborate the most appropriate therapeutic strategies. JRCD 2016; 3 (1): 5–8

Key words: rare disease, mitochondrial cytopathy, sudden cardiac death, pigmented retinopathy, ophthalmoplegia, ptosis, cardiac pacing, electrocardiography

Introduction

Kearns-Sayre Syndrome (KSS) is a rare mitochondrial cytopathy described for the first time in 1958 at Mayo Clinic as a case report of two patients [1].

Mitochondrial cytopathies include wide spectrum of biochemical and structural abnormalities affecting mitochondria, which can be inherited or acquired. Mitochondria play a principal role in generating adenosine triphosphate (ATP) through oxidative phosphorylation, as well as and in regulating other cell functions, such as response to oxidative stresses, heat production, and apoptosis [2]. Dysfunction of mitochondrial respiratory chain results in aerobic metabolism impairment, therefore tissues and organs which present high aerobic metabolism are mainly affected [3].

Clinically, KSS is a heterogeneous, neurodegenerative syndrome involving musculoskeletal, central nervous, cardiovascular, and endocrine systems. The exact prevalence is unknown. It is estimated between 1/100 000 – 1/30 000 based on over 200 cases published so

far [4]. It is classified as a mitochondrial DNA (mtDNA) deletion syndrome [5,6].

The most common mutation associated with KSS includes deletion of 4997 nucleotides accounting for twelve mitochondrial genes. Deletions of mtDNA result in loss of mitochondrial proteins, impairment of oxidative phosphorylation and a decrease in cellular energy production [7]. Regardless of which genes are affected, any step of oxidative phosphorylation may be compromised. Like in other mitochondrial diseases no clear correlations between genotype and KSS phenotype have been determined so far [7]. Inherited and sporadic mutations have been identified affecting both males and females [8].

KSS comprises of classical triad of diagnostic criteria: chronic progressive external ophthalmoplegia (CPEO), pigmentary retinopathy (RP) and onset in young adults before the age of 20. Additional findings essential for diagnosis of KSS include one or more of the following features: cardiac conduction disorders, cerebellar ataxia or increased cerebrospinal fluid protein level of >100 mg/dL [1,9]. The onset of the disease normally occurs in childhood, usu-

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Table 1. Symptoms and signs of the Kearns-Sayre Syndrome together with their prevalence

Sign/Symptom	Percentage [8,23]
Onset age <20 yrs	100%
Pigmentary retinopathy	100%
Progressive External Ophthalmoplegia	100%
Cerebellar syndrome	84%
Limb weakness	94%
Sensorineural hearing loss	97%
Impaired intellect	86%
cardiac symptoms	57%
syncope	46%
sudden death	23%
cardiomyopathy	20%
Diabetes mellitus	13%
Seizures	2%

ally with ocular manifestations at first. The most common is CPEO, a gradual weakening of eye muscles and restriction of eye movements coexisting with ptosis. Ocular signs can be associated with central nervous system dysfunctions such as proximal skeletal muscle weakness, mental retardation, dementia, dysarthria, dysphagia, dystonia, hearing loss, ataxia, bilateral facial weakness and encephalopathy. Endocrine disorders such as diabetes mellitus, hypoparathyroidism, irregular menstruations and growth hormone deficiency have been reported in many cases (Table 1) [9]. Although identification of KSS is achieved on the ground of clinical features, confirmation require histological, molecular and biochemical testing [8]. Muscle biopsy is considered to be the gold diagnostic standard. Typically for KSS, it reveals characteristic “ragged red fibres” on trichrome stain as a manifestation of abnormal mitochondrial proliferation and “ragged blue fibers” when succinate dehydrogenase histochemical staining is performed (Table 2) [10]. Muscle specimen is taken from affected skeletal muscle. Apart from routine light microscopy, other several specimen tests are available, such as: electron microscopy to reveal abnormally shaped or sized mitochondria, paracrystalline inclusions, and proliferation of mitochondria, electron transport chain enzyme activity, carnitine disorders, fatty acid oxidation activity, and glycogen storage disease analysis [11].

Genetic testing shows a large scale mtDNA deletions among 90% of affected individuals, which can be accompanied by large-scale duplications of mtDNA in some cases [6].

Treatment for KSS is only symptomatic. It includes coenzyme Q10 administration at daily doses of 120–150 mg, which can be effective in improving abnormal metabolism of pyruvate and NADH oxidation in skeletal muscle, monitoring and surgical management of ocular manifestations and management of cardiac complications such as pacemaker implantation [12].

Table 2. Diagnostic procedures for Kearns-Sayre Syndrome

Echocardiogram and electrocardiogram	to evaluate cardiac conduction and contractility
Electromyogram and nerve conduction studies	Consistent with a myopathy, but neuropathy may coexist
Muscle biopsy	Typically shows ragged-red fibers (RRF) with the modified Gomori trichrome stain and hyperactive fibers with the succinate dehydrogenase stain. Both RRF and some non-RRF fail to stain with the histochemical reaction for cytochrome c oxidase
Brain Magnetic Resonance Imaging	Sometimes shows leukoencephalopathy, often associated with cerebral or cerebellar atrophy or basal ganglia lesions
Lactate and pyruvate concentrations in blood and cerebrospinal fluid (CSF)	Commonly elevated at rest and increase excessively in blood after moderate activity
Fasting serum glucose concentration	to screen for diabetes mellitus
Biochemical studies of respiratory chain enzymes in muscle extracts	Usually show decreased activities of respiratory chain complexes containing mtDNA-encoded subunits, especially when enzyme values are referred to the activity of citrate synthase, a good marker of mitochondrial “mass”. However, depending on the mutational load, biochemical studies may also be normal

Cardiac manifestations

Cardiac manifestations occur in 57% of patients with KSS [13]. Typically patients with KSS present with progressive degeneration of cardiac conduction system. Other cardiovascular features include: syncopal attacks, heart failure and cardiac arrest. The most important prognostic factor in KSS patients is the involvement of the heart, typically characterized by progressive conduction system degradation [14].

ECG findings include wide range of abnormalities, which may change over the patients’ lifetime, often without any prodromal signs. All types of sino-atrial, atrio-ventricular and intraventricular conduction delays have been reported. Preexcitation syndromes such as Wolff-Parkinson-White syndrome has also been reported [14,15]. Ventricular tachyarrhythmia in the presence of normal or prolonged QT interval are not uncommon. Predominantly, onset of a complete heart block, has been suggested as a mechanism of sudden death in individuals with KSS. Long QT syndrome is another possible reason for sudden death accounting for cardiac arrests due to ventricular tachycardia [16].

Patients with KSS with less advanced conduction defects may experience a rapid progression to complete heart block with an associated mortality rate of 20% [13].

Permanent pacemaker implantation in KSS is taken into consideration even in patients with less advanced symptoms, because of the rapid progression of involvement of the conduction tissue. Due to progressive nature of the disease, a form of “prophylactic” car-

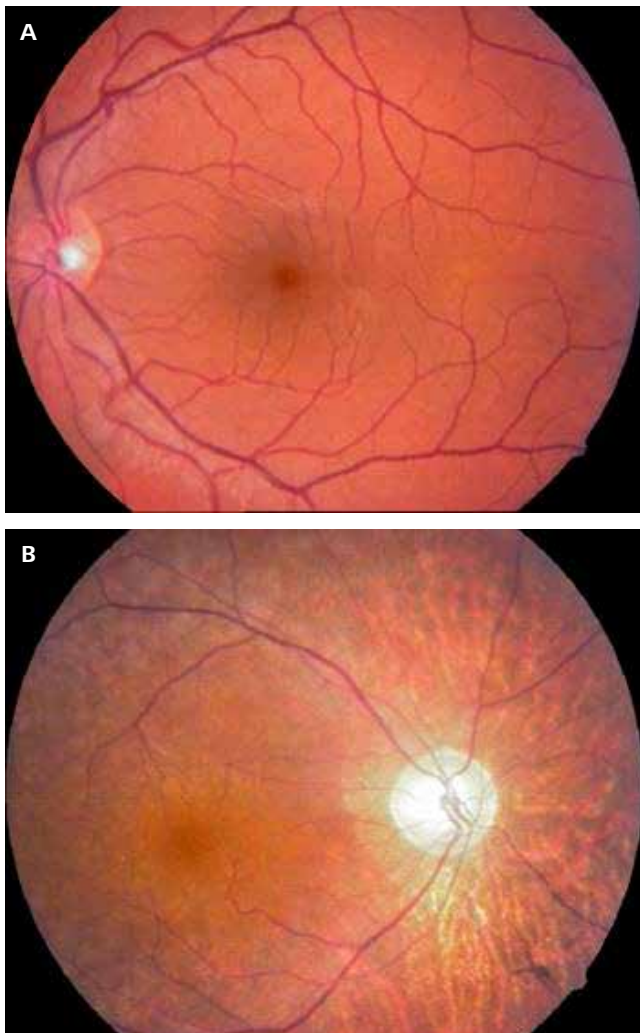


Figure 1. A. Normal eye fundus. B. Salt and pepper type changes of the eye fundus

diac pacemaker implantation may sometimes be considered also in patients without contemporary guideline – based indications [17].

Ocular manifestations

Patients with KSS often show no abnormalities at birth, but many of them have a history of encephalitis or meningitis in childhood [18]. The most common ophthalmic symptoms include ptosis, CPEO and pigmentary retinopathy.

Ptosis

Ptosis is the very first sign of KSS in majority of described cases. It usually starts in adolescence, always before the age of 20. Drooping of the upper eyelid is predominantly bilateral, but can be asymmetric. It is characterized by a sudden onset and slowly progressive course leading almost always to severe dysfunction. Palpebral levator muscle function test is significantly reduced and can induce visual field deficiency and visual acuity impairment.

This test can be performed by doctor of any specialty. The levator function is determined by holding the brow immobile with a thumb, placing a millimeter ruler over the lid in the plane of the pupil and measuring the levator excursion from extreme downgaze to extreme upgaze. Levator function can be graded as: normal >15 mm, good: 12–14 mm, fair: 5–11 mm, poor <4 mm. To compensate this disturbances, patients have the tendency to use their brow muscles to elevate their eyelids, lift up their chins and lean their heads backwards. Management of ptosis is always surgical. The most frequently recommended correction procedure is lid brow suspension with the use of either silicone tape or fascia lata autograft [18–20].

Chronic progressive external ophthalmoplegia

CPEO usually begins after ptosis onset. Weakening of eye muscles is bilateral, symmetric, gradually deteriorating with no episodes of exacerbations nor remissions. Usually, upward gaze is affected at first and it is soon followed by horizontal gaze limitation. Downward gaze is very often spared, but eventually eye bulbs become completely immobile and fixed in the primary position. Eye movements can be examined by having the patient look in all directions without moving their head. Patients with KSS very often complain about problems with reading due to convergence insufficiency. Less common manifestation of CPEO is incomitant strabismus, however diplopia is very rare because eye movement restrictions develop slowly and symmetrically. Pupil muscles are never affected [19].

Pigmentary retinopathy

Pigmentary retinopathy (retinitis pigmentosa) is a group of clinically and genetically heterogenous diffuse retinal dystrophies, characterized by night blindness (nyctalopia), gradual loss of peripheral visual field and typical finding in eye fundus examination such as optic nerve waxy pallor, bone spicules – midperipheral retinal hyperpigmentation in a characteristic pattern, atrophy of the retinal pigment epithelium in the mid periphery of the retina, retinal arteriolar restriction and abnormal electroretinographic responses. Symptoms typically occur in early adulthood as night blindness and prolonged period of time needed to adapt from light to dark, followed by slowly deteriorating peripheral visual field loss, often described as a “tunnel vision”. In some cases central retina may be affected as well, leading to functional blindness. Prognosis depends on many factors such as age of onset or type of inheritance [19]. The underlying defect is thought to be apoptosis of rod photoreceptor cells, but cone photoreceptors and retinal pigment epithelium may also be affected [21]. In KSS however, pigmentary retinopathy occurs in atypical presentation. Eye fundus examinations usually reveals mild “salt and pepper” appearance (Figure 1), whereas bone spicules formations are very uncommon. Visual symptoms are less severe comparing to classic pigmentary retinopathy [19]. Treatment of retinitis pigmentosa is limited

and only symptomatic. Low vision devices such as magnifiers or high – powered spectacles may be useful for maximizing remaining vision. Dietary supplements such as vitamin A may have some positive influence [22]. Clinical research is mainly focused on gene therapies and retinal transplant options. Differential diagnosis includes any disease caused by large mtDNA deletions such as: Pearson syndrome or maternally-inherited progressive external ophthalmoplegia, MELAS, MERRF, NARP as well as pigmentary retinopathy, miasthenia gravis or myotonic dystrophy [4,8].

Summary

Despite existing studies, KSS remains a difficult syndrome to recognize because of the variety of clinical manifestations and the lack of any large case series to date. Prognosis for patients with KSS is variable and very often difficult to predict. In majority of cases death occurs in the third or fourth decade of life. Cardiac complications often decrease life expectancy. Accordingly, patients with this life threatening condition should be monitored precisely by interdisciplinary team at any stage of their disease, in order to apply an appropriate therapy without any delay. Patients presenting with early onset of progressive cardiac disturbances should always be monitored for ophthalmic symptoms. The association of ophthalmic presentation with cardiac complications could accelerate the accurate diagnosis of the KSS.

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