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CASE REPORT

A Holistic Approach to a Rare Case of Kearns–Sayre Syndrome

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Mitochondrial disease, which was previously considered as a rare clinical entity, is presently identified as a significant cause of a broad range of muscle, cardiac, neurologic, as well as endocrine disorders. One of the rare mitochondrial diseases is Kearns–Sayre syndrome (KSS). Here, we present a case of a 22-year old male with progressive bilateral blepharoptosis of 5-year duration, which was painless and not associated with diplopia or vision loss. There were no similar abnormalities in his family. On neurologic examination, prominent bilateral blepharoptosis was evident with restriction of ocular movements. There was a salt-and-pepper pigmentary retinopathy with normal optic disks and vessels. Cerebrospinal fluid protein concentrations were increased, and a diagnosis of KSS was made.

Key words: Kearns–Sayre, neurologic, retinopathy, salt and pepper

INTRODUCTION

Mitochondrial disorders are considered to be the most common type of inherited metabolic disorders. The mitochondrial diseases are a clinically heterogeneous group of disorders, which are caused due to a dysfunction in the mitochondrial respiratory chain.[1] In 1958, Kearns and Sayre reported this syndrome first time, with a diagnostic triad of external ophthalmoplegia, pigmentary degeneration of the retina, and complete heart block. The syndrome occurs sporadically and is rarely autosomal dominant.[2]

Kearns–Sayre syndrome (KSS) is a rare variety of mitochondrial disease, which is characterized by onset before 20 years of age. A minimum one of the signs (cerebellar ataxia, cardiac conduction defect, or increased cerebrospinal fluid [CSF] protein concentration [>100 mg/dL]) usually aids in the diagnosis.[3] KSS is caused due to mitochondrial DNA (mtDNA) deletions, which results in the impairment of oxidative phosphorylation and reduction of adenosine triphosphate production.[4]

The significance of the entity lies in the fact that it may mimic other neuromuscular disorders and may remain undiagnosed, leading to increasing complications and other abnormalities such as heart conduction defects (50% cases), neurological degenerations, growth abnormalities, and multiorgan endocrine disorders.[5,6]

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Because of the rarity of this disorder and due to its variable presentation, we present a case report of a 22-year-old male who had features suggestive of KSS to propagate our clinical experience of this syndrome.

CASE REPORT

A 22-year-old male patient, driver by occupation, presented to the neurology clinic of our hospital with chief complaints of drooping of both eyelids for the past 5 years. The drooping of the eyelids was insidious in onset, with gradual progression, symmetrical, and painless. He had no history of visual impairment, diplopia, facial and/or limb weakness/sensory deficit, difficulty in swallowing, nasal regurgitation, hoarseness of voice, vertigo, tinnitus, hearing loss, seizures, headache, or fever. Bladder and bowel functions were also normal. He had no history of any chronic medical disease. Family history was negative of any such condition.

He was a nonsmoker and nonalcoholic with no history of drug abuse. The general physical examination showed no abnormality. Cardiac and respiratory system examination and mental status were normal.

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Eye examination showed bilateral reactive pupils. The bilateral ptosis was present which progressed over since childhood with present palpebral aperture/fissure of 6 mm [Figure 1]. Vision was 6/6 in both eyes. Fundus revealed pigmentary retinopathy (salt-and-pepper appearance) [Figure 2]. Extraocular movements were restricted in all planes. Levator excursion was 7 mm. The face was symmetrical with intact sensations.

Blood investigations showed normal blood counts and liver and kidney functions. CSF examination was acellular, but showed high protein (74 mg/dL) and normal sugar (67 mg/dL). Electrocardiogram (ECG) and magnetic resonance imaging of the brain and the orbit showed no significant changes [Figure 3]. Due to nonavailability of the facility of genetic testing at the institute, it could not be performed. Sartorius biopsy showed "ragged-red fibers" on Masson's trichrome stain, and a diagnosis of KSS was made. The patient was managed conservatively and advised education at home, coenzyme Q10 and α-lipoic acid supplementation, and mild isotonic exercises.

DISCUSSION

KSS is a variety of mitochondrial disease and is usually maternally transmitted.[7] The index case showed a classical early presentation before 20 years of age with no history for any such disease in the family.[6] Our findings of early age presentation with progressive deterioration of the eye muscles were in line with previous studies by Islam *et al*., Leal *et al*., Bhatnagar and Gupta, and Holloman *et al*.[1,4,6,7] In contrast, few of the studies reported a late onset of the disease, suggesting that some atypical variants of KSS may present later in life.[8,9]

The index case presented with only ptosis, which is a subtle clinical finding of one of the various phenotypes of KSS. As reported previously, the complaints in a KSS patient may depend on the proportion and degree of mtDNA mutation and encompass a list of presentations such as fibromyalgia, skeletal muscle weakness, ptosis, pain, fatigue, exercise intolerance (progressively worsening with time), slowly progressive peripheral muscle weakness, multisystem organ failure, or respiratory insufficiency requiring mechanical ventilation.[1,8] Diabetes mellitus, growth hormone deficiency, and hypoparathyroidism are the endocrine disorders that are found to be related with KSS. Certain cardiac abnormalities such as atrioventricular blocks, right bundle branch block, and cardiomyopathy have also been found to be associated along with ptosis as seen in the case reports by Bhatnagar and Gupta,[7] Song,[8] and Ahmad SS *et al*.[9] However, none of such cardiac, endocrine, and other complications were seen in our case.

Ophthalmologic manifestations are the early and chief complaint of the patients with KSS, including ptosis and external ophthalmoplegia.[1,5-7] Our patient had features of both myopathy and neuropathy along with ocular involvement sparing pupil, but had no fatigable weakness which helped us to rule out myasthenia gravis. Among other previous reports, KSS has been confused with differentials such as progressive external ophthalmoplegia (PEO), myasthenia gravis, MELAS syndrome, Pearson's syndrome, and retinitis pigmentosa. Islam *et al*. confused whether they were dealing with patient of myasthenia gravis or myopathy or hereditary neuropathy.[1] Bhatnagar and Gupta reported a case of a 14-year-old boy who was initially misdiagnosed as myasthenia gravis.[7] As there is low prevalence and less documentation of cases of KSS, its diagnosis is challenging. When a patient presents with the classic triad of KSS, i.e., pigmentary retinitis, PEO, and alterations in cardiac conduction, a clinical suspicion should arise. However, even in the absence of cardiac dysfunction and presence of retinal degeneration, one must keep a differential of KSS and must opt for further investigations such as CSF examination.[6]

It has been seen that increased protein concentration with normal sugar and no cells in CSF examination and the characteristic pigmentary degeneration of retina termed as "salt-and-pepper" or "moth-eaten appearance" may help substantiate the evidence of diagnosis toward KSS.[7] However, one of the studies showed the absence of characteristic salt-and-pepper retina, and the diagnosis was confirmed on biopsy of the orbicularis muscle.[8,9] Even in our case, sartorius muscle biopsy was done which revealed characteristic "ragged-red fibers" on trichrome stain. In the absence of genetic testing facility and standard guidelines, muscle biopsy

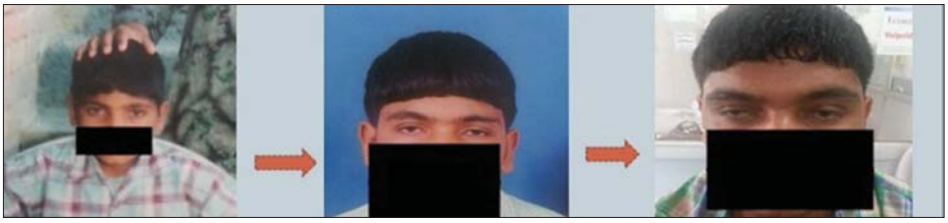

Figure 1: Progression of bilateral ptosis since childhood

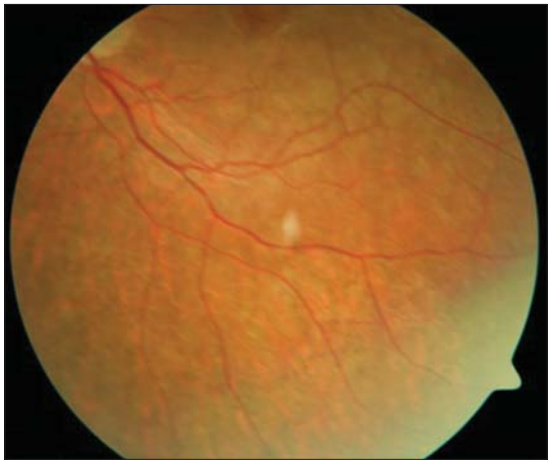

Figure 2: Fundus showing salt-and-pepper degeneration

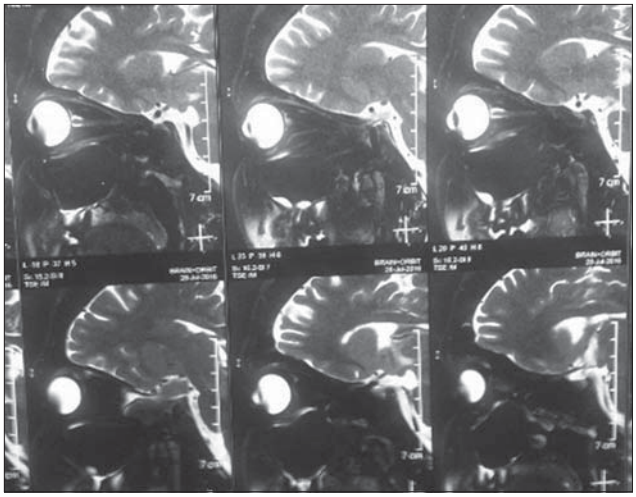

Figure 3: Magnetic resonance imaging of the brain and orbit showing no significant changes

is one of the confirmatory tests for the diagnosis of KSS as seen in various previous case reports.[6,9-11]

Even after a daunting task of the diagnosis, there is no permanent cure to it. The management of the mitochondrial disease is largely supportive, as there is no way of simply increasing the capacity of the cell to generate energy. The index case was also managed conservatively, and the patient showed improvement in the follow-up of 1 month. Treatment involves optimizing energy production, reducing energy losses, meeting lifestyle needs such as education, and monitoring for complications along with proper counseling of the patient and his caregivers.[12,13] Some of the patients can get benefit from coenzyme Q10. It helps in improvement of the lactate metabolism and heart and muscle function; however, ocular manifestations do not improve.[1]

Recently, various empiric interventions have been used in the treatment of mitochondrial diseases. Dietary and pharmacological agents include creatine monohydrate (CrM) (alternative energy source and antioxidant), α-lipoic acid (antioxidant and CrM uptake enhancer), Vitamin C, E, and K (antioxidants), lutein, selenium (antioxidant), and coenzyme Q10 (antioxidant and bypass supplement for defected complex I). A study by Rodriguez *et al*. showed that a combination therapy with CrM, coenzyme Q10, and α-lipoic acid significantly improved resting plasma lactate concentrations, body composition, ankle dorsiflexion strength, and oxidative stress compared to placebo treatment as was seen in the index case.[14]

The index case was followed up for a period of 1 month after which he did not come for routine follow-up investigations such as annual ECG, echocardiography, biochemistry, and audiometry for screening common endocrine disturbances.[15] Usually as seen among other studies, a multiclinic follow-up comprising ophthalmology, audiology, endocrinology, neurology, cardiology, and neuropsychiatry consultations must be done. The patient was also advised at-home exercise to improve endurance, peak work capacity, and oxygen utilization and extraction, thereby slowing and reversing the deconditioning that occurs in patients with mitochondrial disease. The resistance training is hypothesized to decrease the load of mutant mtDNA by stimulating satellite cells to replace or repair the muscle fibers damaged by the exercise.[4]

Limitations of the study

The case report suffers from the limitations to not able to demonstrate the histologic picture of the typical "ragged-red fibers" and the genetic examination to show mutation at mitochondrial gene.

CONCLUSION

We should have a high index of suspicion for KSS when encountering cases of musculoskeletal disorders below 20 years of age. This is in the interest of the patient in view of high morbidity and mortality associated with KSS. Initial presentation of this syndrome may mimic other musculoskeletal disorders such as myasthenia gravis with totally different line of management. The role of ophthalmologist and pathologist is important here to look for the characteristic retinal and muscle degeneration.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name

and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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