Case Report

Journal Homepage: http://crcp.tums.ac.ir

Kearns Sayre Syndrome: A Rare Cause of Mitochondrial Diabetes and Hypogonadotropic Hypogonadism

Sriram Mudraje*, Jaideep Khare, Nancy Garg, Sushil Jindal

Department of Endocrinology, People's College of Medical Sciences and Research Centre, Bhopal,India.

Use your device to scan and read the article online

Citation Mudraje S, Khare J, Garg N, Jindal S. Kearns Sayre Syndrome: A Rare Cause of Mitochondrial Diabetes and Hypogonadotropic Hypogonadism. Case Reports in Clinical Practice. 2024; 9(4): 186-191.

Running Title Kearns Sayre Syndrome

ABSTRACT

Kearns-Sayre syndrome is a rare mitochondrial disease that presents before the age of 20 years with ptosis, external ophthalmoplegia, and pigmentary retinopathy associated with endocrine and cardiac conduction abnormalities. Here we report an 18-year-old female presenting with fever, cough, secondary amenorrhea, diabetes, ptosis, external ophthalmople gia, and ataxia . Fundosc opy revealed pigmen tary retinopathy. ECG showed intraventricular conduction abnormalities, and 2D echocardiography revealed global left ventricular hypokinesia with reduced ejection fraction. Hence, the diagnosis of Kearns-Sayre syndrome was made.

Article info:
Received: July 24, 2024
Revised: August 8, 2024
Accepted: August 20, 2024

Keywords:
Kearns sayre syndrome;
Mitochondrial diabetes;
Pigmentary retinopathy;
Ophthalmoplegia

Introduction

Kearns–Sayre syndrome (KSS) was first described in 1958 as a rare mitochondrial myopathy. The prevalence of KSS is approximately 1–3 per 100,000 individuals. The disease usually presents before 20 years of age with bilateral ptosis and exercise intolerance. Other frequently associated clinical features include cerebrospinal fluid (CSF) protein elevation or cerebellar ataxia, dementia, deafness, proximal myopathy, short stature, and several endocrine disorders such as diabetes mellitus, thyroid dysfunctions, Addison's disease, and hypoparathyroidism. The clinical triad of external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects is sufficient to make a confident diagnosis. Here, we report a rare case of an 18-year-old Indian female with KSS [1π0].

Case presentation

An 18-year-old girl presented with epigastric pain for 2 days. She also complained of fever, cough, and weight loss of 3 kilograms during the last 2 months. The fever was low-grade and associated with evening rises. She expectorated scanty whitish sputum. She had progressive ptosis for the last 6 years. She had no loss of vision, diurnal variation of ptosis, or hearing loss. Additionally, she had no history suggestive of

*** Corresponding Author:**
Sriram Mudraje
Address: *People's College of Medical Sciences and Research Centre, People's University, Bhopal.*
E-mail: *shriram.mudraje@gmail.com*

limb weakness or myasthenia. She also complained of amenorrhea for the last 2 years, which was preceded by oligomenorrhea for 4 months. Her age of menarche was 12 years, and she had regular cycles for 4 years after menarche. She had no history suggestive of cardiac illness, tingling or numbness of limbs, or any history suggestive of tetany.

She was diagnosed with diabetes mellitus 6 years ago and was prescribed basal-bolus insulin, but her compliance with insulin was poor. She was the firstborn child of a non-consanguineous marriage. Family history for diabetes was absent, and there were no similar complaints in the family.

On examination, her pulse rate was 134/minute, and her blood pressure was 106/66 mm Hg. Her height was 135 cm, and her weight was 30 kg, with a BMI of 16.46 kg/m^2. Higher mental functions were normal. Cranial nerve examination revealed ptosis and ophthalmoplegia involving all extra-ocular muscles (Figure 1). Pupils were normal in size and reactive to light. Limb muscle tone, power, and reflexes were normal. Dysdiadochokinesia and ataxia were noted. Meningeal signs were absent. Pubarche was present. Tanner staging was B1P2.

Respiratory system examination revealed signs of cavitary consolidation. Cardiovascular and abdominal examinations were normal.

Serum electrolytes, serum amylase, and serum lipase were normal (Table 1). Arterial blood gas analysis was normal. Sputum for acid-fast bacilli was normal; however, sputum CBNAAT (Cartridge-Based Nucleic Acid Amplification Test) showed a sensitive strain of Mycobacterium tuberculosis.

Electrocardiogram showed right bundle branch block with left anterior fascicular block (Figure 2). 2D-echocardiography revealed global left ventricular hypokinesia with an ejection fraction of 40% and mild mitral valve prolapse.

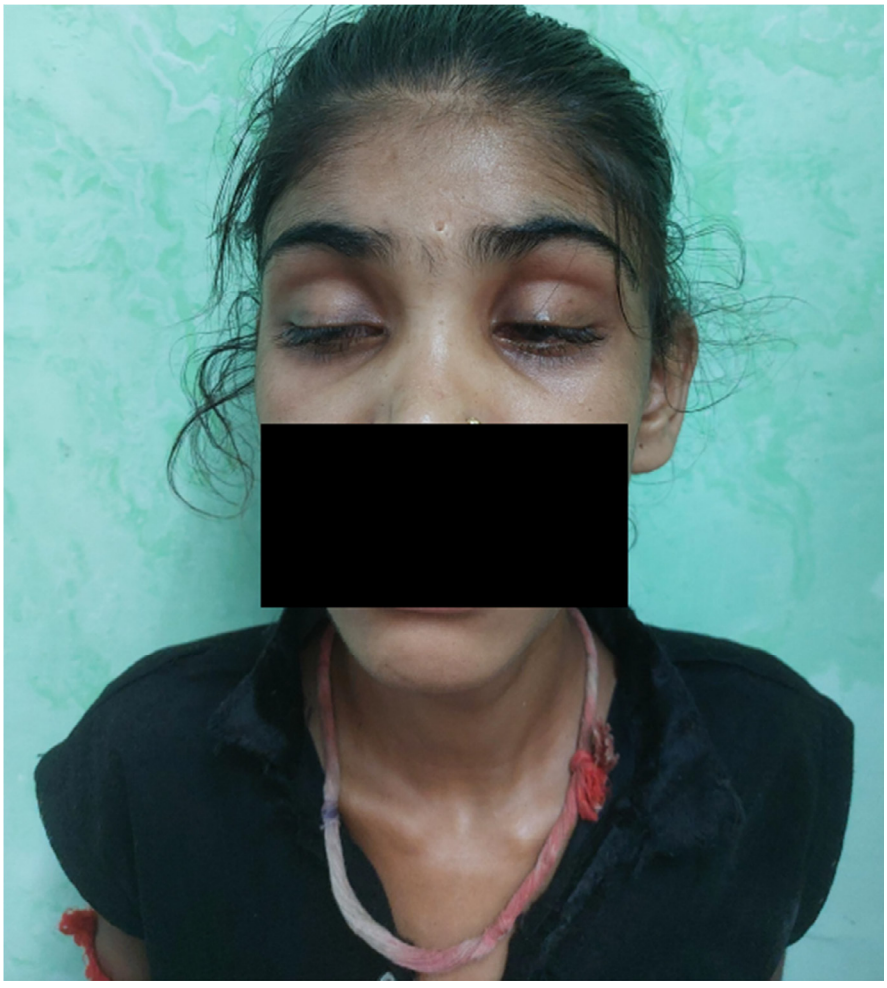

Fig. 1. Ptosis and ophthalmoplegia

Table 1. Laboratory findings

PARAMETER	RESULT		REFERENCE RANGE
	AT PRESENTATION	AT 6 MONTH FOLLOW UP	
Hemoglobin (g/dL)	9.5	11.8	12-14
ESR (mm/hour)	65	18	0-20
Random blood sugar (mg/dL)	542	146	100-140
Serum creatinine (mg/dL)	0.8	0.9	0.6-1.3
Urine Ketones	3+		NIL
Urine sugar	3+		NIL
Urine albumin	2+		NIL
Serum Albumin (g/dL)	2.42	4.1	3.2-5.5
Serum Total Calcium (mg/dL)	8.5	9.1	8.5-10.5
Serum Alkaline phosphatase (IU/L)	123	86	<110
Serum Triglycerides (mg/dL)	202	-	<150
Serum LDL cholesterol (mg/dL)	74	-	<100
Serology for HIV	Non-Reactive	-	-
TSH (µIU/mL)	2.1	2.6	0.55-4.2
Free T4 (ng/dL)	1.0	1.1	0.7-1.6
Follicle-stimulating-hormone (mIU/mL	-	0.2	3-10
Luteinizing-hormone (mIU/mL)	-	0.3	5-25
Serum prolactin (ng/mL)	-	10.2	<25
8AM-Cortisol (µg/dL)	-	16.4	4-22

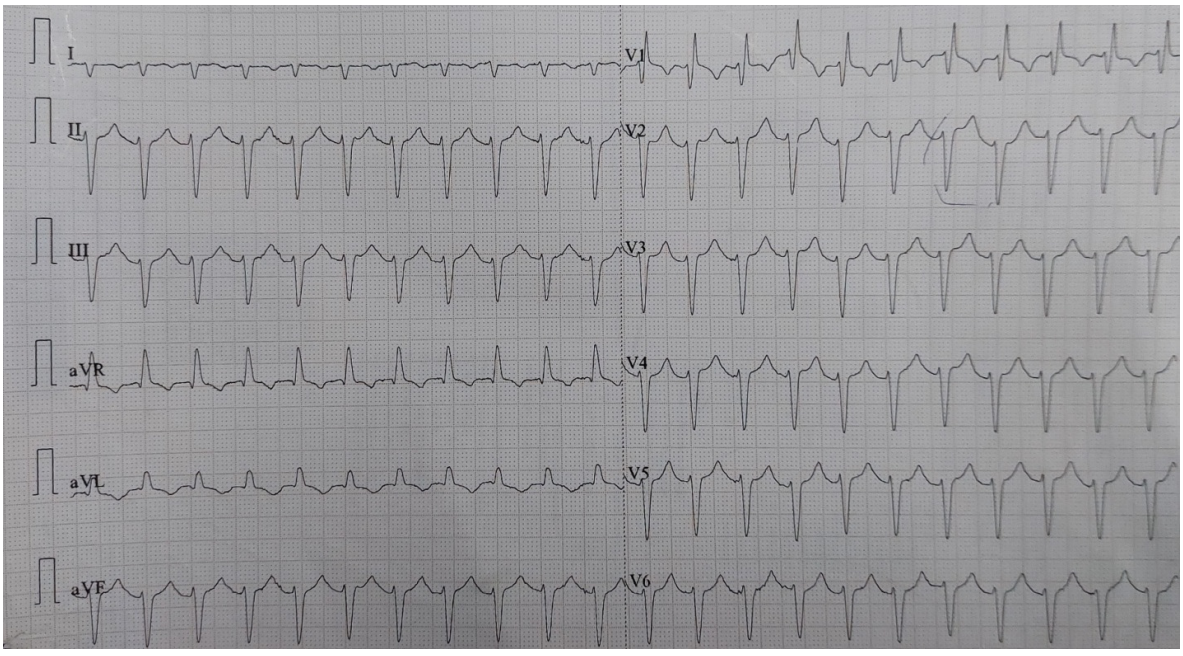

Fig. 2. ECG, Right bundle branch block with left anterior fascicular block.

Ophthalmological fundoscopy revealed pigmentary retinopathy (Figure 3). Ultrasound of the abdomen and pelvis was normal. MRI of the brain and orbit with contrast was normal. Audiogram was normal.

A final diagnosis of Kearns-Sayre Syndrome with Pulmonary Tuberculosis was made as the patient had ptosis, external ophthalmoplegia, cerebellar ataxia, intraventricular conduction abnormalities, diabetes mellitus, hypogonadotropic hypogonadism, and pigmentary retinopathy.

For treatment, she was hydrated with intravenous fluids, and regular insulin infusion was given. Basal-bolus insulin with glargine U-100 and regular insulin, respectively, was initiated later on. Anti-tubercular drugs (Isoniazid 300 mg + Rifampicin 450 mg + Ethambutol 800 mg + Pyrazinamide 750 mg) were started as per standard protocol. Pyridoxine and multivitamins were given. Tablet Ivabradine 5 mg once a day and tablet telmisartan 20 mg once a day were started as advised by the cardiologist. She was advised on a diabetic diet, and insulin education was given.

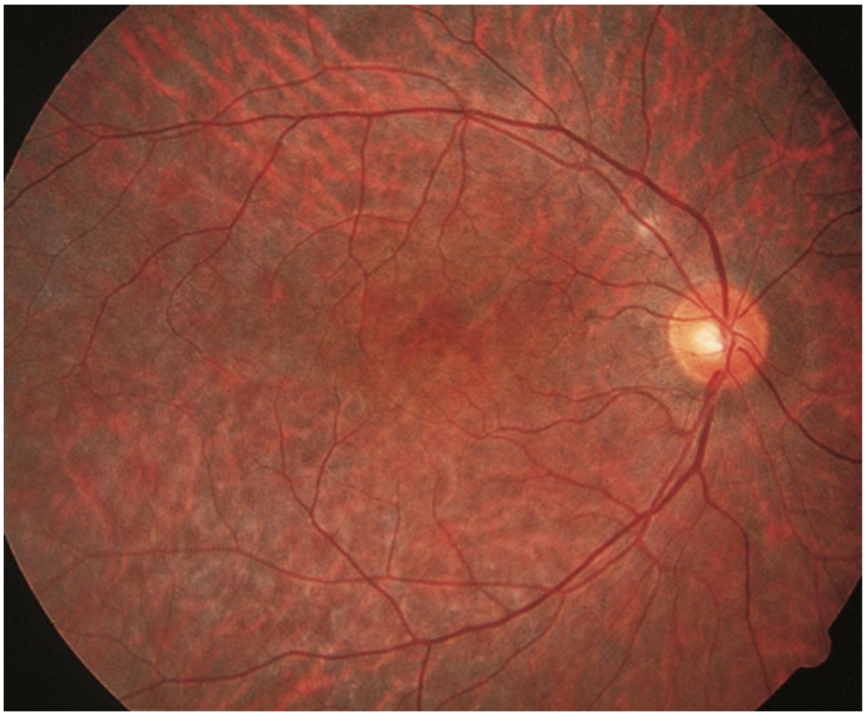

Fig. 3. Fundoscopy picture showing pigmentary retinopathy

At this point, amenorrhea was attributed to chronic malnutrition due to pulmonary tuberculosis leading to hypothalamic amenorrhea. The patient's glycemic control was achieved with basal-bolus insulin. Fever and cough subsided. Her appetite improved, and she gained 5 kilograms in weight. At 2 months, her sputum CBNAAT came back negative, and she completed ATT at the end of 6 months.

However, amenorrhea persisted during follow-up at the 6th month. Follicle-stimulating hormone and luteinizing hormone levels were low, indicating hypogonadotropic hypogonadism. Serum prolactin levels, 8 AM cortisol, and thyroid function tests were normal. She was started on combined pills and regained her menstrual cycles. She was advised to follow up regularly in the Endocrinology and Cardiology clinics.

Discussion

Kearns-Sayre syndrome (KSS) is a slowly progressive, rare mitochondrial genetic disorder with multisystem involvement. KSS is defined by the clinical diagnostic triad: onset before the age of 20 years, chronic progressive external ophthalmoplegia, and pigmentary retinopathy. Affected individuals have at least one of the following associated conditions: heart block, cerebrospinal fluid protein greater than 1000 mg/L, cerebellar ataxia, short stature, deafness, dementia, and endocrine abnormalities. The clinical triad of external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction defects is sufficient to make a confident diagnosis [1-3].

The exact prevalence of this condition is unknown. However, the approximate prevalence is 1 to 3 per 100,000 individuals. The etiology is a single, large deletion of mitochondrial DNA, ranging from 1,000 to 10,000 DNA nucleotides. It is generally not inherited but arises from mutations that occur after conception. Approximately 90% of cases of KSS are sporadic. Rarely, mitochondrial inheritance (i.e., mother to children) is seen. Symptoms may start in the age group ranging from infancy to adolescence. Only 226 cases had been registered in the literature until 1994 [4-6].

Patients present with symptoms involving multiple organs. Clinical manifestations include mild skeletal muscle weakness, ptosis, and external ophthalmoplegia. Cardiac manifestations include recurrent syncope due to conduction blocks, bundle branch blocks, fascicular blocks, non-specific intraventricular conduction disturbances, cardiomyopathies, and ventricular dysfunction. Our patient had ptosis, external ophthalmoplegia, pigmentary retinopathy, and ECG showed non-specific intraventricular conduction abnormalities. CNS manifestations include hearing loss, cerebellar ataxia, impaired cognitive function, hypotonia, reduced tendon reflexes, skeletal muscle atrophy, and progressive intervertebral space narrowing.

Seizures are infrequent. Lumbar puncture will show cerebrospinal fluid protein of more than 1 g/L. Our patient had cerebellar ataxia and dysdiadochokinesia.

Endocrine manifestations include diabetes, anterior hypopituitarism causing growth hormone deficiency, hypogonadism, and hypothalamic-pituitary axis dysregulation. Primary hypothyroidism, hypoparathyroidism, dyslipidemia, and adrenal insufficiency are rare manifestations. Depending on the degree of preservation of beta cell secretory capacity and peripheral muscle insulin sensitivity, the phenotype of mitochondrial diabetes in KSS may resemble that of type 1 or type 2 diabetes mellitus. They may rarely present with diabetic ketoacidosis. Our patient's phenotype resembled type 1 diabetes, and she presented with diabetic ketosis. Most patients with mitochondrial diabetes do not require insulin therapy at diagnosis, but they may progress more rapidly to requiring insulin than patients with type 2 diabetes mellitus. The use of HbA1c for the diagnosis of mitochondrial diabetes has not been validated but can be used for follow-up. Treatment of mitochondrial diabetes in KSS should be individualized based on phenotype [7, 8].

Ophthalmologic symptoms were seen in most of the patients. Cardiac conduction defects cause syncope and heart failure in up to 57% of KSS patients and play a role in the mortality of 20% of these patients. Cognitive decline is seen in 31% of patients. The frequency of endocrine disturbances has been reported to range from 35% to 67%, and 13% develop mitochondrial diabetes [9, 10]. Endocrine dysfunction can be the initial presenting symptom preceding other neurological manifestations of KSS [11].

Muscle pathology will show ragged-red fibers, ragged-blue fibers, or cytochrome c-oxidase-negative fibers. Furthermore, postmortem neuropathology of patients can be associated with severe demyelination of the white matter tracts of the brain. It is not known why the loss of myelin occurs [11-13].

Treatment is mainly symptomatic and supportive and involves multiple specialties depending on the organs involved. Pacemaker implantation can prevent syncope and reduce morbidity in patients presenting with advanced AV conduction abnormalities. Arginine, citrulline, and taurine have been shown to have limited efficacy. Respiratory chain cofactors (succinate, riboflavin, thiamine, and Coenzyme Q10), antioxidants (Coenzyme Q10, idebenone), and agents like creatine, levocarnitine, and folate have been tried, but evidence is lacking for most of these therapies. Aerobic and resistance exercise training have shown to improve respiratory chain enzyme activity, strength, and mitochondrial biogenesis. Prognosis varies depending on the severity and number of organs involved [10, 14].

The patient expressed gratitude for the care received and satisfaction with the treatment. She stated that she had gained weight and was feeling better after glycemic control was achieved with the treatment. She added that she was satisfied after she regained her menstrual cycles.

Conclusion

Kearns-Sayre Syndrome is a rare cause of mitochondrial diabetes, and KSS should be suspected when a patient presents with diabetes, ptosis, ophthalmoplegia, and pigmentary retinopathy. Suspicion of syndromic diabetes is important when a patient presents with young-onset diabetes and multi-system involvement. Meticulous fundoscopy should be an important part of the examination in diabetic patients. A multidisciplinary approach is necessary for management and better outcomes in KSS.

Limitations

CSF analysis, pyruvate levels, IGF-1, and GH stimulation tests were not performed. Genetic testing was not available for this patient.

Ethical Considerations

There were no ethical considerations to be considered in this article. The patient provided written informed consent to publish this case report and accompanying images.

Funding

No funding was received to assist with the preparation of this manuscript.

Conflict of Interests

The authors have no conflicts of interest to declare.

References

[1] Koka K, Patel BC. Ptosis Correction. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539828/.

[2] Abu Diab A, AlTalbishi A, Rosin B, Kanaan M, Kamal L, Swaroop A, et al. The combination of whole-exome sequencing and clinical analysis allows better diagnosis of rare syndromic retinal dystrophies. Acta Ophthalmol. 2019;97(6):e877-e886 . https://doi.org/10.1111/aos.14095

[3] Goldstein A, Falk MJ. Single Large-Scale Mitochondrial DNA Deletion Syndromes. 2003 Dec 17 [updated 2023 Sep 28]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. PMID: 20301382.

[4] Nguyen MTB, Micieli J, Margolin E. Teaching NeuroImages: Kearns-Sayre syndrome. Neurology. 2019;92(5):e519-e520 . https://doi.org/10.1212/WNL.0000000000006861

[5] Tsang SH, Aycinena ARP, Sharma T. Mitochondrial disorder: Kearns-Sayre syndrome. Adv Exp Med Biol. 2018;1085:161-2. https://doi.org/10.1007/978-3-319-95046-4_30

[6] Saldaña-Martínez A, Muñoz ML, Pérez-Ramírez G, Montiel-Sosa JF, Montoya J, Emperador S, et al. Whole sequence of the mitochondrial DNA genome of Kearns-Sayre syndrome patients: Identification of deletions and variants. Gene. 2019;688:171-81. https://doi.org/10.1016/j.gene.2018.11.085

[7] Holloman CM, Wolfe LA, Gahl WA, Boerkoel CF. Kearns-Sayre syndrome presenting as isolated growth failure. BMJ Case Rep. 2013;2013:bcr2012007272 . https://doi.org/10.1136/bcr-2012-007272

[8] Harvey JN, Barnett D. Endocrine dysfunction in Kearns-Sayre syndrome. Clin Endocrinol (Oxf). 1992;37(1):97-103. https://doi.org/10.1111/j.1365-2265.1992.tb02289.x

[9] Khambatta S, Nguyen DL, Beckman TJ, Wittich CM. Kearns-Sayre syndrome: a case series of 35 adults and children. Int J Gen Med. 2014;7:325-32. https://doi.org/10.2147/IJGM.S65560

[10] Yu M, Yu L, Wang ZX. Diagnosis and management of Kearns-Sayre syndrome rely on comprehensive clinical evaluation. Chin Med J (Engl). 2016;129(20):2519-20. https://doi.org/10.4103/0366-6999.191855

[11] Shemesh A, Margolin E. Kearns-Sayre Syndrome. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482341/.

[12] Lee SJ, Na JH, Han J, Lee YM. Ophthalmoplegia in mitochondrial disease. Yonsei Med J. 2018;59(10):1190-6. https://doi.org/10.3349/ymj.2018.59.10.1190

[13] Padhy SK, Kumar V, Mandal S. Pigmentary retinopathy in Kearns-Sayre syndrome. BMJ Case Rep. 2018;2018:bcr2018225635 . https://doi.org/10.1136/bcr-2018-227394

[14] Trivedi M, Goldstein A, Arora G. Prophylactic pacemaker placement at first signs of conduction disease in Kearns-Sayre syndrome. Cardiol Young. 2018;28(12):1487-8. https://doi.org/10.1017/S1047951118001609