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Endocrine disorders in Kearns-Sayre syndrome with different severity of symptoms: two case reports and a literature review

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Abstract

Kearns-Sayre Syndrome (KSS) is a variant of mitochondrial disorder caused by a Mitochondrial Deoxyribonucleic Acid (mtDNA) deletion. Clinical manifestations of KSS can include different organ and system involvement. Different organ malfunctions, more often cardiac dysfunction, can lead to death. No effective treatment of this condition exists to date. Here, we report two patients with KSS. A female patient with a large-scale deletion of 7,020 base pairs (bp) suffered from hypogonadism, diabetes mellitus with fluctuating glucose levels, and had poor general health. A male patient with a common 4,977 bp deletion did not have diabetes mellitus but had impaired glucose tolerance. He also had a higher level of general health than our female patient. Both patients had reduced Bone Mineral Density (BMD). In the female patient, calcium and vitamin D supplementation combined with metabolic therapy and nutritional drink supplements helped increase BMD (up to 32% in L1-L4). Comparing these two patients suggests that the larger the mtDNA deletion is, the more severe the course of the disease is. Not only does the size of the mtDNA deletion probably determine the severity of the disease, but also such factors as mtDNA heteroplasmy level, presence of mtDNA duplications, and pleioplasmy. Moreover, continuous nonconsecutive metabolic therapy and nutritional supplements are helpful in the prevention of deterioration of symptoms and general health.

Key Words: mitochondrial DNA, Kearns-Sayre syndrome, mitochondrial diseases, diabetes mellitus, bone density.

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Kearns-Sayre Syndrome (KSS) is a mitochondrial DNA deletion syndrome that impacts multiple systems of the body, affecting an estimated 1.6 out of 100,000 with an equal sex incidence. The mitochondrial variant is due to a defect in the OXPHOS system caused by an mtDNA deletion.[1] Approximately one-third of the patients with KSS have the common 4,977 base pair (bp) (within nucleotides 8,470–8,482 and 13,447–13,459) deletion.[2,3]

KSS is characterized by the following triad: onset prior to 20 years of age, Chronic Progressive External Ophthalmoplegia (CPEO), and Retinitis Pigmentosa (RP). The following may also develop: cardiac conduction disorders, ataxia, increasing cerebrospinal fluid protein level greater than 100 mg/dL.[4,5] Patients may also present with endocrine disorders. 20% of patients with KSS have gonadal dysfunction with onset before or after puberty. Diabetes mellitus can be seen in 12-15% of patients, hypothyroidism in 3-9%, hypoparathyroidism in 7-8%, adrenal insufficiency in 6%, and hyperaldosteronism in in 3%. Moreover, short stature with or without growth hormone deficiency can be found in 38% of patients.[6-8]

Case Report

Case Report 1

This initially asymptomatic female patient was diagnosed with ventricular septal defect and both mitral and tricuspid valve prolapse on screening.

The diagnosis of KSS was established at the age of eleven when neurological symptoms appeared, and a deletion of 7,020 bp (from 6,074 bp to 13,094 bp) in mtDNA was detected.

From nine years of age, she received continuous metabolic therapy (L-carnitine, coenzyme Q_{10}, cytochrome C, biotin, riboflavin, cytochrome c, α-lipoic acid, ascorbic acid, etc). Since she had malabsorption syndrome, she also received nutritional drink supplements ("Nutridrink", "FortiCare", "Liquigen", "Nutricomp", and others).

Since the age of twenty-one, metabolic therapy was not available and she missed months of having metabolic therapy and stopped nutritional supplements. Subsequently, a standard diet led to a worsening of gastrointestinal symptoms, including vomiting, diarrhea, and abdominal pain. The patient then refused to eat and experienced intermittent tremors in her hands and head, and cold hands and feet (peripheral neuropathy with a "stocking-and-glove" distribution). Then, she developed an unsteady gait with falls (ataxia). The patient lost weight (from 35 kgs to 32 kgs). Two months after returning to metabolic therapy, she felt better, with improvement in the gastrointestinal and neurological symptoms.

At the age of fourteen, she was diagnosed with diabetes mellitus (DM), with hyperglycemia being detected on routine testing. At the age of twenty-one, she received subcutaneous injections of degludec 17 U at 12:00 p.m. and lispro 1 U for every meal. Almost every meal contained about 30 g of carbs (125 ml of NutriDrink), and she took it seven to eight times daily. On these insulin doses, she had significant fluctuations in blood glucose levels from 2 to 20 mmol/L.

At the age of twenty, secondary hyperparathyroidism was diagnosed. Parathyroid hormone (PTH) – 17.32 pmol/L (N 1.6-6.9); serum 25(OH)D – 23.51 ng/ml (vitamin D insufficiency); total serum calcium – 2.35 mmol/L (N 2.10-2.55); ionized serum calcium – 1.16 mmol/L (N 1.15-1.35). According to dual-energy x-ray absorptiometry (DEXA) results we found bone mass density (BMD) to be lower than average values for a person of the same age and gender – Z-score=-2.8 SD at the lumbar spine (L_1-L_4). On metabolic therapy, nutritional drink supplements, calcium supplements, alfacalcidol, and cholecalciferol, she gained BMD up to -1.9 SD (Z-score) in lumbar spine area (L_1-L_4) in a year.

Roentgenography of the hands at twenty years old showed incomplete ossification and fusion of the distal radial growth plate and epiphyseal plates of both hands' proximal and middle phalanges. She had not had her first period by the age of twenty (primary amenorrhea).

Case Report 2

The second patient is male and experienced febrile convulsions at an early age. At nine years of age, delayed physical development and progressive ptosis were noticed. At the age of 12, mtDNA deletion specific to KSS was detected (deletion of 4,977 bp from 8,470 bp to 13,447 bp).

Metabolic therapy was prescribed (L-carnitine, coenzyme Q_{10}, biotin, riboflavin, cytochrome c, α-lipoic acid, ascorbic acid, etc) from the age of 12 but was only received for a short period.

At 22, hyperglycemia was not detected on routine laboratory tests. A 75g Oral Glucose Tolerance Test (OGTT) was then undertaken that revealed an impaired glucose tolerance (IGT) (baseline glucose – 4.3 mmol/L; 2-h plasma glucose – 9.6 mmol/L (N <7.8)). Functional assessment of pancreatic β-cells revealed decreased fasting insulin level <2.0 mIU/mL (N 2.0-29.0) and 2-h insulin level 31.2 mIU/mL. The fasting C-peptide level was 367 pmol/L (N 298-2,350) and 2-h C-peptide – 3,641 pmol/L). A recommendation to avoid fast-digesting carbs in the diet was made, and no hypoglycaemic medications were prescribed.

At 22 years of age, DEXA revealed a decrease in BMD in the lumbar spine below the age-expected values (Z-score L_1=-3.0 SD, L_2=-2.5 SD, L_3=-2.1 SD, L_4=-2.0 SD). The BMD in the proximal left femur was also lower than the age-expected values (Z-score: -3.9 SD). We recommended treatment with calcium and vitamin D on par with routine monitoring of total and ionized calcium and vitamin D levels in the blood serum.

Also, at 22 years of age, the level of insulin-like growth factor 1 (IGF-1) was lower than the reference values. At the same time, according to the results of the test with glucagon (at 22 y.o.), growth hormone deficiency and adrenal insufficiency were excluded (the peak level of GH (growth hormone) during the test was 5.39 μg/L (N >5.0); the peak level of total cortisol during the test was 538 nmol/l (N >500)). Therefore, growth hormone was not required (Table 1).

Discussion

Most of the clinical features were common in both cases. A low BMD was likely to be associated with myopathy and growth hormone deficiency, as well as with the interaction of growth hormone with its target cells. In the male patient impaired interaction of somatotropin with target cells can be confirmed by low IGF-1 levels with the absence of growth hormone deficiency, based on the glucagon test. In addition, low BMD can be explained by malabsorption of nutrients, caused by gastrointestinal (GI) involvement that can be associated with KSS.

The administration of GH therapy to patients with KSS remains controversial. In patients with mitochondrial disease and confirmed GH deficiency, treatment is recommended.[9, 10] In one study, 6 out of 8 patients with Kearns-Sayre and GH deficiency had improved height with therapy.[11] On the other hand, somatropin injections can be harmful in mitochondrial disease because growth hormone, as an anabolic hormone induces cell proliferation. This, in turn, requires more Adenosine Triphosphate (ATP), and ATP production is abnormal in mitochondrial diseases.[12] However, some research supports the use of somatropin even in children without growth hormone deficiency, confirmed with stimulation testing, but with growth retardation and with a low GH peak during sleep. We decided not to administer somatropin for both of our patients (patient 2 had no GH deficiency due to a glucagon stimulation test). Moreover, GH administration, with a subsequent increase in IGF-1 levels, can lead to neu-

Table 1. *Comparing the data of two patients.*

	Patient № 1 (21 y.o. female)	Patient № 2 (22 y.o. male)
Number of deleted bp	7,020	4,977
Deleted bp was responsible for NADH dehydrogenase, subunit 3 (complex i) synthesis (10,059-10,404)	+	+
Deleted bp was responsible for NADH dehydrogenase, subunit 4 (complex i) synthesis (10,470-10,766)	+	+
Deleted bp was responsible for NADH dehydrogenase, subunit 4l (complex i) synthesis (10,760-12,137)	+	+
Deleted bp was responsible for NADH dehydrogenase, subunit 5 (complex i) synthesis (12,337-14,148)	partially	partially
Deleted bp was responsible for cytochrome c oxidase, subunit 1 (complex iv) synthesis (05,904-07,445)	partially	-
Deleted bp was responsible for cytochrome c oxidase, subunit 2 (complex iv) synthesis (07,586-08,269)	+	-
Deleted bp was responsible for cytochrome c oxidase, subunit 3 (complex iv) synthesis (09,207-09,990)	+	+
Deleted bp was responsible for atp synthase, fo subunit 6 (complex v) synthesis (08,527-09,207)	+	+
Deleted bp was responsible for atp synthase, fo subunit 8 (complex v) synthesis (08,366-08,572)	+	partially
Deleted bp was responsible for trna-arginine synthesis (10,405-10,469)	+	+
Deleted bp was responsible for trna-aspartic acid synthesis (07,518-07,585)	+	-
Deleted bp was responsible for trna-glycine synthesis (09,991-10,058)	+	+
Deleted bp was responsible for trna-histidine synthesis (12,138-12,206)	+	+
Deleted bp was responsible for trna-leucine synthesis (12,266-12,336)	+	+
Deleted bp was responsible for trna-lysine synthesis (08,295-08,364)	+	-
Deleted bp was responsible for trna-serine synthesis (07,446-07,514)	+	-
Deleted bp was responsible for trna-serine synthesis (12,207-12,265)	+	+
Av-block	3rd degree	-
Left (lbbb) and right bundle branch block (rbbb)	-	+
Crt (cardiac resynchronization therapy)	+	-
Chronic progressive external ophthalmoplegia (cpeo) or ptosis	+	+
Ataxia	+	+
Snhl (sensorineural hearing loss)	+	-
Peripheral neuropathy	+	-
Scoliosis	+	+
Bulbar pulsy	+	-
Dm or impaired glucose tolerance	DM	glucose intolerance
Glucose-lowering therapy	basal-bolus insulin regimen	none
Hypogonadism	+	-
Gi tract involvement	+	-
Secondary hyperparathyroidism	+	-
BMI (at the age of 20-22 y.o.)	12.3-15.0	12.81
Bone fractures	-	-
BMD lower than average values	+	+

AV-block, atrioventricular block; bp, base pairs; BMD, bone mass density; BMI, body mass index; DM, diabetes mellitus; NADH, nicotinamide adenine dinucleotide (reduced form); tRNA, transport ribonucleic acid.

rologic impairment. Hypotonia and cerebellar ataxia can develop alongside a decrease in language and memory skills and a decrease in appetite. Multiple organ dysfunction, such as renal failure that eventually requires dialysis, and insufficiency of other organs may also appear. These effects can develop even in the case of GH deficiency, as verified by pharmacological stimulation tests.[13,14] It is not known whether the acute deterioration of patients immediately after GH administration is caused by this medication or not. However, after discontinuing GH, the general condition of patients improved (including language and memory skills, appetite, and muscle strength). Furthermore, GH therapy does not universally increase the rates of height velocity, and target height is not reached in all cases.

Aetiologies of a low BMD include malabsorption leading to vitamin D and calcium deficiency, growth hormone deficiency, renal tubulopathy (chronic kidney disease), and liver diseases. [15] The rate of bone fractures is high in KSS, as well as in other mitochondrial diseases: 14% of KSS patients had bone fractures, 55% of bone fractures occurred at the age of 9 or earlier, 37.5% are fragility fractures, and 37.5% are traumatic fractures. All bone fractures occurred in patients with BMD -2.0 SD or less. The sites that were fractured most often were the femur, humerus/elbow, and radius/ulna.[15]

For osteoporosis treatment, antiresorptive (bisphosphonates, denosumab) and anabolic therapy (teriparatide) can be considered. However, these agents have no evidence to support osteoporosis treatment in KSS. Gandhi *et al.* (2017) described a 29% improvement in lumbar spine bone mineral density and 8.3% in left femoral neck in a 13-year-old boy with mitochondrial disease who had received three injections of pamidronate. At baseline, the patient had a low BMD without any bone fractures.[15] Our patients had no history of bone fractures, but both had scoliosis and BMD values lower than average values. No treatment to increase BMD was administered to either one of our patients. However, we observed a 32% improvement in lumbar spine BMD on vitamin D supplementation (cholecalciferol and active metabolites) in patient 1.

An interesting finding was a secondary hyperparathyroidism detected in patient 1. The causes of hyperparathyroidism were likely to be malabsorption due to gastrointestinal involvement in KSS and a break in metabolic therapy and nutritional drink supplement intake. When metabolic therapy and nutritional drink supplements were resumed alongside calcium and vitamin D supplements, serum PTH and calcium levels were normalized. There were no other cases of secondary hyperparathyroidism in KSS found in the literature.

DM is one of the most common endocrinopathies in KSS. According to a review of 226 cases of KSS, 29 patients had DM (12.8%), and 13 of them took insulin (44.8% of all cases of KSS).[6] However, none of those patients had elevated levels of autoantibodies to pancreatic β-cell antigens (neither Islet Cell Antibodies, ICA, Glutamic Acid Decarboxylase antibodies, GAD, Insulin Antibodies, IA2, nor Insulin Autoantibodies IAA).

IGT was diagnosed in patient 2 (mtDNA deletion of 4,977 b.p.) at 22. Based on his case history and symptoms, we decided not to administer glucose lowering therapy. We recommended that he repeat blood tests for glycated hemoglobin and repeat 75g per OGTT in 3 months to assess the need for basal insulin to be initiated. After hospital discharge, the patient was lost to follow-up, so we don't know what happened next. We didn't consider metformin administration in his case as he was underweight, and there was no insulin resistance (HOMA-IR=<0.38 (N <2.7)).

In the first patient with large-scale mtDNA deletion (7,020 bp), DM manifested at 14, and insulin therapy was requested from the beginning. Later, she noticed high glucose variability during the day. This glucose variability can be explained by malabsorption due to GI disease relapse or by increased sensitivity to physical activity. Rapid-acting insulin requirements before meals were meager. Considering all of these, a Continuous Subcutaneous Insulin Infusion (CSII) with a real-time Continuous Glucose Monitoring (CGM) device can be reasonable for our patient. According to the German/Austrian DPV diabetes registry, 16.7% of patients with mitochondrial diabetes use CSII. Among patients with T1DM (type 1 diabetes mellitus), according to the German/Austrian DPV diabetes registry, 56% use insulin pumps.[16,17]

Diabetes mellitus in KSS can manifest differently and have a different natural history. Isotani H. et al., 1996 demonstrated an acute onset of diabetes in a 17-year-old patient with KSS who had a 6,741 b.p. mtDNA deletion. Their patient presented with high blood glucose levels of up to 31.0 mmol/L, HbA_{1c} (glycated hemoglobin) 16.5%, and mild Diabetic Ketoacidosis (DKA).[18] After improvement in DKA and glucose toxicity, she was placed on insulin. Her daily insulin dose, which improved glycemic control, was determined to be 24-30 units/day despite her small body weight of 25 kg. Her blood tests detected a reduced excretion of urinary C-peptide at 3.97 nmol/day. Pang *et al.* (2022) reported a similar case of a patient with KSS in whom diabetes debuts with glycemia 32.8 mmol/L and ketoacidosis.[19] Obara-Moszynska *et al.* (2013) reported a case of IGT diagnosed in a 15-year-old patient with KSS with a 7,663 b.p. mtDNA deletion. The diagnosis was established based on blood glucose levels in OGTT. Furthermore, the hyposecretion of insulin was demonstrated. GAD, IAA, and IA2 antibodies were all negative. Long-acting insulin therapy commenced, and blood glucose levels normalized. Non-insulin glucose-lowering agents are supposed to be ineffective for diabetes treatment in KSS.[14] Artuch *et al.* (1998) reported a case of diabetes in a 16-year-old boy with KSS (fasting glucose – 10.9 mmol/L and HbA_{1c} – 9.4%). Glibenclamide was administered as he had a usual pancreatic reserve, BMI=27.7 kg/m^2, and negative immunological markers (ICA, IAA, Ab GAD). However, metabolic control was inadequate two months after starting glibenclamide (HbA_{1c} >8%). Therefore, insulin therapy was started (0.3 U/kg/day), and reasonable metabolic control was obtained.[20] However, there are reports on the potential efficacy of dipeptidyl peptidase-4 inhibitor (DPP-4i) in the treatment of Diabetes of Mitochondrial Origin (DMO), and this can be explained by the fact that first-phase insulin secretion is missing in diabetes of mitochondrial origin.[16] Moreover, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glu-

cagon-like peptide-1 (GLP-1) receptor agonists are also proposed as first-line agents.[9] Furthermore, some data supports that coenzyme Q, which is used as a metabolic therapy in KSS, may enhance insulin secretion.[16]

Histological examination of post-mortem pancreatic specimens from a KSS patient with insulin therapy for fourteen years revealed a complete absence of β-cells, and a concomitant lack of C-peptide secretion was detected according to laboratory testing.[21] For comparison, histological examination of post-mortem pancreatic specimens from another patient with T1DM revealed that it was not part of a hereditary syndrome (insulin therapy for sixteen years). Approximately 10% of the islets from the T1DM patient contained at least one cell immunoreactive for insulin. Islets in both patients contained a high proportion of glucagon-containing cells (α-cells). However, islet cells in T1DM patients had an irregular shape, and the islets were more prominent in size. Moreover, in KSS patients, endocrine cells were retained within well-defined islet boundaries, and islets were approximately three times smaller. This suggests that in contrast to β-cell autoimmune destruction in T1DM, which can be confirmed by the irregular shape of islet cells, in mitochondrial diabetes, insulin deficiency development is associated with mitochondrial dysfunction due to mtDNA deletion. Therefore, mtDNA deletion leads to β-cells developmental and functional disturbances, and the number of β-cells is decreased in newborns with mitochondrial disorders. In mitochondrial dysfunction, ATP production is reduced. As a result, ATP-dependent potassium channels don't close, and the influx of calcium ions required for insulin synthesis doesn't occur. This leads to decreased glucose-dependent insulin secretion. It suggests a limited number of β-cells in pancreatic islets in newborns. However, mtDNA mutation accumulates throughout a person's life, and eventually, absolute insulin deficiency develops.[21] This suggests that mitochondrial diabetes does not require insulin replacement therapy at the beginning of a disease, but eventually, insulin administration will be inevitable.[22,23]

There are two primary mutations associated with diabetes in KSS. The first is heteroplasmy, in which wild-type (normal) mtDNA and one type of deleted mtDNA are present. The second one is tandem duplications, in which a pattern of nucleotides is repeated, and the repetitions are directly adjacent in tandem. Moreover, pyeloplasty, where mutated mtDNAs with various deletions coexist with normal-size mtDNA, is also associated with diabetes in KSS. When the proportion of mutant mtDNA exceeds a certain threshold for an organ, the ATP synthesis of the mitochondria may become inadequate, and symptoms may appear.[24]

Comparing these two cases suggests that more significant mtDNA deletion causes a more severe disease course. Such a disease's severity difference can probably be associated with the number of deleted bp. Probably, the higher the percentage of damaging heteroplasmic mtDNA variants, the presence of duplications and pleioplasmy are associated with a more severe course of disease. However, we don't have any data on these points in our patients. Furthermore, continuous nonconsecutive metabolic therapy is seen to help prevent deterioration of symptoms and general health.

Diagnosis of KSS might be challenging due to the involvement of multiple systems. However, if KSS is diagnosed, metabolic therapy might improve patients' general health and the course of associated diseases. We believe that gathering information about rare genetic disorders worldwide is critically important to build a full view of genotype-phenotype association. This will help clinicians to recognize the syndrome and initiate treatment promptly.

List of acronyms

Ab, antibody
ATP, adenosine triphosphate
BMD, bone mass density
BMI, body mass index
bp, base pairs
CGM, continuous glucose monitoring
CPEO, chronic progressive external ophthalmoplegia
CSII, continuous subcutaneous insulin infusion
DEXA, dual-energy x-ray absorptiometry
DKA, diabetic ketoacidosis
DM, diabetes mellitus
DMO, diabetes of mitochondrial origin
DPP-4i, dipeptidyl peptidase-4 inhibitor
DPV, Diabetes Patient Follow-up
GAD, glutamic acid decarboxylase
GI, gastrointestinal
GH, growth hormone
HbA_{1c}, glycated hemoglobin
HOMA-IR, homeostasis model assessment of insulin resistance
IA2, insulin antibodies
IAA, insulin autoantibodies
ICA, islet cell antibodies
IGF-1, insulin-like growth factor 1
IGT, impaired glucose tolerance
KSS, Kearns-Sayre syndrome
mtDNA, mitochondrial deoxyribonucleic acid
OGTT, 75-g oral glucose tolerance test
OXPHOS, oxidative phosphorylation
PTH, parathyroid hormone
RP, retinitis pigmentosa
SD, standard deviation
T1DM, type 1 diabetes mellitus

Contributions

IA, YuKh, and MP developed the article's concept, wrote the text, and agreed to take responsibility for all aspects of the article. NL and AS monitored and treated the patient. AS and GM collected patient data and wrote some parts of the manuscript. ES, YuS, and MK helped with the final edition of the manuscript. SL-G revised English as a native speaker. All authors have read and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

No ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patients included in this study.

Patient consent for publication

Written informed consent was obtained from both patients for their anonymised clinical information to be published in this article

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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