Kearns Sayre syndrome: an unusual form of mitochondrial diabetes

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SUMMARY

Kearns Sayre syndrome (KSS) is a mitochondrial disorder characterized by the emergence before age 20 of progressive external ophthalmoplegia, pigmentary retinopathy, together with other heterogeneous clinical manifestations, including cardiac conduction defects, muscle abnormalities and endocrinopathies. KSS is associated with large heteroplasmic deletions in mitochondrial DNA. We report the case of a 43-year-old woman, with diabetes mellitus as a first manifestation at age 19. Later, she exhibited bilateral ptosis and external ophthalmoplegia with progressive worsening. DNA analysis identified a large mitochondrial DNA (mtDNA) deletion, which confirmed the diagnosis of KSS. By reporting this case with diabetes mellitus as first manifestation, we aim at emphasizing problems of diagnosis in these subtypes of mitochondrial diabetes.

Key-words: Kearns Sayre syndrome · Mitochondrial DNA · Mitochondrial diabetes · Monogenic diabetes.

RÉSUMÉ

Le syndrome de Kearns Sayre : une forme inhabituelle de diabète

Le syndrome de Kearns Sayre est une cytopathie mitochondriale caractérisée par l’apparition avant l’âge de 20 ans d’une ophthalmoplegie externe progressive associée à une rétinite pigmentaire. Des anomalies de la conduction cardiaque et une myopathie sont également fréquentes. Ce syndrome est lié à une délétion de l’ADN mitochondrial. Nous rapportons ici le cas d’une patiente de 43 ans dont la maladie a débuté à l’âge de 19 ans par un diabète. Plus tard sont apparues l’ophthalmoplegie d’aggravation progressive et la rétinite pigmentaire. L’analyse génétique a mis en évidence une délétion de l’ADN mitochondrial confirmant ainsi le diagnostic de KSS. Nous rapportons cette observation afin d’attirer l’attention des cliniciens sur le diagnostique étiologique de ces diabètes de présentation atypique qui peuvent entrer dans le cadre de maladies mitochondriales.

Mots-clés : Syndrome de Kearns Sayre · ADN mitochondrial · Diabète mitochondrial · Diabète monogénique.

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In 1958, Kearns and Sayre described a multisystemic syndrome now known as Kearns Sayre Syndrome (KSS) [1]. KSS is a rare, severe mitochondrial disorder. It is characterized by the emergence before the age of 20 of progressive external ophthalmoplegia and pigmentary retinopathy, with a series of other heterogeneous clinical manifestations, including cardiac conduction defects and muscle abnormalities [1,2]. KSS is associated with large heteroplasmic mitochondrial DNA deletions [3].

By reporting on this case of KSS with diabetes mellitus as a first manifestation, we want to draw attention on the problems of diagnosis in these subtypes of mitochondrial diabetes.

**Case report**

A 43-year-old Caribbean woman was referred to the Department of Neurology for worsening of a ptosis and external ophthalmoplegia. She was the product of a normal pregnancy, from normal non-consanguineous parents. Diabetes mellitus (fasting plasma glucose at 8.9 mmol/l) was diagnosed at age 19 at systematic screening before oral contraception. The patient had no family history of diabetes. Phenotype of our patient includes several features, which characterises KSS, as progressive external ophthalmoplegia and pigmentary retinopathy. Ocular motor palsy is sometimes present in patients carrying the A→G 3243 mutation (Maternally Inherited Diabetes and deafness, MIDD), but maternal transmission is then suggestive [4]. The salt and pepper retinitis observed in our patient is characteristic of Kears Sayre syndrome, the “salt and pepper” retinopathy involves the entire retina, including the peripheral retina. While, in MIDD, the pigmentary changes are localized to the macular area, and are combined with localized subretinal macular and peripapillary deposits; in addition, in MIDD, the peripheral retina is normal.

Ptosis, muscle weakness and moderate cognitive deficits are usual in patients with KSS. However, cardiac conduction defects, which have been frequently reported in this disease, were absent in our patient [1,2,3].

Asymptomatic diabetes mellitus was the first sign of the disease in our patient. Diabetes mellitus is reported in 10% of patients with KSS, half of them being insulin requiring [3]. Diabetes appears to be secondary to a failure in insulin sensitivity and a moderate reduction in cognitive performances.

**Discussion**

Phenotype of our patient includes several features, which characterises KSS, as progressive external ophthalmoplegia and pigmentary retinopathy. Ocular motor palsy is some time present in patients carrying the A→G 3243 mutation (Maternally Inherited Diabetes and deafness, MIDD), but maternal transmission is then suggestive [4]. The salt and pepper retinitis observed in our patient is characteristic of Kears Sayre syndrome, the “salt and pepper” retinopathy involves the entire retina, including the peripheral retina. While, in MIDD, the pigmentary changes are localized to the macular area, and are combined with localized subretinal macular and peripapillary deposits; in addition, in MIDD, the peripheral retina is normal.

Endocrine evaluation, including plasma concentration of free T₄, T₃, TSHus, estradiol, progesterone, FSH, LH, and prolactin were within the normal range. Plasma calcium and PTH₁-₈₄ concentrations were normal excluding hypoparathyroidism.

A salt and pepper retinitis was noticed at ophthalmologic examination, without any macular pattern dystrophy (figure 1). Optic disk and retinal vessel calibre were normal. Electroretinogram and flashes visual evoked potentials disclosed severe functional retinal disorders of the photoreceptors and the inner retinal layers. Audiogram was normal. Auditive evoked potentials showed slight conduction abnormalities, predominating on the left side.

High concentration of serum pyruvate was measured (131 µmol/l, normal range: 41-67 µmol/l), serum lactate was normal. Histological analysis of the deltoid skeletal muscle revealed the presence of a typical mitochondrial myopathy associating scattered ragged red fibers on the Gomori trichome staining (figure 2). Numerous muscle fibers with a defective cytochrome C oxidative activity and normal or increased succinate dehydrogenase activity were observed at histochemistry (figure 2). Ultrastructural analysis of muscle revealed numerous mitochondria with heterogeneous size and shape. Normal organelles were mixed with strikingly abnormal mitochondria containing paracrystalline inclusion bodies (figure 3).

The A3243G point mutation was absent. Southern blot analysis of muscle mitochondrial DNA (mtDNA) disclosed a unique large deletion of the mtDNA, representing 60% of total mtDNA molecules.
production. First, the histological appearance of the islets in
a patient with KSS shows a complete absence of β-cells con-
comitant with lack of C-peptide secretion. Mutations in
mtDNA are likely to contribute to islet development and
function in the foetus, which would result in lower num-
bers of islet cells in patients with abnormalities of mtDNA
[5]. In the second hand, alteration in mitochondrial func-
tion is likely to impair insulin secretion since glucose-stim-
ulated insulin secretion is mediated by closure of ATP
dependent potassium channels in the β-cell membrane.
Thus insulin secretion is dependent of oxidative phospor-
ylation and intracellular ATP production [6]. Diabetic
patients carrying mitochondrial gene mutations are nega-
tive for islet cell antibodies (ICA) and glutamic acid deca-
boxylase antibodies (GAD65) [7], although low titers of ICA
have been described in a few cases [8].

This case illustrates the diagnosis problem in these sub-
types of mitochondrial diabetes. Clinical characteristics,
which should draw attention, include young age at onset,
absence of obesity, and of family history of diabetes, exclud-
ing common type 2 diabetes. Heterogeneous clinical pres-
etation and multisystemic involvement should lead
diagnosis toward a “particular” subtype of diabetes [9].

Others endocrinopathies are common in KSS, including
growth hormone deficiency (37%), hypogonadism (20%),
hypoparathyroidism (7-8%) and thyroid disease (3%) [10].
One case of non-autoimmune Addison disease has been
described [11]. Hypomagnesaemia, bone, tooth and calcifi-
cation abnormalities are uncommon [12].

Standard biological profile is usually normal. Metabolic
acidosis, high serum pyruvate or lactate levels, due to respi-
ratory chain dysfunction, can be observed, as it is the case
for this patient. Computed tomography shows nonspecific
findings such as white matter and basal ganglia hypoden-
sity, calcifications of cortex and basal ganglia, atrophy of the
pons and cerebellum [9,13]. The most frequent brain Mag-
netic Resonance abnormalities are widespread white matter
hyperintensity, supratentorial cortical and cerebellar atro-
phy. The absence of basal ganglia hyperintensity is well cor-
related with KSS [14].

Muscle sample biopsy confirms the diagnosis and shows
cytochrome C oxidase-negative ragged red fi bbers on mod-

Figure 2
Muscle biopsy. A: Ragged red fibers on Gomori staining. (Original
magnification x 150). B and C: Muscle fibers with a defective cytochrome
C oxidase (cox) activity and normal or increased succinate
dehydrogenase (SDH) activity. One fiber is cox negative and SDH
negative. (Original magnification B x 60, C x 150).
ified Gomori stain. Electron microscopy reveals subsarcolemmal accumulation of abnormal mitochondria with paracrystalline inclusion bodies [3,15,16].

Molecular basis of KSS is the existence of deletion in the mitochondrial DNA varying in location, size and percentage [3,4,8,9]. A large variety of mitochondrial DNA deletions have been described [8], approximately one third of KSS patients harbour the same kind of deletion, extending over 4,977 bp within the region 8470–13459 [2,3]. In subjects carrying mitochondrial gene defects, cells possess a variable number of mitochondria containing either normal or abnormal mitochondrial DNA, defining the level of heteroplasmy [16]. Mitochondrial DNA deletion leads to generalized defects in mitochondrial polypeptides synthesis, and finally impairs oxidative phosphorylation and energy metabolism in the respiratory chain. Biochemical analysis shows a various combination of decreased activities of the four enzymes of the mitochondrial respiratory chain containing subunits encoded by mitochondrial DNA: cytochrome C oxidase I, III, IV, V [10]. The quantitative relationship between deleted mitochondrial DNA and the clinical course of KSS remains poorly understood. No correlation has been observed between the size and place of the deletion, biochemical abnormality, mitochondrial enzymes or clinical severity [15,17]. The differential expression of mitochondrial DNA deletions in multiple tissue, and individual tissue dependence on mitochondrial energy production, explains the heterogeneity of clinical manifestations [16].

Typically, mitochondrial DNA deletion is a sporadic event [15], but it can exhibit maternal transmission, as in other mitochondriopathies [18]. Prognosis is poor, and there is no specific treatment. Coenzyme Q 10 (cofactor of the respiratory chain) replacement therapy has been reported to be effective in some patients with KSS [19]. Its effects seem to be due to antioxidant properties and action of coenzyme Q 10 as an electron transfer mediator, circumventing the reduced activity of the complex of the respiratory chain [19].

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