Kearns-Sayre Syndrome "Plus": A Case Report

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Citation

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Abstract

Objective: To report multisystemic abnormalities found in a patient with Kearns-Sayre syndrome.

Patient Methods: The case report of the 26 years old female with Kearns-Sayre syndrome started about 16 years ago has some uncommon cardiological aspect apart from endocrine dysfunction, pancerebellar manifestation, progressive external ophthalmoplegia, neurosensorial hearing loss, and peripheral neuropathy among others abnormalities. Ophthalmologic examination showed dystrophic features in the cornea and retina. CT Scan of the brain showed generalized cerebral and cerebellar atrophy and dilatation of the ventricular system, etc. In the skeletal muscle biopsy the typical signs of atrophy and ragged-red fibers were seen. Laboratory tests, CT scan of the chest, ECG and Ultrasound studies showed signs of myocardiopathy, heart block, interventricular septal defect, renal lesions, liver disease and others. Different clinical trial was using looking for improvement of the patient's manifestations.

Results: No improvement of the clinical manifestations was observed. The classical vitamin therapy did not improve this patient's condition. Endocrine dysfunctions such as non-insulin dependent diabetes and hypothyroidism, liver dysfunction and renal disease were well controlled with the common way of managements.Cell Culture, DNA/ RNA Analyses, Determination of mtDNA Copy number and Analyses of Mitochondria Translation Products are not available in our region but the clinical manifestation and laboratory test result were useful for confirmation of Kearns-Sayre syndrome. To our knowledge, this combination of clinical manifestation has never been described in Kearns-Sayre syndrome.

INTRODUCTION

Kearns-Sayre Syndrome (KSS) is a very uncommon fatal multisystem disorder which usually affects female and males before the age of 20, and it is characterized by progressive external ophthalmoplegia, mild skeletal muscle weakness, retinal pigmentation, left bundle branch block or intracardiac conduction defect[1], hearing deficiencies, increased protein level in cerebrospinal fluid, cerebellar signs, impaired cognitive dysfunction, diabetes mellitus[2] , and other endocrine disorders. It is a mitochodrial encephalomyopathy in which many different defects of the central and peripheral nervous system: optic atrophy, vestibular defect, myopathy, pyramidal signs, poor intellectual development or mental deterioration are present apart from hypogonadism, hypothyroidism, hypoparathyrodism, and renal dysfunction. For the other hand the considerable short stature of the patients and the lax posture, poor musculature, frequent secondary kyphoscoliosis, hyperlordosis, frequent wasting and typical fascies all contribute to their characteristic general appearance.

Several authors reported partial deletions of human mitochondrial DNA (mtDNA) in 1988 for a first time[3 4 5] and partial duplication[6 7] or coexistence of deletion and duplication by others [8]

In this presentation, we have chosen to report on the case of a patient diagnosed as KSS with an associated hypothyroidism, hypoparathyroidism, diabetes mellitus and adrenocortical failure.

REPORT OF A CASE

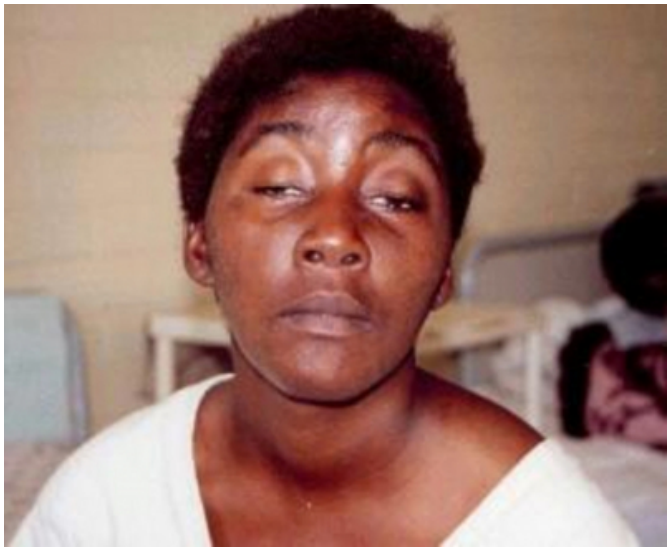
A 26 years-old female patient was born as the third child to healthy non-consanguineous parents. The family history was unremarkable, except for diabetes mellitus in the maternal grandfather and a history of “progressive and generalized weakness of unknown cause” of her oldest sister who remind in bed for the past four years. Pregnancy and birth were normal. Symptoms were first notice in this patient when she was near the age of 12 years. Up to then, she had presented normal neuropsychomotor development, without reference to neo- or perinatal intercurrents. Deficient growth in stature

was evident at the age of 13 years when she began to complain of progressive “dropping eyes” plus sight disturbances without diplopia, and also progressive hearing loss, three years later she began to suffer of unsteady gait which progress slow and gradually up to date.

She also suffered from progressive muscle weakness and generalized muscle wasting resulting in a loss of more than 15 kg of body weight. During this time she repeated the standard level 3 four times at the school due to learning problems while she was complaining of asthenia, anorexia, dysphagia, easy fatigability, and paresthesia of the four limbs. Seven months prior admission she was treated for hyperpigmentation of the skin plus arterial hypotension since then all symptoms became worst and she attended to Neurology OPD clinic because of two attacks of left partial complex motor seizures a week before and to be admitted is decided. On examination in neurology ward she was assessed by two of us (FSH-AA). Her face was an unexpressed-rounded and greasy one with an incomplete palpebral ptosis bilaterally (Figure 1), the nails and teeth were normal She was very thin owing to generalized muscular wasting. Her weight was 41 kg, her height 153 cm (on the 2.5 percentile), and her head circumference 52 cm.

Figure 1

Figure 1: Patient's face (with permission of patient and author)



Skin examination showed hyperpigmentation of the elbow region, in both creases of the hands and mucosal areas. Examination of the neck shows a diffuse enlargement of the thyroid gland. BP 95/65 mmHg She was very cooperative and answered question adequately. She was also well orientated and no language or speech problems were detected, however all memory functions were diminished and the sensory attention was also affected. Cranial nerves VII, IX and X were affected bilaterally. Trousseau's and Chvosteck's signs were negative Ophthalmological examination revealed retinal dystrophy with visual acuity of 3/10 (right) and 5/10 (left).

Complementary exams showed: elevated CSF protein concentration (106 mg/dl) and normal glucose level. Decreased serum level of sodium, chloride, bicarbonate, calcium, low T4 and TSH were seen while serum level of potassium was persistent mild elevated, glucose: 12 mmol/l; mild increase in creatine phosphate and lactate were present, serum phosphate, alkaline phosphatase, creatinine, aspartate aminotransferase, albumin, total protein, and magnesium were normal. Hyperphosphaturia, hyperaminoaciduria and glucosuria were not found in urianalyis. No skeletal abnormalities were observed, and audiological evaluation demonstrated significant bilateral sensorineural hearing loss.

Twelve-lead electrocardiography (ECG) showed a 2:1 atrioventricular (AV) block with slow ventricular rate. Intermittent complete AV block, and complete left bundle branch block (Figure 2). The patient submitted to muscular biopsy of the thigh muscle which showed the presence of ragged-red fibers (RRF) to Masson trichromic stain (Figure 3-4). CT-scan carried out at 16 years of evolution revealed signs of generalized cerebral and cerebellar atrophy and areas of hypointensity in basal ganglia (figure 5) and on CT-scan of the chest signs of dilated cardiomyopathy were observed (Figure 6) and also confirmed by cardiac ultrasonography tests which also showed a small right kidney (5.6 cm) and left kidney (8.2 cm)

Figure 2

Figure 2: ECG

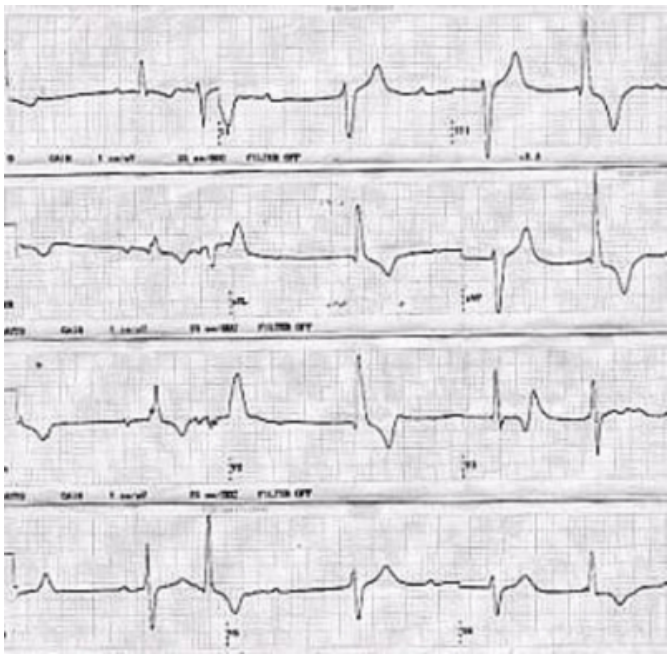


Figure 3

Figure 3: Masson trichromic stain

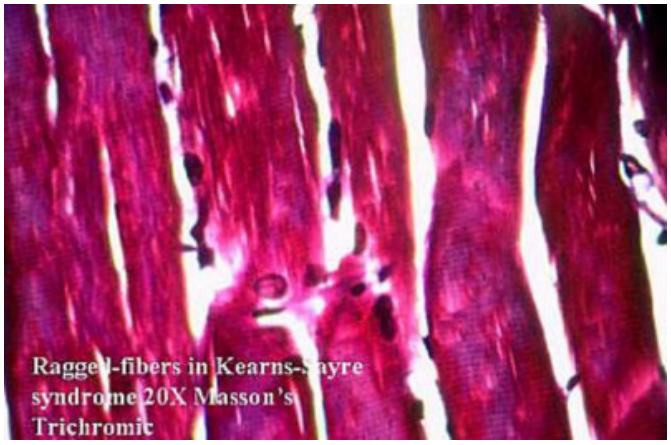


Figure 4

Figure 4: Masson trichromic stain

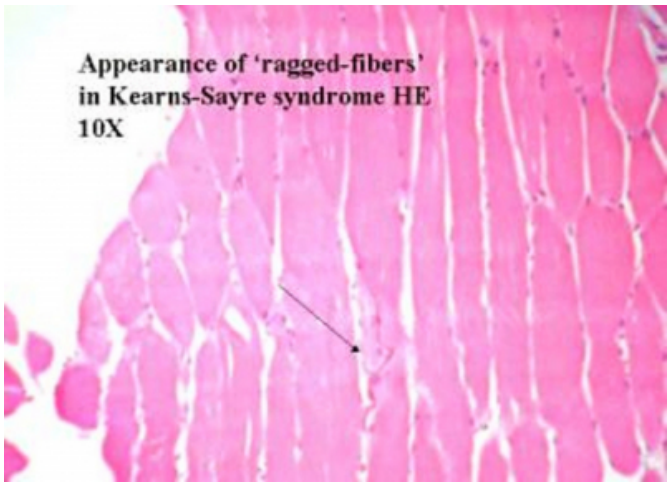


Figure 5

Figure 5: CT Scan

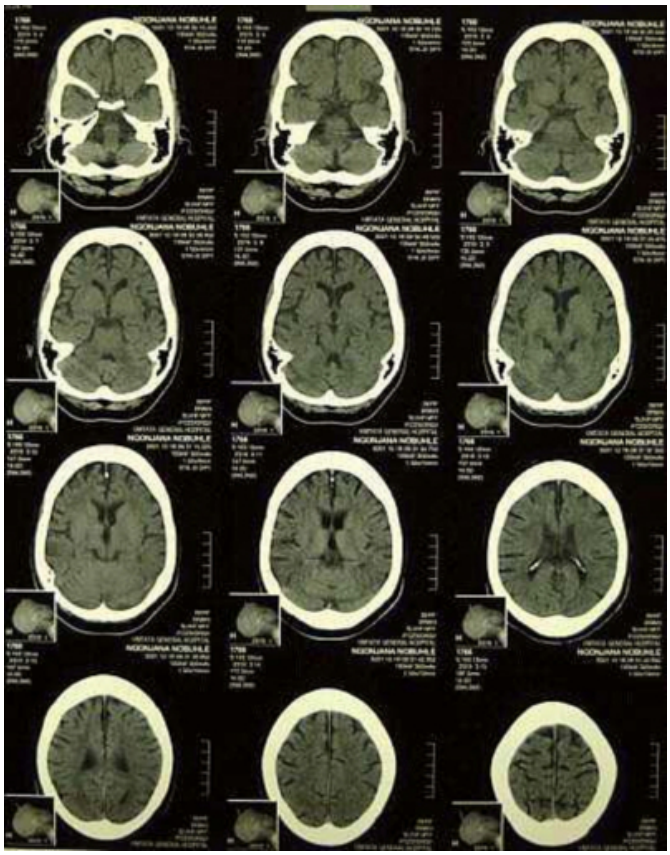
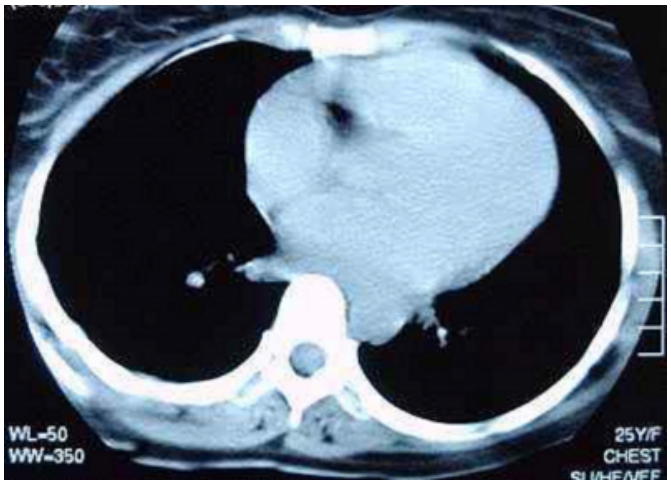


Figure 6

Figure 6: CT Chest



DISCUSSION

Mitochondrial diseases have numerous phenotypic expression, and form an heterogeneous group of genetic diseases in which the production of energy fails, most patients with mitochondrial disorders are diagnosed by finding a respiratory chain enzyme defect or a mutation in the mitochondrial DNA, due to our lack of technological resources the diagnosis for this patient clinically is made. These mitochondrial disease are well known in childhood but can onset in adulthood and its may remains unrecognized[9], although onset before age of 20 years is a general rule, this process has been reported in patients older than 20 years [10] [11]

Most of the combined clinical manifestation present in our patient had been reported previously such as: Short stature due to pituitary growth hormone deficiency2 5, cerebellar ataxia secondary to disconnection of Purkinje cells at the dentate nucleus[12] , progressive ophthalmoplegia,1 dysphagia due to cricopharingeal achalasia[13], hearing loss of cochlear and retrocochlear origin which does not have a pronostic value for the progression of the disorder[14], retinitis pigmentosa because of degeneration of the retina although KSS that involved no retinal pathology had been also reported[15] , heart block is a known associated signs of KSS since the first description in 19581 involvement of the cardiac conduction system due to the mitochondrial disorder is the most important prognostic factor[16] and the prophylactic implantation of definitive pacemarker is recommended16 [17] with a subsequent prolongation of the live expectancy in spite of the probable complications from the dilated cardiomyopathy by itself[18]

Some laboratory investigations also revealed similar results to reported in the medical literature such as: abnormal creatine phosphate, lactate, serum phosphate, alkaline phosphate, aspartate aminotransferase, total protein and electrolytes, and increased CSF protein level due to oncocytic transformation of choroids plexus epithelial cells Delta-mtDNAs-related[19] Anatomopathological examination of the muscle biopsy showed also similarities (ragged-red fibers). We agreed that same comments on radiographic tests, EKG and cardiac ultrasonography could be made. MRI is not performed because is was not available, but the characteristic finding in KSS are well known and consist in a combination of the high-signal foci in subcortical cerebral white matter and in the brain stem, globus pallidus or thalamus[20]

Hypoparathyroidism and an associated renal tubular dysfunction has been recently described[21] Our patient presented normal serum dosage of phosphorus and the serum level for calcium was always decreased, so that the diagnosis of paratyroid disorder was, in spite of absents of episodes of carpopedal spasms and other signs, therefore considered. Have been reported other uncommon associations such as: focal and generalized dystonia with deletion of 5.9 kb from mtDNA [22], Toni-Debre-Fanconi syndrome with focal deficiency of cytochrome-c-oxidase[23] .and acquired primary adrenocortical failure[24] In our patient the classic clinical picture of KSS is associated with some endocrinopathies: diabetes mellitus, hypothyroidism, probable hypoparathyroidism and well documented adrenocortical failure. To the best of our knowledge, this is the first report on this type of association, suggesting “KSS plus”.

ACKNOWLEDGEMENTS

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