The Turkish Journal of Pediatrics 1998; 40: 255-259

KEARNS – SAYRE SYNDROME*
A Case Report

*Şakir Altunbaşak MD***, Gülbin Bingöl MD***, Nazan Özbarlas MD*****
*Zuhal Akçören MD******, Özlem Hergüner MD****

SUMMARY: Altunbaşak Ş, Bingöl G, Özbarlas N, Akçören Z, Hergüner Ö. (Department of Pediatric Neurology, Çukurova University Faculty of Medicine, Adana, Turkey). Kearns-Sayre syndrome: a case report. Turk J Pediatr 1998; 40: 255-259.

Kearns-Sayre syndrome (KSS) is a mitochondrial disorder. There is a large-scale mitochondrial DNA (mtDNA) deletion in most of the cases. In this article, a case of KSS who has progressive external ophthalmoplegia (PEO), retinitis pigmentosa (RP), complete heart block, encephalopathy attacks, type-I diabetes mellitus, ragged-red fiber (RRF) and lactic acidosis is presented and discussed in light of the literature available on this subjects. Diagnosis is confirmed by determination of mtDNA deletion.
Key words: mitochondrial myopathy, Kearns-Sayre syndrome.

Kearns and Sayre described a case with retinitis pigmentosa, progressive external ophthalmoplegia and complete heart block in 1958. Symptoms in KSS appear in childhood. Both sexes are affected equally. Although some familial cases were reported, it is usually sporadic. Large-scale mtDNA deletions have been shown in most cases[1,2].

We report the case of a 15-year-old boy with neuromuscular syndrome of the Kearns-Sayre type, type-I diabetes mellitus and complete heart block (a pacemaker was implanted).

Case Report

A 15-year-old boy was admitted to the hospital with ataxic gait and headache. Two and a half years previously, he had been admitted because of fever, unconsciousness and convulsions. Twenty days before the first admission he had complained of fever, headaches, vomiting and generalized tonic-clonic seizures. He had developed intellectual deterioration and his school performance had become poor during the previous six months. He had also suffered from hearing loss for one year. At that time, his physical examination revealed unconsciousness, hypertonicity of muscles with exaggerated deep tendon reflexes,

* From the Department of Pediatric Neurology, Çukurova University Faculty of Medicine, Adana.
** Associate Professor of Pediatrics, Çukurova University Faculty of Medicine.
*** Research Assistant in Pediatrics, Çukurova University Faculty of Medicine.
**** Associate Professor of Pediatric Cardiology, Çukurova University Faculty of Medicine.
***** Assistant Professor of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

loss of superficial abdominal reflexes, reduced anal sphincter tonus, and signs of meningeal irritation. Results of laboratory examination were: Htc 38.6 percent WBC 10300/mm^3 with 80 percent neutrophils and 20 percent lymphocyte, erythrocyte sedimentation rate (ESR) 43 mm/h, cerebrospinal fluid (CSF) pressure 120 mm H_2O, leukocyte count 40/mm^3, protein 202 mg/dl, glucose 85 mg/dl, and simultaneous serum glucose level 180 mg/dl. Computed tomography of brain (CT) was normal and electroencephalography showed diffuse slowing. He was given nonspecific antimicrobial therapy along with diphenylhydantoin (DPH) for seizures. On the seventh day of hospitalization, he had a complete A-V block and a premanent pacemaker was implanted. On the follow-up, glucose intolerance was determined. After discharge, he was twice admitted to the outpatient clinic of pediatric neurology. DPH was changed to valproic acid. Complaint of hearing loss was progressively increased and his visual performance was reduced. Six months previously he was hospitalized again because of diabetic ketoacidosis and insulin therapy was started. Thyroid hormone therapy was given for goiter. Two months previously he complained of leg pain and headache and of increasing ataxic gait. He was unable to walk without help. He was hospitalized again.

On physical examination, his weight and height were repeatedly below the third percentile. Vital signs were normal and stabile cardiac signs were normal and rhythmic with a permanent cardiac pacemaker. Pulmonary and abdominal examinations were normal. Thyroid was minimally enlarged. Secondary sex characters were poorly developed. On neurological examination, he was lethargic, and direct and indirect light reflexes were bilaterally positive. He had no signs of meningeal irritation. Oculocephalic reflexes were bilaterally poor. Muscle tonus was particularly increased at the lower extremities. He had quadripalsy. Babinski's sign and clonus were positive bilaterally. Sensory loss was absent. Cremasteric reflexes, superficial abdominal reflexes, and perianal reflex were weakly positive. Anal tonus was reduced. On the third day of hospitalization his mental status was improved and he became cooperative. His last neurological examination showed limited eye movements on all sides. He had bilateral ptosis (Fig. 1). He had no dysmetry and dysdiadokokinesis, but apparent ataxic gait. Gower's sign was positive. Fundoscopic examination revealed pigmentary retinopathy.

On laboratory examination. Htc 40.7 percent Hb 13.7 g/dl, WBC 13500/mm^3 with 68 percent neutrophils and 32 percent lymphocyte, ESR 57 mm/h. Blood gas analyses were normal. BUN: 21 mg/dl, Cr: 0.8 mg/dl, Na^+: 149 mEq/L, K^+: 4.4 mEq/L, SGPT: 38 mIU/L, SGOT: 32 mIU/L, LDH: 432 U/L, CPK: 98 U/L, Ca^{++}: 10.2 mg/dl, P: 4.6 mg/dl, ALP: 328 mIU/dl, serum lactic acid: 35 mg/dl (normal value: 10-20 mg/dl), serum pyruvic acid: 3.8 mg/dl (normal value: 0.5-2 mg/dl), parathormone: 20 pg/ml (normal: 1-43) aldosterone: 33 ng/dl (normal: 5-70). Routine examination and metabolic screening of urine, and aminoacid chromatography were

normal. CSF-protein: 220 mg/dl, glucose. 123 mg/dl with simultaneous serum glucose: 144 mg/dl and no pleocytosis were observed on microscopic examination. Cranial computed tomography (CT) was normal. Electromyography (EMG) showed minimal neurogenic pattern. Renal tubular functions were normal. T_3: 109 ng/dl (normal value: 52-176), T_4: 11.3 µg/dl (normal: 4.5-12.5), TSH: 3.5 µlU/ml (normal: 0.6-7.4) while receiving thyroxin replacement therapy. Brain stem auditory evoked response revealed bilateral involvement of eighth nerve. Common mtDNA deletion was determined in peripheral leukocytes (analysis was done in the Department of Medical Biology in Hacettepe University Medical School, Ankara, Turkey). Muscle biopsy showed scattered ragged red fibers; stained red with Gomori's trichrome and dark with oxidative enzyme stains, especially in the periphery. These findings were compatible with mitochondrial myopathy (Fig. 2).

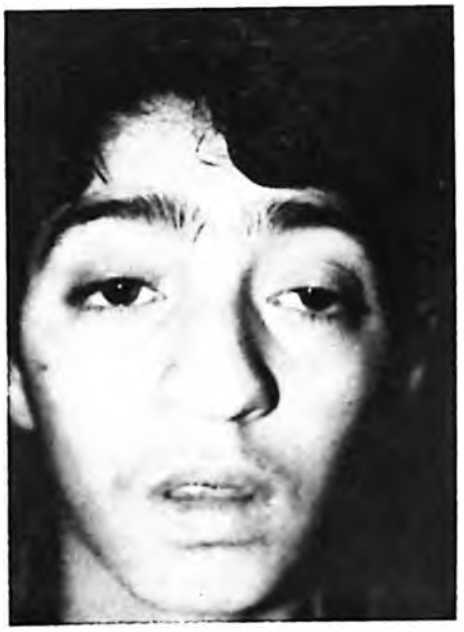

Fig. 1: Showing patient's face and bilateral ptosis.

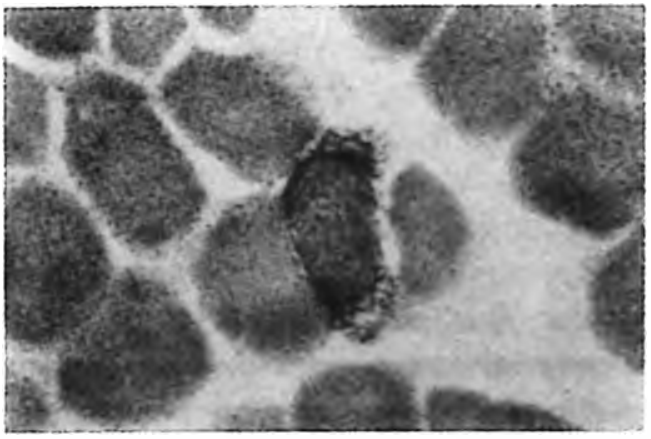

Fig. 2: Darkly stained muscle fiber especially in the periphery, "ragged red fiber" (x 132, succinic dehydrogenase).

Discussion

mtDNA is a small, circular, extra-nuclear chromosome encoding essential components of the respiratory chain. mtDNA-related syndromes can be divided into two groups: mitochondrial encephalomyopathies, characterized by the presence of raggedred fibers (RRF) as the morphological hallmark, or "pure" encephalopathies with no gross morphological abnormalities in the muscle. The first group includes myoclonic epilepsy with raggedred fibers (MERRF), mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO) and a new entity, maternally inherited myopathy and cardiomyopathy. The second group includes Leber's Hereditary Optic Neuropathy (LHON) and the newly described ataxia-retinitis pigmentosa-dementia complex[3]. Our case must be considered within the first group because of his having myopathy, encephalopathy attacks, and lactic acidosis.

Three kinds of molecular lesions have been identified: point mutations of protein-encoding mtDNA genes, point mutation of mtDNA-tRNA genes, and large-scale rearrangements of mtDNA. Point mutations are usually maternally inherited, while large-scale mtDNA rearrangements are either sporadic or are inherited as mendelian traits[3]. Large-scale rearrangements (deletions and insertions) and some point mutations are commonly associated with RRF and lactic acidosis as in KSS. The nuclear defects involving mitochondrial function are not generally associated with RRF[1]. Our case was found to have common mtDNA deletion.

KSS is a form of mitochondrial myopathy in which specific clinical features, namely progressive external ophthalmoplegia, pigmentary retinal degeneration and cardiac conduction defects occur[4]. Children with KSS usually appear normal at birth. Early development may be normal or mildly delayed. Ptosis and PEO are usually the first evidence of the disease. Later, mild visual loss with pigmentary retinopathy and sometimes optic atrophy may occur. The most common neurological feature is cerebellar syndrome which may become severe. Mental retardation or regression may be present. Usually, seizures do not occur unless there is concomitant hypoparathyroidism. Babinski's sign may be present[5]. Reported ECG abnormalities include first degree A-V block, fascicular blocks, sinus dysrhythmia and complete heart block as well as nonspecific S-T changes and T wave abnormalities[6]. Our case has most of these clinical features, such as ptosis, progressive external ophthalmoplegia, retinitis pigmentosa, myopathy, encephalopathy attacks, cerebellar dysfunction, pyramidal signs, and complete A-V block associated with implantation of a pacemaker. Although he does not have hypoparathyroidism, he had convulsions.

KSS has also been associated with a variety of endocrine and metabolic disorders, in particular short stature, gonadal failure, diabetes mellitus, thyroid disease, hyperaldosteronism, hypomagnesemia, and bone, tooth and calcification abnormalities. Short stature was not uncommon, being documented in 38 percent of cases. Gonadal dysfunction before and after puberty was also common (20%) of cases) and affected both sexes equally. Diabetes mellitus was recorded in 13 percent of cases, half of which required insulin. Thyroid disease, hyperaldosteronism, hypomagnesemia, and renal tubular dysfunction were uncommon[4]. Of these endocrinological abnormalties, our case has short stature, hypogonadism, insulin-dependent diabetes mellitus, and thyroid disease, but not hypoparathyroidism, renal tubular dysfunction, or hyperaldosteronism.

As shown in this case and cases in literature, KSS has variable clinical features due to differences of mtDNA deletion. However, progressive external ophthalmoplegia, pigmentary retinal degeneration and onset in childhood or adolescence are invariant features[5].

REFERENCES

1. De Vivo DC. The expanding clinical spectrum of mitochondrial diseases. Brain Dev 1993; 15: 1-22.
2. Schon EA. Mitochondrial disorders in muscle. Curr Opin Neurol Neurosurg 1993; 6: 19-26.
3. Zeviani M, Antozzi C. Defects of mitochondrial DNA. Brain Pathol 1992; 2: 121-132.
4. Harvey JN, Barnett D. Endocrine dysfunction in Kearns-Sayre syndrome. Clin Endocrinol Oxf 1992; 37: 97-103.
5. Aicardi J. Disease of the nervous system in childhood. New York: Cambridge University Press; 1992: 455-456.
6. Ulicny KS Jr, Detterbeck FC, Hall CD. Sinus dysrhythmia in Kearns-Sayre syndrome. PACE Pacing Clin Electrophysiol 1994; 17: 991-994.