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Kearns-Sayre Syndrome -3 Case Reports and Review of Clinical Feature-

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Kearns-Sayre syndrome, first described by Kearns and Sayre in 1958, is a rare disorder consisting of ptosis, limited movement of both eyes and atypical retinal pigmentary change (salt-pepper like appearance). Most cases have shown an increase in the concentration of mitochondria and ragged-red fiber under Gomori-trichrome staining on muscle biopsy. Occasionally, it is combined with other neurologic and endocrinologic symptoms such as ataxia, dementia, diabetes, and hyperaldosteronism. We recently experienced three cases of male teenaged patients who expressed the clinical features of Kearns-Sayre syndrome.

Key Words: Atypical retinal pigmentary change, kearns-sayre syndrome, ptosis, ragged-red fiber

INTRODUCTION

Kearns-Sayre syndrome is a rare disorder resulting from the dysfunction of the mitochondria. The first sign of this syndrome is ptosis, and after several years chronic progressive ophthalmoplegia may occur. Other presentations include atypical retinal pigment changes (salt and pepper like appearance) on fundus examination and high concentration of mitochondria in the extraocular muscles. Occasionally, incomitant strabismus, complete heart block, neurologic and endocrinologic symptoms may occur.[1-3] Upon muscle biopsy, ragged- red fiber can be seen under Gomori-trichrome staining and aggregations of abnormal mitochondria have been demonstrated on electron microscopic examination.[4,5]

We report here in this paper on three suspected cases of Kearns-Sayer syndrome. To confirm the diagnosis, fundus examination and fluorescein angiography, ERG, EOG, 24-hour holter monitoring and muscle biopsy with Gomori-trichrome staining were performed. We were able to confirm the diagnosis in two cases of Kearns-Sayre syndrome. This article will review the clinical experiences and observations we made from these three cases.

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CASE REPORT

Case 1

A 19-year-old male visited to our clinic and presented with a 4 years history of ptosis and limitation of movement in both eyes (Fig. 1). He had no past history of diabetes, hypertension, or trauma, but he had previously experienced bacterial meningitis three times. On ophthalmic examination his visual acuity was 0.9 OD, and 0.8 OS with an intraocular pressure of 12 mmHg OD and 11 mmHg OS. The examination of ocular motility showed a marked limitation in all directions of gaze for both eyes. On the ptosis study, the interpalpebral fissure (IPF) was 3.0 mm OD, 2.5 mm OS, and levator function was 2.0 mm in both eyes. The pupil size was within normal limits and direct, and the indirect pupil light reflex was intact. The anterior segments of both eyes were within normal limits. During funduscopic examination, multiple pigmentary changes (salt and

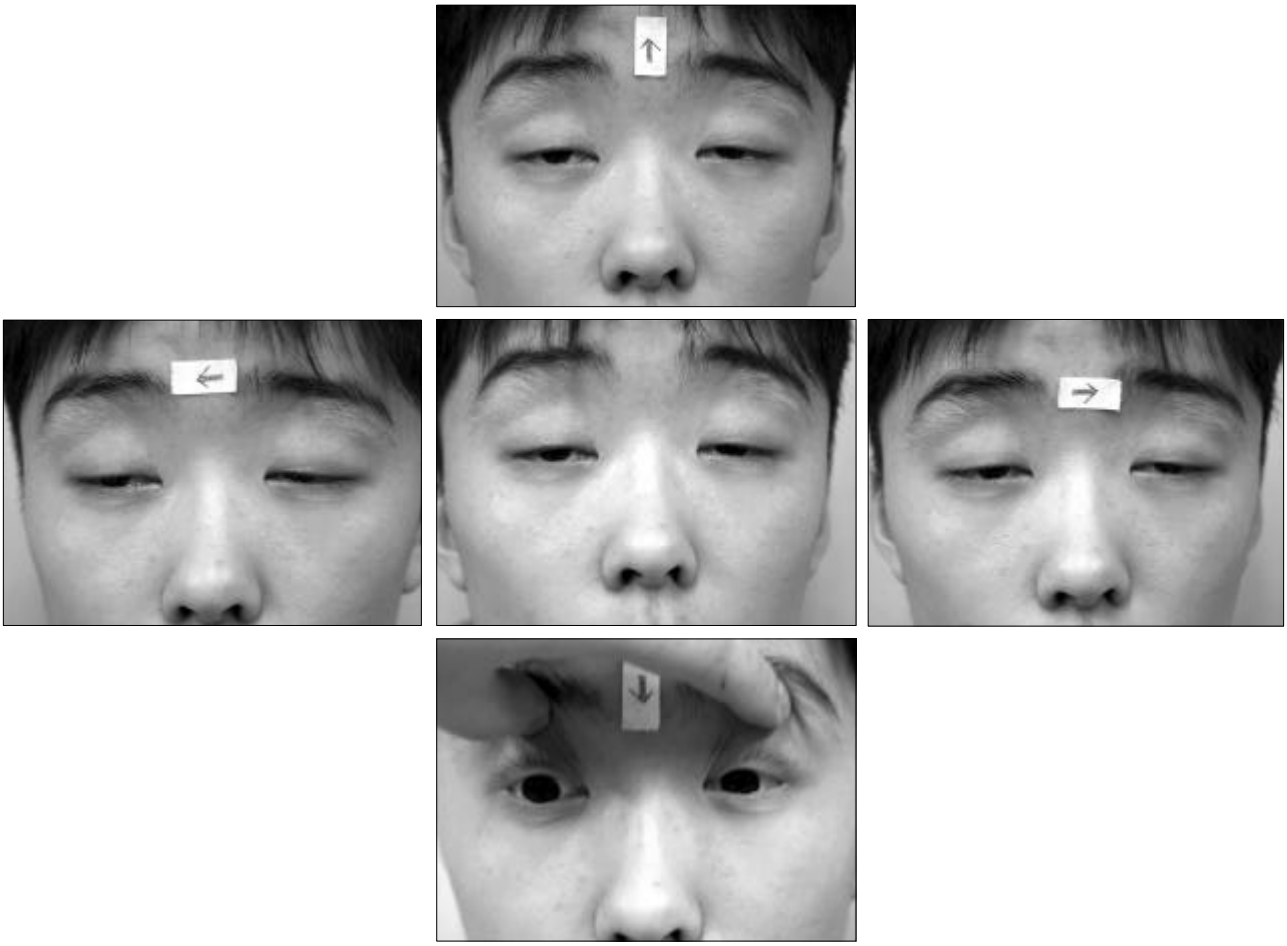

Fig. 1. (case 1) 4 years history of ptosis and limitation of movement is noted. Ptosis is the first sign of this syndrome and usually ophthalmoplegia affects horizontal and upward gazes, but downward gaze is often spared in Kearns-Sayre syndrome. However this case shows marked limitation in all directions of gaze in both eyes.

pepper-like appearance) were noted at the posterior pole, and the optic disc showed deep cupping with a cup/disc ratio of 0.9 in both eyes (Fig. 2). Fluorescein angiography showed extensive retinal pigment epithelial atrophy (Fig. 3). The ERG was normal, however, the EOG was abnormal: the Arden ratio was 73% OD, and the subnormal Arden ratio was 141% OS. On HRT, a glaucomatous optic nerve head was noted (Fig. 4) and the visual field showed a high rate of fixation loss. On the laboratory findings, serum lactate was 5.30 mg/dl and serum pyruvate was 1.60 mg/dl (above normal limits). Muscle biopsy performed on the left biceps showed ragged-red-fiber upon Gomori-trichrome staining, and under electron microscope examination multiple large, atypical mitochondria with electron dense round bodies were noted (Fig. 5). The patient was then transferred to the Department of Cardiology under the diagnostic impression of Kearns-Sayre syndrome. No specific finding was noted on the echocardiogram. However, EKG and 24-hour Holter monitoring showed right bundle branch block and premature ventricular contracture.

Case 2

A 15-year-old male visited to our clinic presenting with a 2 years history of ptosis in both eyes and exotropia (Fig. 6). He had no past history of diabetes or hypertension. On ophthalmic examination, his visual acuity was 0.8 OU with an intraocular pressure of 12 mmHg OD and 13 mmHg OS.

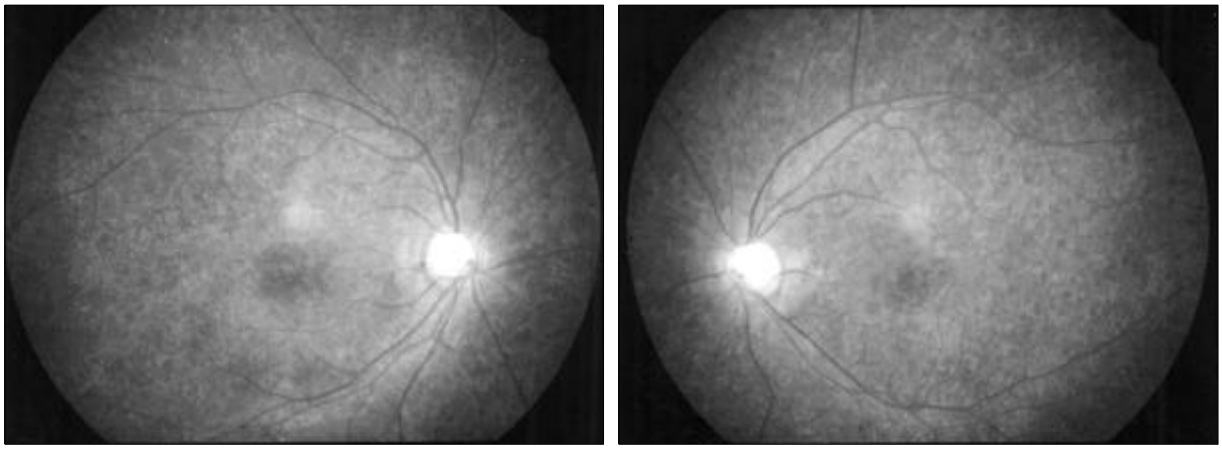

Fig. 2. (case 1) . During detail funduscopic examination, multiple pigmentary changes (salt and pepper-like appearance) are noted at posterior pole and optic disc shows deep cupping. Atypical retinitis pigmentosa is ocular characteristic in Kearns-Sayre syndrome, and pigmentary epithelial change is not confined to the posterior pole.

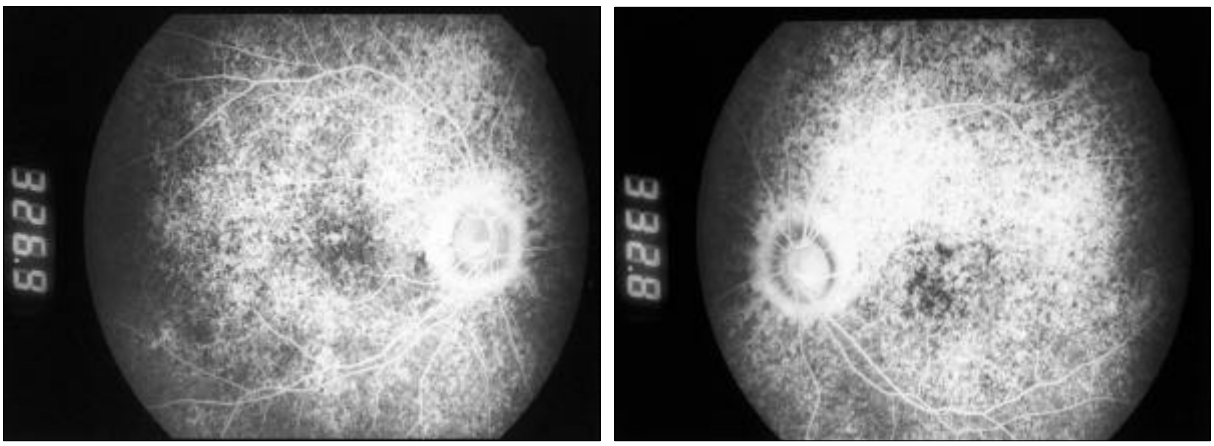

Fig. 3. (case 1) Fluorescein angiography shows extensive retinal pigment epithelial atrophy. This pigmentary retinopathy indicates that the retinal pigment epithelium is affected by this disorder.

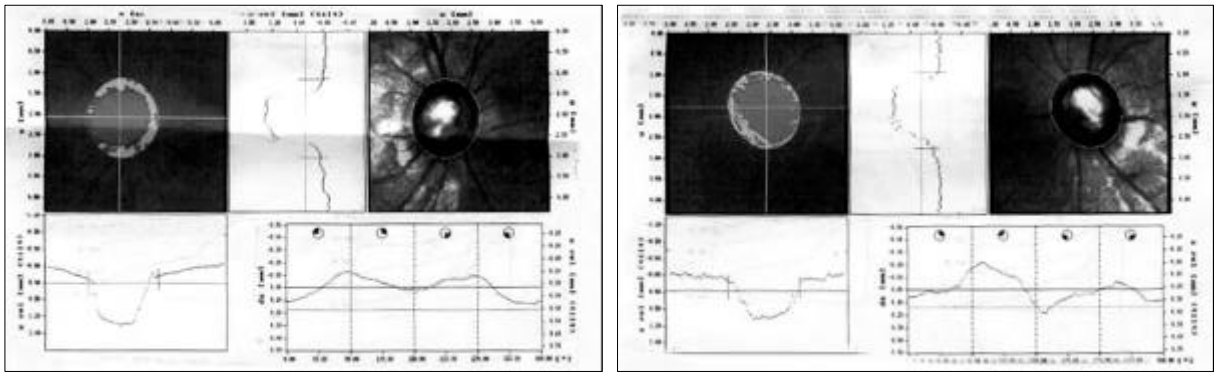

Fig. 4. (case 1) On HRT, glaucomatous optic nerve head was noted. Optic disc showed deep cupping with a cup/disc ratio of 0.9 in both eyes.

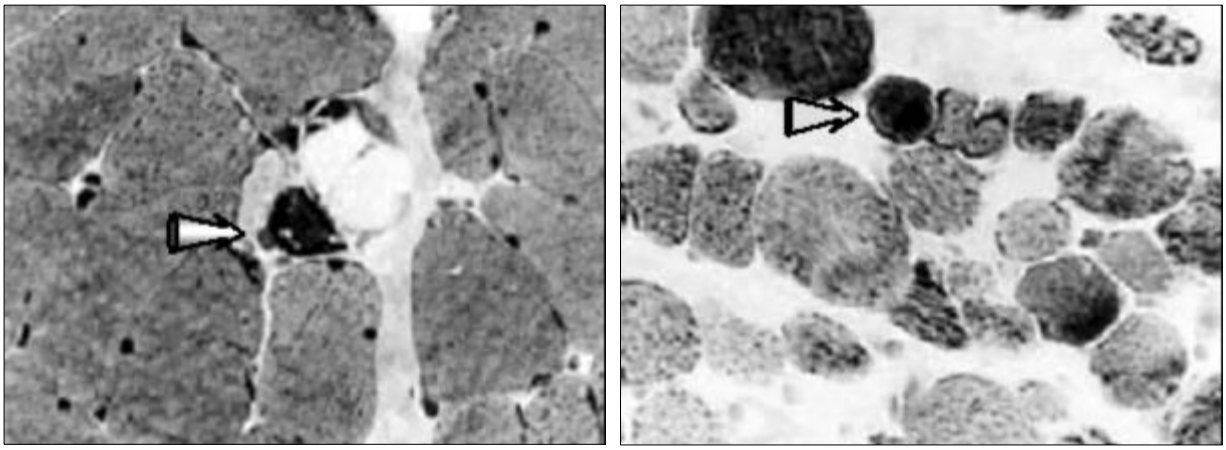

Fig. 5. (case 1) Muscle biopsy shows ragged-red-fiber(arrow) under Gomori-trichrome staining. Under electromicroscopic examination, multiple, large, atypical mitochondria with electron dense round body are noted.

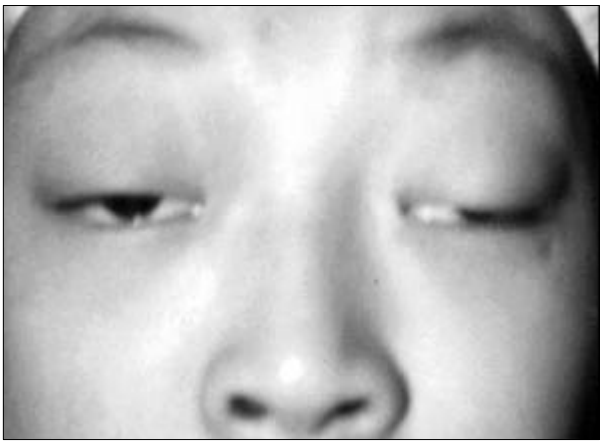

Fig. 6. (case 2) 2 years history of ptosis and exotropia is seen in 15 year-old boy. Prism cover test shows 14-16D exotropia at near and far distance.

The examination of ocular motility showed mild limitations in all directions of gaze in both eyes. The prism cover test showed 14 - 16 exotropia at near and far distances with left inferior oblique overaction 1 - 2 (+). On the ptosis study, the interpalpebral fissure (IPF) was 4.0 mm OD, 3.5 mm OS, and the levator function was 5.0 mm OD, and 4.0 mm OS. The pupil size was within normal limits and the direct and indirect pupil light reflex was intact. Detail funduscopic examination showed mild pigmentary changes on entire peripheral fundus in both eyes (Fig. 7). Fluorescein angiography showed mild retinal pigment epithelial atrophy (Fig. 8). ERG, EOG and VEP were normal.

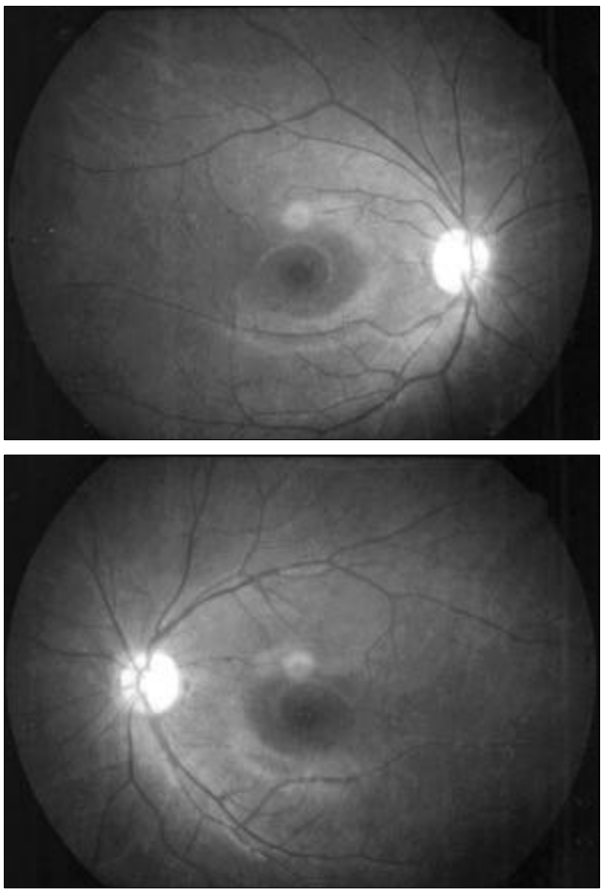

Fig. 7. (case 2) Detail funduscopic examination shows mild pigmentary changes at entire peripheral fundus in both eyes.

On the laboratory findings, serum lactate was 5.30 mg/dl (within normal limits). The patient was

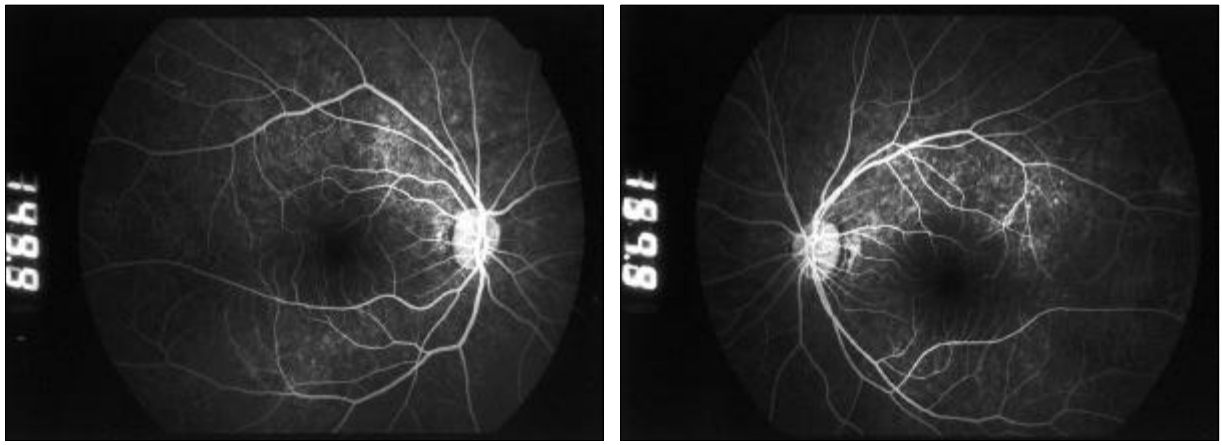

Fig. 8. (case 2) Fluorescein angiography shows mild retinal pigment epithelial atrophy.

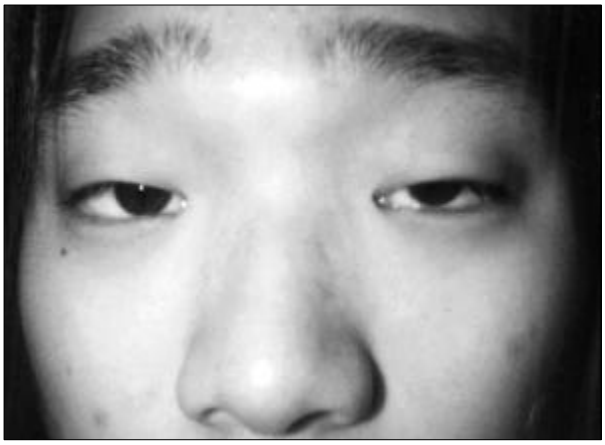

Fig. 9. (case 3) 4 years history of ptosis and left exotropia is seen in 18 year-old boy. Prism cover test shows 18D left exotropia at right gaze.

then transferred to the department of neurology under the diagnostic impression of Kearns-Sayre syndrome. According to laboratory findings performed in department of neurology, the serum lactate was 1.69 mg/dl and repetitive nerve stimulation showed no significant decremental response to stimulation. The result of a pharmacologic test for myasthenia gravis was negative. After these evaluations, frontalis suspension with a silicone rod was performed to correct blepharoptosis.

Case 3

A 18-year-old male visited our clinic and presented with a 4 years history of ptosis, which was more severe in the left eye, and exotropia (Fig. 9). He had no past history of diabetes, hypertension or trauma. On ophthalmic examination, his visual acuity was 1.0 OD, 0.9 OS with an intraocular pressure of 18 mmHg OU. The examination of ocular motility showed a marked limitation in all directions of gaze in the left eye. On the ptosis study, the interpalpebral fissure (IPF) was 6.0 mm OD, 4.0 mm OS, and levator function was 9.0 mm OD and 6.0 mm OS, and instillation of 10% topical phenylephrine showed an improvement of ptosis. The prism cover test showed 8△ exophopia at the primary gaze, but 18△ left exotropia at the right gaze. The pupil size was within normal limits and direct, and the indirect pupil light reflex was intact. The anterior segments of both eyes were within normal limits. Detail funduscopic examination showed mild pigmentary changes on the entire peripheral fundus in both eyes (Fig. 10). Fluorescein angiography showed mild retinal pigment epithelial atrophy at the peripheral fundus (Fig. 11). Conjunctivomullerectomy was performed on the left eye for the ptosis. Immediately after the operation, proper correction of the left eye ptosis was noted, but the lid drooping worsened in both eyes as time passed by. ERG was abnormal for all stimuli, and EOG was subnormal: the Arden ratio was 145% OD and there was an abnormal Arden ratio of 119% OS. The patient was then transferred to the department of neurology and cardiology under the im-

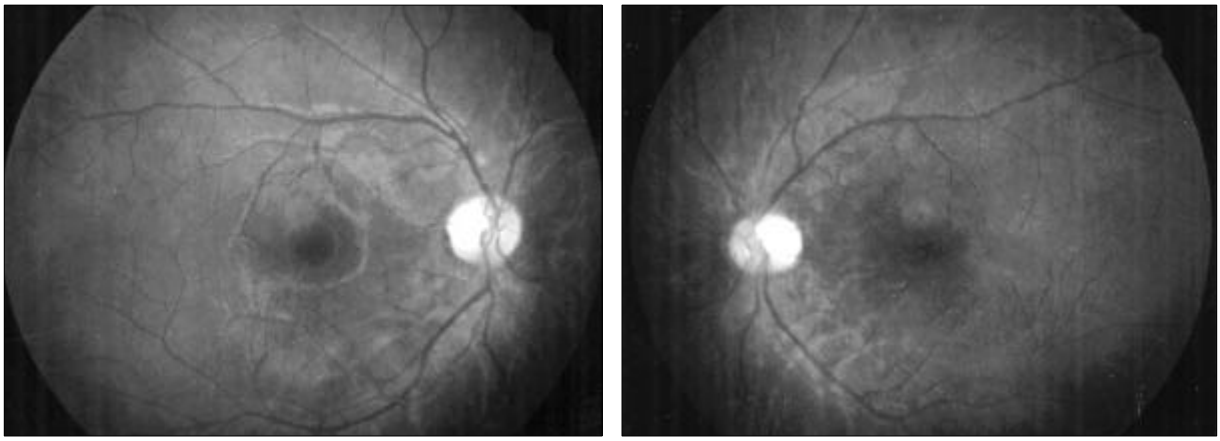

Fig. 10. (case 3) Detail funduscopic examination shows mild pigmentary changes at entire peripheral fundus in both eyes.

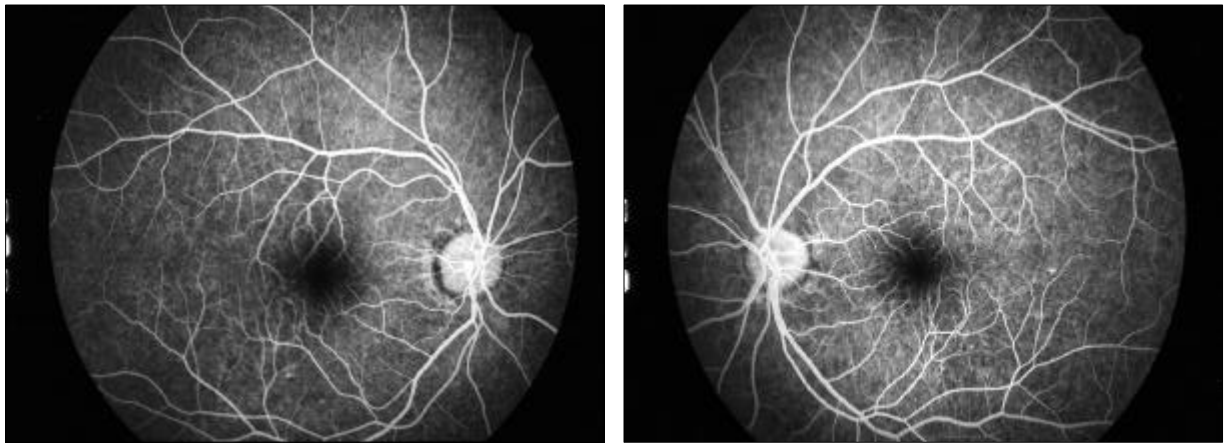

Fig. 11. (case 3) Fluorescein angiography shows mild retinal pigment epithelial atrophy at peripheral fundus.

pression of Kearns-Sayre syndrome. On the laboratory findings performed in the department of neurology, the serum lactate was 1.01 mg/dl and repetitive nerve stimulation showed no significant decremental response to stimulation. The result of a pharmacologic test for myasthenia gravis was negative, and for the cardiologic evaluation, no specific finding was noted on the echocardiogram. However, the EKG showed right bundle branch block and marked sinus arrhythmia.

DISCUSSION

Kearns-Sayre syndrome, which was first described by Kearns and Sayre in 1958, is a rare disorder. It is one of the mitochondrial diseases characterized by chronic progressive external ophthalmoplegia, pigmentary retinopathy (salt-pepper like appearance), cardiac conduction defect, elevated cerebrospinal fluid protein and cerebellar dysfunction.[1-3] Serum and cerebrospinal fluid lactate and pyruvate levels are usually increased and the muscle biopsy shows ragged-red fibers. It is occasionally combined with other neurologic and endocrinologic symptoms such as ataxia, dementia, diabetes and hyperaldosteronism,[4,5] and nearly all cases are sporadic and associated with clonally expanded rearrangements of mitochondrial DNA (mtDNA).[6,8]

Genetics and biochemistry

In Kearns-Sayre syndrome, mitochondrial DNA

deletions vary from 1.3 to 8.0 kb subunits of the oxidative phosphorylation enzymes and several t-RNA genes are affected. Mitochondrial DNA deletions can cause problems for mitochondrial protein synthesis in general and this may cause multiple problems in respiratory chain function.[6,8]

The main cause of this syndrome is the spontaneous mitochondrial mutations within the oocyte or zygote. There may be a somatic mutation or selective elimination of mutant mitochondria in certain cell lines. Many patients show no detectable mitochondrial DNA deletions, and this may be due to point mutations or deletions too small to detect with the typical RFLP analysis technique. Reduced mitochondrial electron transport activity, and particularly cytochrome-c oxidase deficiency, can be detected and this causes muscle fiber degeneration.[7,8]

The heart may be particularly susceptible to the effects of decreased oxidative phosphorylation because the heart depends on fatty acid beta oxidation for its energy. Therefore, accumulation of NADH with cytochrome-c oxidase deficiency, which results in the inhibition of beta-oxidation, can usually cause a problem in the heart.[9,10]

Characteristics

Children with Kearns-Sayre syndrome usually appear normal at birth. Male and female are equally affected and although some patients have episodes of either meningitis or encephalitis in childhood, this is not universal.[1-4] Ptosis is usually the first sign, and so using their brow muscles to elevate the eyelids is often noted. Ptosis is followed within a few years by progressive external ophthalmoplegia. The ophthalmoplegia usually begins after the age of five. This weakness is not characteristically in a particular neural distribution, but it affects all muscles equally and never affects the pupils clinically. Usually, both the horizontal and upward gazes are affected, but the downward gaze is often spared.[5]

Incomitant strabismus is another presentation of Kearns-Sayre syndrome, even though diplopia is unusual due to the slow progressive nature of the ophthalmoplegia. Sometimes it can mimic myasthenia gravis, but the serum creatine kinase levels may be slightly elevated.[3,5]

Atypical retinitis pigmentosa is another ocular characteristic, but in Kearns-Sayre syndrome, bone-spicule formation is uncommon, and pigmentary epithelial change is not confined to the posterior pole. Therefore, the pigmentary change is called atypical to distinguish it from the typical bone-spicules found in the distribution as seen in retinitis pigmentosa.[11,12] However, this pigmentary retinopathy indicates that the retinal pigment epithelium is affected by this disorder.[11] Visual symptoms are usually mild. The ERG is usually normal or it shows mildly attenuated a- and b-wave amplitudes, and skeletal muscle biopsy has shown typical ragged-red fibers in almost all patients with Kearns-Sayre syndrome.

Cardiac dysfunction

Patients with Kearns-Sayre syndrome die suddenly of cardiac conduction disorders within the His bundle and also because of infrequent syncopal episodes, both of which seemed to be preventable by implantation of a pacemaker.[1] Abnormality in cardiac conduction usually begins with left fascicular block with or without right bundle branch block. Eventually, complete heart block develops and His bundle recordings show trifascicular block. ST depression on EKG may be seen without overt coronary disease. Heart failure caused by congestive cardiomyopathy without conduction defects can also develop.[1,2]

Neurologic abnormalities

Nystagmus, ataxia, hearing loss and dementia can develop, and spongiform degeneration may be seen in the cerebral cortex, basal ganglia and brain stem. These lesions may affect the cranial nuclei, including the oculomotor nuclei. Brain stem lesions in the medulla may account for respiratory distress and the tendency for episodic coma in these patients.[13,14] Moreover, intracranial calcifications are common and the CSF protein content is usually elevated. A mild cellular lymphocytic pleocytosis may be seen, although this is usually no more than 20 cells. The CSF protein may rise with time, and some values exceeding 200 mg/dL have been described.[15]

Endocrine disturbances

Endocrinologically, patients with Kearns-Sayre syndrome may have delayed sexual maturation and have a short stature. Diabetes mellitus appears in approximately 20% of patients with Kearns-Sayre syndrome. Thyroid abnormalities, hypoparathyroidism and hyperaldosteronism can also be seen.[1,4]

Histopathology

Pigment epithelial atrophy with overlying photoreceptor degeneration occurs at first and reduced phagocytosis of photoreceptor debris can be noted. Macrophages containing the outer segments of the photoreceptors may be observed within the affected RPE, and the peripheral photoreceptors are relatively spared.[8,15]

As shown in our first case, a clinical history of ptosis, ophthalmoplegia and pigmentary change (salt and pepper like appearance) on fundus examination, and retinal pigment epithelial atrophy on fluorescein angiography are frequently combined in Kearns-Sayre syndrome.

In this case, there is no difficulty in making a diagnosis due to the obvious clinical features, but attention should be made to other combined abnormalities. The muscle biopsy showed a higher concentration of mitochondria and ragged-red fiber. In addition, right bundle branch block and premature ventricular contracture was noted on EKG and 24-hour Holter monitoring. From these signs and symptoms, our first case was diagnosed as a typical example of Kearns-Sayre syndrome. However, the second case was very difficult to diagnose Kearns-Sayre syndrome.

In general, Kearns-Sayre syndrome is defined by three criterian that seem invariable. This triad includes (1) an onset at less than 20 years of age, (2) progressive external ophthalmoplegia, and (3) pigmentary retinopathy. Also, patients with Kearns-Sayre syndrome should have at least one of the secondary triad of (1) cardiac conduction defect, (2) CSF protein of 100 mg/dL or more, and (3) a cerebellar syndrome.[15] Many other abnormalities have been found in patients with Kearns-Sayre syndrome, including mental retardation, Babinski signs, limb weakness, hearing loss, seizures, short stature, delayed puberty and various endocrine abnormalities.[1,3,4]

In our second case, the 15-year old boy had the invariable triad of symptoms, but he lacked the secondary triad. However he had the combined abnormalities of short stature and mild mental retardation. These abnormalities can emphasize the possibility of Kearns-Sayre syndrome despite the lack of the secondary triad. Another observation that supported his diagnosis was his age. He was just 15 years old when first examined, and since the signs and symptoms of Kearns-Sayre syndrome are normally expressed by the age of 20, we assumed that the symptoms would be shown in later years before the patient turned 20 years old.[2,4,10]

In our third case, the patient had ptosis, ophthalmoplegia, peripheral pigmentary change on the fundus examination, and peripheral retinal pigment epithelial atrophy on fluorescein angiography, which satisfied the invariable triad of Kearns-Sayre syndrome. Additionally, his cardiac problems of right bundle branch block and marked sinus arrhythmia represented one of the secondary triad. From these symptoms we were able to diagnose our third patient as a typical case of Kearns-Sayre syndrome.

Invasive procedures were refused by the two patients. For example, muscle biopsy and CSF study might have shown ragged red fiber and a high CSF protein concentration, respectively, which would represent Kearns-Sayre syndrome. Repetitive nerve stimulation testing showed no significant decremental response, and the pharmacologic test for myasthenia gravis showed a negative sign, and this meant the cause of the ptosis resulted from mitochondrial dysfunction. Considering these factors, we could conclude that our second and third patient were probable cases of Kearns-Sayre syndrome.[10]

In some patients with Kearns-Sayre syndrome, and not in all patients, there is deficiency of the Ubidecarenone, or coenzyme Q10 in the serum and muscles. Q10 is essential for normal mitochondrial respiration. Treatment with coenzyme Q10 in some patients with mitochondrial cytopathies has resulted in improved pyruvate metabolism, cardiac function, exercise tolerance, CSF protein levels, and ataxia, but it has no effect on

the ophthalmoplegia, ptosis or retinopathy. Concerning heart block and belpharoptosis, these can be treated the same as for non-Kearns-Sayre syndrome patients, and strabismus may be treated surgically if it is stable. Especially, the rectus muscle resection would be more effective than recession.[16,17]

We experienced three cases of ptosis, chronic progressive ophthalmoplegia and pigmentary degeneration of the retina, and these symptoms are an invariable triad of Kearns-Sayre syndrome. The abnormalities and dysfunctions of this syndrome can cause a life-threatening situation. Furthermore, this is a rare disease and the mechanism of Q enzyme is uncertain. Therefore, further comprehensive studies about Kearns-Sayre syndrome must be performed.

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