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Case Report

Kearns-Sayre syndrome with restricted diffusion in subcortical white matter and extraocular muscle atrophy ☆

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ABSTRACT

Kearns-Sayre Syndrome (KSS) is a rare multisystem mitochondrial disorder affecting muscles, the central nervous system, and the endocrine system. KSS is characterized by T2WI/FLAIR hyperintensities in the subcortical white matter, brainstem, globi pallidi, thalami, and middle cerebellar peduncles. Here, we report a case of KSS with extraocular muscle atrophy in which MRI performed approximately 10 years after the initial MRI examination revealed lesion expansion and diffusion restriction of subcortical white matter affecting U-fibers.

Introduction

Chronic progressive external ophthalmoplegia (CPEO) and Kearns-Sayre Syndrome (KSS) are caused by mutations in mitochondrial DNA and appear to represent a clinical continuum: CPEO is a disease characterized by ptosis and external ophthalmoplegia, whereas KSS is a multisystem disorder characterized by onset before age 20 years, pigmentary retinopathy, and external ophthalmoplegia [1]. In addition, the diagnosis of KSS requires the presence of at least one of the following: cardiac conduction abnormalities, cerebellar ataxia, cerebrospinal fluid (CSF) protein levels ≥100 mg/dl, short stature, endocrine abnormalities, or cognitive decline [2]. MRI findings in young adults and children with KSS have been reported to be characterized by T2-weighted imaging (T2WI)/FLAIR hyperintensities in the subcortical white matter and one or more regions of the brainstem, globi pallidi, thalami, and middle cerebellar peduncles [3,4].

☆ Competing Interests: The authors declare that they have no conflict of interest.

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KSS is a rare disease, and there are no reports of long-term imaging follow-up studies beyond 10 years. Here, we report a case of KSS in which significant changes in MRI findings were observed 10 years after the initial MRI.

Case presentation

An 8-year-old boy visited a hospital with a chief complaint of right eyelid ptosis for the past year. Regarding family history, his grandfather had myasthenia gravis, but there was no family history of mitochondrial disease. At that time, only right inferior oblique muscle overaction was present and no other abnormalities were noted. Two years later, he presented with the complaint of bilateral ptosis and muscle weakness, and was referred to our hospital for brain MRI examination. MRI was performed using a 1.5T MR scanner (Achieva, Philips Healthcare, Best, The Netherlands). FLAIR showed mild cerebral atrophy and high signal areas in the left caudate nucleus and dorsal midbrain (Fig. 1), and severe atrophy of extraocular muscles was found on the both sides (Fig. 2). No diffusion restriction was observed, and no abnormal signals were found in the subcortical white matter, middle cerebellar peduncle, or cerebellum. He had ptosis, restricted eye movement, short stature and hearing loss, and CSF showed high lactate and pyruvate levels. As a result, a tentative diagnosis of mitochondrial disease was made. At the age of 11, a muscle biopsy on his left arm revealed red ragged fibers, and mitochondrial DNA sequence analysis revealed a large deletion of approximately 4 kB, leading to a diagnosis of CPEO. Treatment with fursultiamine and ubidecarenone was initiated. At the age of 14, retinitis pigmentosa was pointed out, confirming the diagnosis of KSS. At the age of 15, he enrolled in a clinical trial of 5-ALA treatment for Leigh encephalopathy. Although the treatment had little effect, he continued it at his own request. He developed diabetes mellitus at the age of 18.

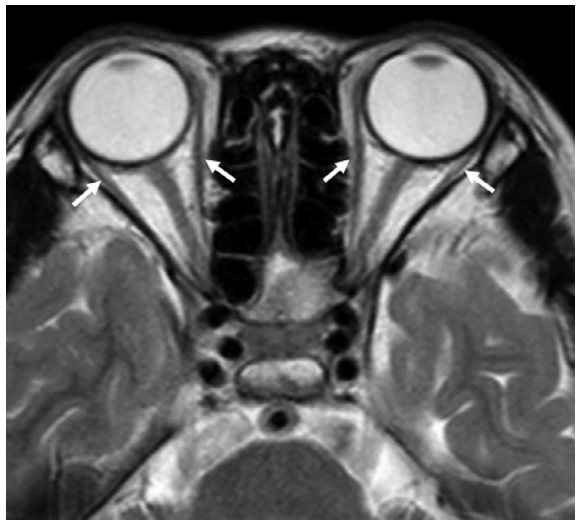

Fig. 2 – T2-weighted image (TR/TE 3652/90 msec, slice thickness/gap, 5/1 mm) shows atrophy of the bilateral medial and lateral rectus muscles (arrows).

The patient was referred to our hospital at the age of 20 with almost no eye movement. He had slight paralysis on the left side of his face and difficulty protrud-

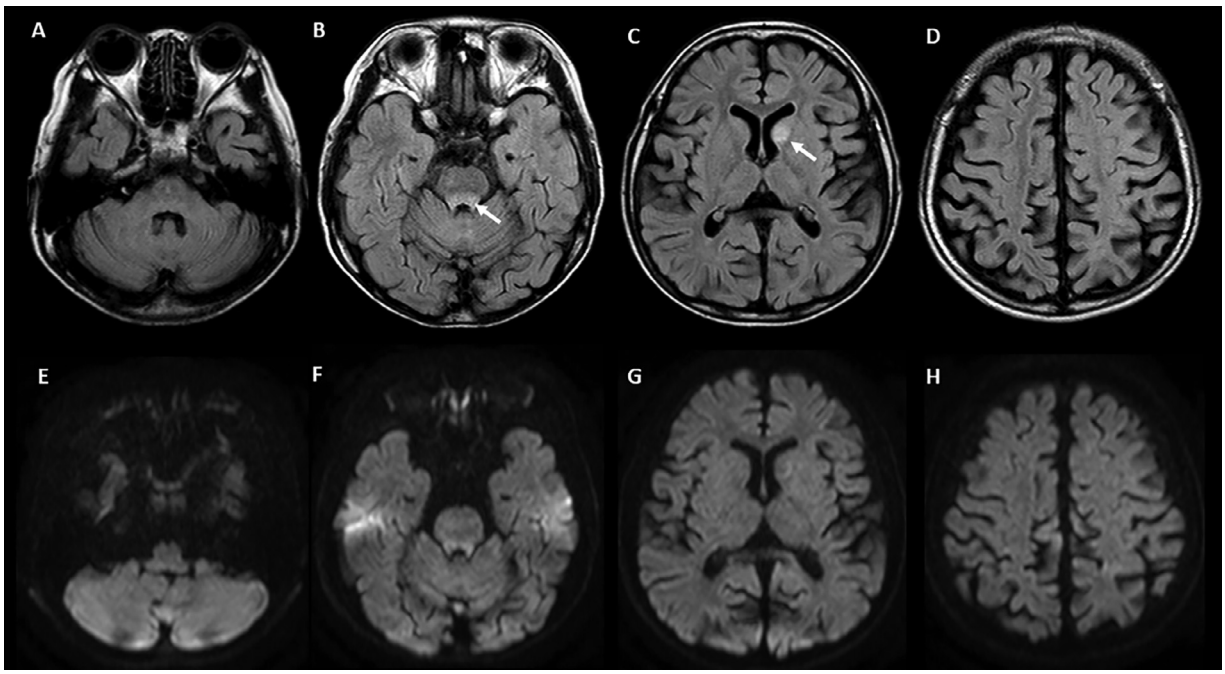

Fig. 1 – MRI at age 10 years shows mild cerebral atrophy. FLAIR (TR/TE/TI, 8000/140/2400 msec, slice thickness/gap, 5/1 mm) images (A-D) show high signals in dorsal midbrain (B: arrow) and left caudate nucleus (C: arrow). DWI (b = 1000 s/mm^2, TR/TE, 2365/60 msec, slice thickness/gap, 5/1 mm) demonstrates no restricted diffusion (E-H).

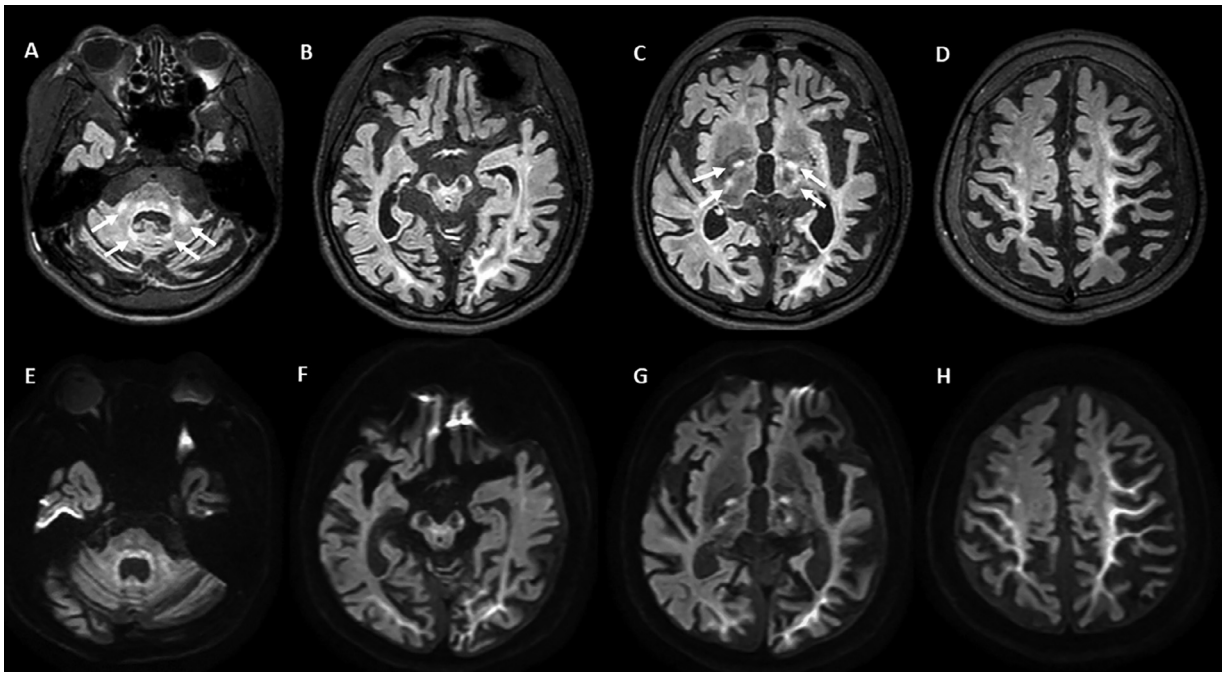

Fig. 3 – MRI at age 20 years shows severe atrophy of the brain, including the cerebrum, cerebellum, and brainstem. 3D FLAIR (TR/TE/TI, 6000/386/2000 msec, slice thickness, 1 mm) images (A-D) show signal hyperintensities in the middle cerebellar peduncles, paravermal regions (A: arrows), brainstem, globi pallidi, thalami, internal capsules (C: arrows), and subcortical white matter involving U-fibers. DWI (b = 1000 s/mm^2, TR/TE, 6273/84 msec, slice thickness, 3mm without gap) shows hyperintensities in these lesions with restricted diffusion (E-H).

ing his tongue. Muscle atrophy was evident in his lower limbs, making it difficult for him to stand or walk. His muscle tone was generally increased, and his limbs were rigid. He had no sensory or autonomic symptoms. Laboratory analysis revealed diabetes (blood glucose 121mg/dL; normal: 73-109 mg/dL, HbA1c 7.1%; normal: 4.9%-6.0%, C-peptide 3.5ng/mL; normal:0.8-2.5ng/mL), hypercholesterolemia (total cholesterol 268mg/dL normal:142-248mg/dL), and liver dysfunction (AST:53U/L; normal:13-30U/L, ALT:86U/L; normal:10-42U/L, γ-GTP:76U/L; normal:13-64U/L, ALP 148U/L; normal:38-113U/L, cholinesterase 268U/L; normal:142-248, LDH:256U/L; normal:124-222U/L). Echocardiography revealed no morphological or functional abnormalities, and left ventricular contractility was at the lower limit of the normal range. An electrocardiogram showed complete right bundle branch block and left axis deviation. MRI was performed using a 3T MR scanner (Ingenia, Philips Healthcare, Best, The Netherlands). Brain MRI showed severe atrophy of the cerebrum, brainstem, and cerebellum, which had worsened over the past 10 years (Fig. 3). All extraocular muscles were thinning (Fig. 4). 3D FLAIR showed hyperintensities in the left caudate nucleus, bilateral globi pallidi, pyramidal tracts, middle cerebellar peduncles, paravermal areas, brainstem, and bilateral subcortical white matter including U-fibers with sparing periventricular regions (Fig. 3). DWI showed restricted diffusion in these lesions (Fig. 3). Contrast-enhanced MRI was never performed in this patient.

Discussion

Roosendaal et al. investigated MRI features in a large population of patients with mitochondrial leukodystrophies and described that T2WI or FLAIR hyperintensity patterns primarily affecting U-fibers, the globi pallidi, and the substantia nigras were associated with KSS [4]. However, in the present case, abnormal hyperintensities in these regions were not observed at age 10 years and appeared at age 20 years. Thus, our report suggests that subcortical hyperintensities, including U-fibers, may not be initially recognized in pediatric patients with KSS, and this may need to be taken into consideration when diagnosing mitochondrial diseases.

It is noteworthy that in this case, diffusion restriction of subcortical U-fibers was observed at the age of 20. This DWI finding in KSS has been reported in several reports [5,6], and this may be a characteristic finding of KSS. Considering only the DWI finding of the subcortical regions in this case, several differential diagnoses are possible, including disorders caused by CGG repeat expansions, such as neuronal intranuclear inclusion disease (NIID), fragile X tremor/ataxia syndrome (FXTAS), oculopharyngeal myopathy with leukoencephalopathy (OPML), and oculopharyngodistal myopathy (OPDM) [7–12]. MRI findings in these disorders are characterized by DWI hyperintensity in the subcortical white matter affecting U-fibers, and occasionally T2WI/FLAIR hyperintensity in the bi-

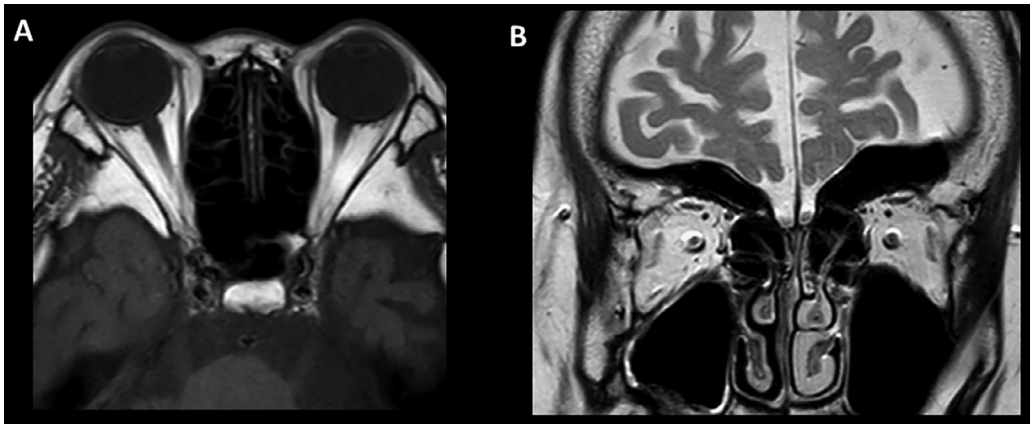

Fig. 4 – At age 20 years, T1-weighted image (TR/TE, 588/14 msec, slice thickness/gap, 3/0.5 mm) shows severe atrophy of the bilateral medial and lateral rectus muscles (A), and coronal T2-weighted image (TR/TE, 3500/80 msec, slice thickness/gap, 3/0.5 mm) shows obvious atrophy of all bilateral extraocular muscles (B).

lateral paravermal regions and bilateral middle cerebellar peduncles may be seen [7–12]. Since abnormal expansion of the CGG repeat sequence is observed in the above 4 diseases, it is the abnormal expansion of the repeat sequence itself that causes the common pathological condition and MRI findings [9]. These diseases share core symptoms of leukoencephalopathy, neuropathy, and oculopharyngeal myopathy, and their MRI findings are similar. Recently, Ishiura et al. proposed the term "FXTAS, NIID, and oculopharyngeal myopathy" (FNOP) spectrum disorder as a new concept [13]. Similar clinical and MRI findings were observed in the current case, and it seems likely that KSS should also be considered as a differential diagnosis when such findings are present.

There have been several reports that quantitatively examined the atrophy of the extraocular muscles in KSS and CPEO [14,15]. Although it is not always possible to visually determine the atrophy of extraocular muscles, in this case the extraocular muscles appeared to be sufficiently thin. OPDM is clinically characterized by progressive ophthalmoplegia, extraocular muscle atrophy may be seen on MRI, and DWI hyperintensities have been reported in the subcortical white matter affecting U fibers [11]. It should be noted that although mitochondrial DNA analysis and mitochondrial enzyme activity tests are normal in OPDM, features of OPDM may be similar to those of KSS [16].

Conclusion

We reported a case in which there was no abnormality in the subcortical white matter at the age of 10 years, but abnormalities appeared 10 years later. The DWI findings were similar to those of diseases caused by CGG repeat expansions, such as NIID, FAXTAS, OPML, and OPDM. Although the diagnosis of KSS is based on findings other than MR findings, radiologists should keep these MR findings in mind.

Patient consent

Written informed consent for publication of the case report was obtained from the patient.

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