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MR of the Brain in Mitochondrial Myopathy

Shirley H. Wray, James M. Provenzale, Donald R. Johns, and Keith R. Thulborn

PURPOSE: To determine the spectrum of MR findings in patients with mitochondrial myopathy and correlate them with central nervous system symptoms and signs. **METHODS:** We performed a prospective evaluation of the MR findings of eight patients with mitochondrial myopathy (three with Kearns-Sayre syndrome and five with chronic progressive external ophthalmoplegia), six of whom had central nervous system symptoms or signs (ataxia, sensorineural hearing loss, or cognitive dysfunction). **RESULTS:** All six patients with neurologic symptoms or signs had multiple abnormal MR findings, whereas patients without neurologic symptoms had either normal MR findings (one patient) or the solitary finding of cortical atrophy (one patient). Abnormal MR findings consisted of cerebral cortical atrophy (seven patients), cerebellar atrophy (six patients), and hyperintense signal abnormalities on T2-weighted images within the cerebral white matter (three patients), cerebellar white matter (one patient), basal ganglia (three patients), brain stem (one patient), and thalamus (one patient). In two patients, the cerebral white matter signal abnormalities were primarily peripheral and involved the arcuate fibers. All patients with ataxia had abnormal cerebellar findings on MR imaging, but there was poor correlation between other neurologic features and MR findings. **CONCLUSIONS:** Cerebral and cerebellar atrophy are the most common MR findings in Kearns-Sayre syndrome and chronic progressive external ophthalmoplegia. White matter and deep gray nuclei abnormalities, presumed to result from the diffuse spongiform encephalopathy reported in these patients, can also be seen. Patients with abnormal neurologic findings typically have multiple abnormalities on MR imaging, which frequently do not correlate with specific symptoms.

Index Terms: Muscles, diseases; Degenerative disease; Brain, magnetic resonance

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Chronic progressive external ophthalmoplegia (CPEO) and the Kearns-Sayre syndrome (KSS) are two easily clinically recognizable syndromes within the spectrum of diseases caused by mitochondrial myopathy (1). There is variable involvement of multiple organs (eg, heart, brain, and retina) in CPEO and KSS, which may be attributable to a mixed population of mutant and normal genomes in varying amounts in different tissues (2–4). The clinical central nervous system findings in KSS and CPEO, which may include ataxia, dementia, and sensorineural hearing loss (5), are usually less prominent than ophthalmoplegia and ptosis, the characteristic features of these syndromes. Both muscle and brain are also involved in patients with central nervous system dysfunction related to a mitochondrial abnormality, that is, so-called mitochondrial encephalomyopathy, which includes the syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS syndrome), and that of myoclonic epilepsy with ragged red fibers (MERRF syndrome) (6, 7). Considerable overlap of symptoms and signs exists between CPEO and KSS, on the one hand, and MELAS and MERRF syndromes, but there is general agreement that even cases of CPEO and KSS with involvement

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TABLE 1: Mitochondrial myopathy: clinical features

Patient	1	2	3	4	5	6	7	8
Sex	F	M	M	F	M	F	F	F
Age of onset, y	9	8	18	6	50	23	30	7
Ophthalmoplegia	+	+	+	+	+	+	+	+
Retinopathy	+	+	+	+	+	+	−	−
Heart Block*	30	24	25	−	−	−	−	−
Ataxia*	57	22	20	−	−	48	−	30
Deafness*	30	21	21	−	54	−	−	<10
Cognitive Impairment*	45	20	24	−	60	−	−	−
Ragged red fibers	+	+	+	+	+	+	+	+
mtDNA deletion, kilobases	9.1	8.6	3.8	5.0	−	−	5.2	···

Note.— +, indicates present; −, absent.
* Numbers refer to age in years at which symptoms/signs developed.

of the brain should be considered separately from the MELAS and MERRF syndromes.

Previous reports have noted that magnetic resonance (MR) imaging findings in patients with KSS and CPEO can include generalized atrophy and hyperintense signal abnormalities in white matter, deep gray nuclei, and the brain stem (8–12). A few of these reports correlated neurologic features and MR findings (8, 9). We performed a prospective evaluation of MR findings in patients with KSS or CPEO to define further the spectrum of MR findings and correlate them with neurologic features.

Patients and Methods

The study group consisted of eight patients (five women and three men), 20 to 62 years of age (average, 43 years) diagnosed with KSS or CPEO on clinical grounds, the presence of ragged red fibers, and/or mitochondrial DNA (mtDNA) deletions. The follow-up period after initial diagnosis ranged from 2 to 26 years (average, 12 years). Each patient underwent neurologic and neuroophthalmologic examinations, and seven underwent muscle biopsy. Table 1 lists the clinical features of the patients. Three patients (patients 1–3) had heart block and atypical retinal pigmentary degeneration, meeting KSS criteria. Atypical retinal pigmentary degeneration was also present in three patients with CPEO (patients 4–6). Neurologic symptoms or signs were present in six patients (three with KSS and three with CPEO) and included sensorineural hearing loss (unilateral in patients 2, 3, 5 and 8 and bilateral in patient 1), progressive cognitive impairment (patients 1, 2, 3, and 5) and ataxia (patients 1, 2, 3, 6, and 8). All of these features were present in each of the patients with KSS. One patient with KSS (patient 2) also had seizures and a sensory neuropathy. The two patients who lacked neurologic symptoms had CPEO and had the least severe degree of ophthalmoplegia and ptosis.

Total DNA was extracted from 100-mg aliquots of biopsied skeletal muscle in seven patients. Molecular genetic analysis of mtDNA was performed by Southern blot analysis and a widely interspaced primer polymerase chain technique (13, 14). One patient (patient 8) was not biopsied. This patient, who had a history of hypocalcemic tetany, has been previously reported (15).

Spin-echo MR imaging was performed with a 1.5-T system. T1-weighted images were taken in the sagittal plane (eight patients), axial plane (three patients), and coronal plane (two patients) using 600–800/10–20/2 (repetition time/echo time/excitations) and a section thickness of 5 mm. T2-weighted images were taken in the axial plane using 2000–3270/30,80/1 and a section thickness of 5 to 7 mm. The time from symptom onset to MR imaging varied from 12 to 52 years (average, 22.3 years).

Results

Deletions of mtDNA in skeletal muscle, ranging in size from 3.8 to 9.1 kilobases, were found on muscle biopsy in five patients (Table 1).

Abnormal MR findings were present in seven patients (Table 2) and consisted of cerebral atrophy in seven patients (patients 1–3 and 5–8), cerebellar atrophy in six patients (patients 1–3, 5, 6, and 8), and hyperintense signal abnormalities on T2-weighted images within the cerebral white matter in three patients (patients 2, 5, and 8), cerebellar white matter in one patient (patient 8), basal ganglia in three patients (patients 2, 5, and 8), thalamus in one patient (patient 2), and brain stem in one patient (patient 2). All of the patients with neurologic findings had multiple MR abnormalities, including cerebral and cerebellar atrophy. Patients with KSS and those with CPEO with neurologic symptoms had similar findings, with each group having a spectrum of severity of MR abnormalities. Of the two patients without neurologic features, one had normal MR findings (patient 4), and the other had the sole finding of cerebral atrophy (patient 7).

Cerebellar atrophy was demonstrated in all five patients with ataxia and in one patient with-

TABLE 2: Mitochondrial myopathy: MR findings

Patient	1	2	3	4	5	6	7	8
Age, y	61	23	38	20	62	52	47	37
Years from symptom onset to MR	52	15	20	14	12	29	17	30
Cerebral atrophy	+	++	+++	−	+	++	++	+++
Cerebellar atrophy	+++	++	++	−	+	++	−	++
Abnormal signal								
White matter	−	++	−	−	+	−	−	++++
Brain stem	−	++	−	−	−	−	−	*
Basal ganglia	−	++	−	−	+++	−	−	++++
Thalamus	−	+	−	−	−	−	−	−

Note.—−, indicates absent; +, mild involvement; ++, moderate involvement; +++, moderately severe involvement; ++++, severe involvement; and *, brain stem atrophy.

out neurologic symptoms (patient 5). There was generally good correlation between severity of cerebellar symptoms or signs and MR findings. The most severe cerebellar atrophy was seen in patient one, a patient who had KSS with moderately severe truncal and appendicular ataxia (Fig 1). Patient 2, who was confined to a wheelchair at age 22 years because of severe gait ataxia, was found to have a moderate degree of cerebellar atrophy. In the other three patients, mild limb ataxia was associated with moderate cerebellar atrophy.

The presence of cerebral atrophy correlated poorly with clinical findings. Five patients had moderate or moderately severe cortical atrophy, but only two of these had cognitive impairment (Table 2). Conversely, of the four patients with cognitive impairment, all had some degree of cortical atrophy, but it was mild in two patients and may have been related to age.

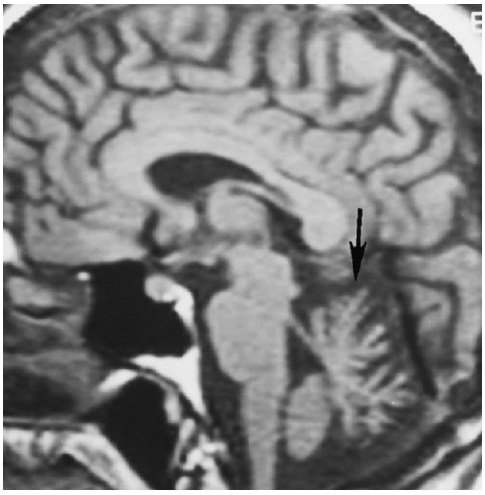

Fig 1. A 61-year-old woman (patient 1) with KSS, moderately severe truncal and appendicular ataxia, and a documented mtDNA deletion. A T1-weighted sagittal image (600/20/2) demonstrates severe cerebellar vermian atrophy (*arrow*).

Cerebral white matter signal abnormalities were predominantly found in the peripheral white matter (including the arcuate fibers) in patient 2 (Fig 2) and patient 8 but also involved regions of the deep white matter in patient 8 (Fig 3). In another patient (patient 5) the white matter signal changes were mild and periventricular in location and may have been related to age.

Two patients, who had the most severe MR findings, had brain stem abnormalities: hyperintense signal (patient 2, Fig 2) and brain stem atrophy (patient 8). Both patients had external ophthalmoplegia related to the underlying myopathy, but neither had clinical brain stem involvement.

Basal ganglia findings were detected in three patients: hyperintense signal abnormality in the globus pallidus in patient 8 (Fig 3), within the head of caudate in patient 2 and, in patient 5, numerous enlarged perivascular spaces. None of these patients had neurologic symptoms related to the basal ganglia.

Abnormal hyperintense signal on T2-weighted images within both thalami was seen in one patient (patient 2).

There was no correlation between the severity of MR findings and the duration of symptoms or the size of the mtDNA deletion.

Discussion

KSS and CPEO, two of the major forms of mitochondrial myopathy, are characterized by: (*a*) external ophthalmoplegia and progressive bilateral ptosis (which are the dominant clinical features); (*b*) the ragged red appearance of muscle fibers seen with the modified Gomori trichrome stain, caused by peripheral and intermyofibrillar accumulations of abnormal mito-

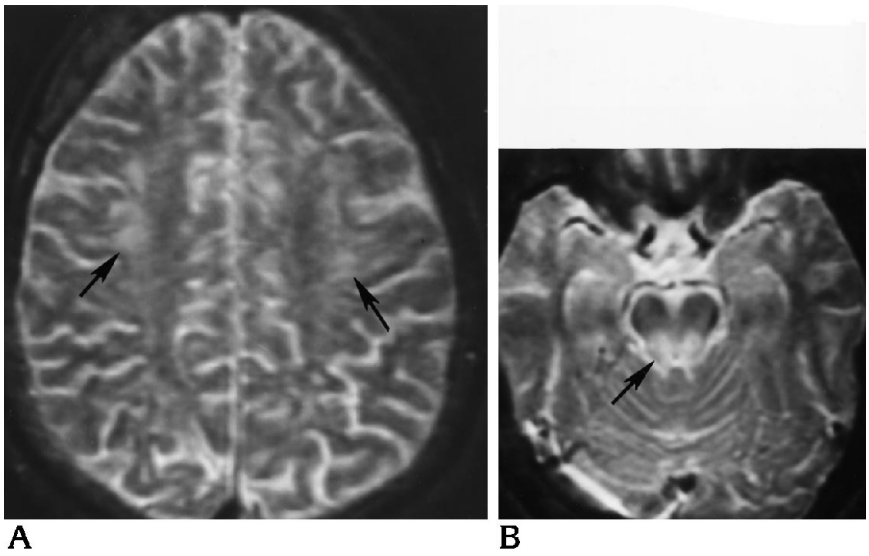

Fig 2. A 23-year-old man (patient 2) with KSS, cognitive impairment, ataxia, and an mtDNA deletion.

A, T2-weighted image (2700/80/1) demonstrates regions of hyperintense signal (*arrows*) in the subcortical white matter. The periventricular regions were spared.

B, T2-weighted image (2700/80/1) shows foci of hyperintense signal (*arrows*) in the dorsal midbrain.

chondria; (*c*) the complete lack of histochemically demonstrable cytochrome c oxidase activity in some muscle fibers; and (*d*) deletions of mtDNA in skeletal muscle (3, 16–20). A wide spectrum of clinical manifestations is seen in both syndromes. In patients with KSS, external ophthalmoplegia develops before the age of 20 years, and they have pigmentary retinopathy, complete heart block, and/or elevated spinal fluid protein levels (1, 21). In patients with CPEO, ptosis and ophthalmoplegia develop at any age; these patients tend to be less severely affected than patients with KSS. A 4.9-kilobase mtDNA deletion, which encompasses structural genes for the mitochondrial respiratory chain and is associated with impaired mitochondrial function, has been detected in an identical location in patients with KSS and CPEO (20).

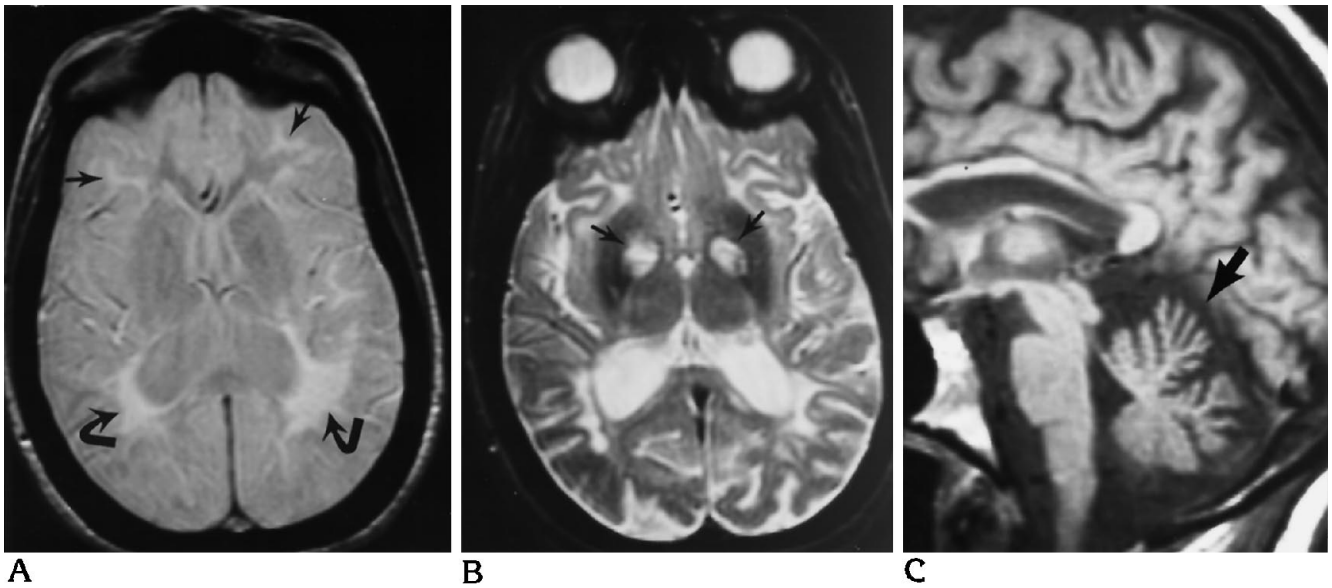

Fig 3. A 37-year-old woman (patient 8) with CPEO manifested by external ophthalmoplegia, ataxia, and sensorineural hearing loss.

A, Long-repetition-time/short-echo-time (proton density) (3000/30/1) axial image. In the frontal lobes, abnormal hyperintense signal predominates in the subcortical white matter (*arrows*), whereas in the posterior temporal and parietal lobes the abnormal signal extended from the subcortical regions to the ventricular surface (*curved arrows*).

B, T2-weighted (3000/80/1) axial MR image demonstrates bilateral hyperintense signal abnormalities in the globus pallidus (*arrows*). Hyperintense white matter abnormalities and ventricular dilatation are also present.

C, T1-weighted (600/20/2) sagittal image demonstrates cerebral cortical and cerebellar vermian atrophy (*arrow*) and thinning of the corpus callosum.

Muscle mtDNA deletions are often, but not always, detectable. Therefore, the absence of detectable muscle mtDNA deletions in two of our patients with CPEO is not unexpected. Furthermore, this fact does not exclude the possibility of mtDNA mutations as the basis for their disease, because very small deletions, or point mutations, may have been present but not detected (18).

As our findings demonstrate, and as previous reports have noted (2, 8, 9, 12), a wide spectrum of MR findings can be seen in KSS and CPEO. The findings are the same in both syndromes, presumably reflecting the same fundamental deficiencies of brain energy metabolism. Hyperintense signal abnormalities within white matter, corresponding to hypodense white matter abnormalities on computed tomography (22, 23), are one of the major features, although they are not seen in all patients. Two previous studies have noted a predilection for involvement of the peripheral white matter (including the arcuate fibers) with relative sparing of the periventricular fibers (8, 9). A similar distribution of abnormal white matter signal was seen in two of our patients but also extended to involve regions of the deep white matter in patient 8. In the absence of serial MR examinations in this patient, we cannot determine whether the white matter changes in these sites also began in the peripheral white matter. The causes of these abnormalities are not known with certainty, because none of our cases have come to postmortem examination. Possible causes include brain necrosis, demyelination, or spongiform degeneration. Multiple foci of white matter softening of both hemispheres and basal ganglia have been reported in a young patient with KSS who had hypodense basal ganglia lesions on computed tomography (24). Degeneration of oligodendrocytes and demyelination of the spinal cord have been seen in patients with MELAS, suggesting that inhibition of mitochondrial metabolism produces secondary degeneration of oligodendrocytes and diffuse demyelination and microvacuolation of the inner myelin sheath (25). This hypothesis is supported by experiments in which demyelination of the mouse brain has been induced using cuprizone, a chelating agent that inhibits mitochondrial metabolism (26). The most common neuropathologic finding in KSS and CPEO, however, is diffuse spongiform encephalopathy predominantly involving the white matter, and, to a lesser degree, the deep gray nuclei, brain stem and spinal cord (27–32). This distribution correlates well with the pattern of MR findings in our patients, making spongiform encephalopathy the most likely cause. Spongiform degeneration is not pathognomonic for CPEO and KSS, because it can be seen in Canavan disease and Leigh syndrome (subacute necrotizing encephalomyelopathy), both diseases of infancy resulting from mitochondrial dysfunction (8).

Cerebral and cerebellar atrophy were present in all our patients with neurologic symptoms but can be seen even in the absence of neurologic symptoms or signs (9, 33). Although cerebellar atrophy in KSS and CPEO is usually present in the setting of generalized atrophy (9), it was restricted to the cerebellum in one patient (patient 1). Abnormal cerebellar white matter signal in CPEO, as was present in patient 8, has been previously reported (10). Cerebellar findings are not unexpected, because ataxic KSS patients have been found at autopsy to have widespread cerebellar spongiform degeneration (30–32), atrophy of the folia and vermis (31), diffuse loss of Purkinje cells (30, 31), and abnormal cerebellar mitochondria (34, 35). In one KSS case with progressive ataxia, vermian atrophy, and widespread cerebellar spongiform degeneration, although ultrastructural examination of the cerebellar cortex did not reveal mitochondrial abnormalities, the authors suggested that a deficiency of respiratory chain enzymes caused by a mtDNA deletion was of pathogenic importance (31).

Abnormal MR signal within the brain stem and brain stem atrophy have been previously reported in individual cases of KSS and CPEO (8, 10, 22). In one series, however, signal abnormalities were not demonstrated in the infratentorial brain (9), suggesting that brain stem signal abnormalities are uncommon. Coarse vacuolization of the dorsal pons and midbrain has been noted in a patient with CPEO, which may account for the MR signal changes (27).

In this series, the presence of neurologic symptoms correlated well with the finding of multiple abnormalities on MR imaging. Cerebellar ataxia, however, was the only neurologic finding that was consistently associated with a lesion on MR imaging. In one previous study, all four patients with CPEO or KSS and ataxia were found to have abnormal MR findings, but cerebellar MR findings were not always present (9). We found poor correlation between other neu-

rologic features and MR abnormalities or between severity of MR abnormalities and age of symptom onset, length of symptoms, or size of mtDNA deletion. It is apparent that there is wide variability in the timing and severity of MR findings, because some of the patients with the shortest symptom durations had the most severe MR findings. We presume that individual clinical and neuroradiologic variations are related to the amount of abnormal mtDNA within particular brain sites.

The other mitochondrial disorders to be considered in the differential diagnosis of our patients are the MELAS and MERRF syndromes. Patients with MELAS have seizures, headache, and recurrent strokelike episodes (21). MR findings include multiple strokelike lesions primarily involving the parietal and occipital cortex, and to a lesser degree the subcortical white matter, basal ganglia, brain stem and cerebellum, which typically do not correspond to a major vascular territory (8, 11, 33, 36). These findings have been attributed to mitochondrial angiopathy (37). Patients with MERRF syndrome have myoclonic epilepsy, ataxia, muscle weakness and fatigue (6), and MR findings of hyperintense white matter signal abnormalities and generalized atrophy (38), involvement of the deep gray matter nuclei (8), and degeneration and calcification of the cerebellar dentate nucleus and globus pallidus (39). Positron emission tomography with fludeoxyglucose F 18 in a patient with a mitochondrial encephalomyopathy has demonstrated prominent alterations of brain glucose metabolic rates in all gray matter structures, predominantly the posterior cortical regions and the thalamus, with relative sparing of the anterior cortical areas and basal nuclei (40). One recent review of the MR findings in a variety of mitochondrial disorders concluded that although no single set of findings is diagnostic of these disorders, and even though MR abnormalities do not allow distinction among the different mitochondrial syndromes, the combination of deep gray matter involvement and peripheral white matter involvement in children or young adults should suggest the diagnosis of a disorder of mitochondrial function (8). Based on our findings, we propose that cerebellar and cerebral atrophy should also be considered a common feature in patients with KSS and CPEO. When these abnormalities are present along with peripheral white matter signal abnormalities and involvement of the deep gray matter nuclei, a mitochondrial disorder should be considered, if not already diagnosed on clinical grounds. Our findings indicate that involvement of the brain in mitochondrial myopathy may be more prevalent than hitherto reported. MR is useful for definition of the precise relation between clinical and molecular phenotypes once clinical testing and DNA analysis are complete.

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