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Neuroradiologic Findings in Children with Mitochondrial Disorders

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PURPOSE: We report the neuroradiologic findings in 25 children with various mitochondrial diseases.

METHODS: Twenty-two children with a mitochondrial disorder had MR imaging of the brain and three children had CT studies. In all cases, the diagnosis was based on examination of muscle morphology, analysis of oxygen consumption and respiratory chain enzyme activity in isolated muscle mitochondria, and analysis of rearrangements of the mitochondrial DNA.

RESULTS: Fifteen patients were found to have the classical syndromes of mitochondrial diseases. Four children had Kearns-Sayre syndrome, but only one had the typical neuroradiologic findings of basal ganglia and brain stem lesions, T2 hyperintensity of the cerebral white matter, and cerebellar atrophy; the others had nonspecific or normal findings. Eight patients had Leigh syndrome, and all showed changes in the putamina. Involvement of the caudate nuclei, globus pallidi, thalami, and brain stem was common, and diffuse supratentorial white matter T2 hyperintensity was seen in two of these patients. Three patients had mitochondrial encephalopathy with lactic acidosis and strokelike episodes (MELAS), with infarctlike lesions that did not correspond to the vascular territories. Ten children with complex I or IV deficiencies and abnormal muscle morphology had nonspecific imaging findings, such as atrophy and abnormal or delayed myelination. One patient with combined complex I and IV deficiency had extensive white matter changes. None of the patients with clinical encephalopathy had normal findings.

CONCLUSION: MR imaging is helpful in the diagnosis of the classical mitochondrial diseases; however, nonspecific findings are common.

Mitochondrial diseases are a heterogeneous group of disorders caused by defects in intracellular energy production. Clinical symptoms originating from all organ systems have been described, but tissues with high-energy requirements, such as muscle and brain, are particularly vulnerable. In adults, muscle weakness, exercise intolerance, and ophthalmoplegia dominate, together with slowly progressive cognitive dysfunction (1–4). Multisystem disorders are more common in children (5, 6). The diagnosis of a mitochondrial disorder is based on the presence of clusters

of abnormal mitochondria in muscle cells (ragged red fibers) and a biochemically defined defect in the respiratory chain enzymes or, more recently, also on mutations in the mitochondrial DNA (mtDNA) (7, 8).

Several distinct syndromes have been recognized among the variable clinical phenotypes of mitochondrial disorders, including chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome (KSS), mitochondrial encephalopathy with lactic acidosis and strokelike episodes (MELAS), myoclonus epilepsy with ragged red fibers, and neurogenic muscle weakness with retinitis pigmentosa (8). However, especially in children, nonspecific neurologic symptoms are common. MtDNA defects are often absent, and biochemical and morphologic findings can be marginal. Neuroimaging has proved useful in the diagnosis of mitochondrial syndromes. KSS and MELAS show characteristic lesions on computed tomography (CT) and magnetic resonance (MR) imaging studies (9–17) and typical imaging findings are the hallmark of the diagnosis of Leigh syndrome (18–22). In chronic progressive external ophthalmoplegia and myoclonus epilepsy with ragged red fibers, however,

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TABLE 1: Clinical and mitochondrial findings of the patients

Patient/Sex	Age at Diagnosis	Clinical Presentation	Mitochondrial Abnormality	Central Nervous Symptom
1/F	2 y	Pearson	CI, CIV, mtDNA deletion	Cognitive impairment
2/F	7 y	Pearson/KSS	RRF, CI, CIV, mtDNA deletion	Ataxia, ophthalmoplegia, cognitive impairment
3/M	12 y	Pearson/KSS	RRF, CIV, mtDNA deletion	Cognitive impairment
4/M	13 y	KSS	RRF, CI, CIV	Seizures, hearing deficit, cognitive impairment
5/F	11 y	Leigh	CI	Epilepsy, ataxia, bulbar signs, mental retardation
6/F	1.5 y	Leigh	CI	Ataxia, spasticity, cognitive impairment
7/M	12 y	Leigh	CIV	Spastic tetraparesis, epilepsy, mental retardation
8/M	2 y	Leigh	CIII	Spastic tetraparesis, mental retardation
9/M	5 y	Leigh	CIV	Spastic tetraparesis, mental retardation
10/F	2 y	Leigh	CI	Spastic tetraparesis, mental retardation
11/F	6 mo	Leigh	mtDNA 8993 mutation	Spastic tetraparesis, mental retardation
12/M	2 y	Leigh	mtDNA 8993 mutation	Spastic tetraparesis, mental retardation
13/F	4 y	MELAS	RRF, CI, mtDNA 3243 mutation	Strokelike episodes, severe focal epilepsy, cognitive impairment
14/F	6 y	MELAS	mtDNA 3243 mutation	Strokelike episodes, severe focal epilepsy
15/F	8 y	MELAS	RRF	Strokelike episodes, focal epilepsy, mental retardation
16/M	7 y	Encephalomyopathy	RRF, CI	Athetosis, dyskinetic movements, spasticity, cognitive impairment
17/M	3 y	Encephalomyopathy	RRF, CI	Cognitive impairment
18/M	5 y	Encephalomyopathy	CI	Severe hypotonia, mental retardation
19/M	8 mo	Encephalomyopathy	CI	Severe hypotonia, mental retardation
20/F	6 y	Encephalomyopathy	RRF, CI	Cognitive impairment
21/M	1 mo	Encephalomyopathy	CIV	Severe hypotonia, cognitive impairment
22/F	13 y	Encephalomyopathy	CI+CIV	Ataxia, dyskinetic movements
23/F	14 y	Myopathy	RRF, CI	None
24/M	1 mo	Myopathy	RRF, CIV	None
25/F	1 y	Cardiomyopathy	RRF, CIV	None

Note.—KSS indicates Kearns-Sayre syndrome; MELAS, mitochondrial encephalopathy with lactic acidosis and strokelike episodes; RRF, ragged red fibers; and CI through CIV, defect of the respiratory chain enzyme complex I to IV.

the imaging findings are nonspecific (13, 15, 23) and little is known about the value of neuroradiologic studies in patients in whom specific features are lacking.

We report the neuroradiologic findings and their association with cerebral symptoms in 25 children with mitochondrial disease.

Methods

Our study group of 25 children with mitochondrial disorders consisted of 13 girls and 12 boys, ranging in age from 1 month to 15 years. The diagnosis was based on the presence of ragged red fibers in a muscle biopsy sample and/or impaired oxygen consumption and reduced activities of respiratory chain enzymes in isolated muscle mitochondria (24) and/or the presence of mtDNA rearrangements in muscle DNA. Twenty-two patients were examined clinically by one of us, and three patients were included after an mtDNA point mutation was detected in muscle samples taken at autopsy. Detailed information concerning the clinical symptoms of these patients, as well as biochemical and molecular genetic data, are presented in Table 1.

All clinical patients were examined with MR imaging; six of them twice, and one three times. Three of these patients had previous CT studies available for comparison. Only CT studies were available in the three patients with autopsy-proved disease. The MR studies were performed either on a 1.0-T or 1.5-T unit. T1-weighted images were obtained in sagittal and axial planes, and T2- and proton weighted-images were ob-

tained in axial and coronal planes. Contrast enhancement was used when indicated by the noncontrast study.

The radiologic studies were interpreted by two experienced neuroradiologists. Previous CT scans and MR images of the patients were reviewed, when obtainable. The three patients in whom only CT studies were obtained included an infant who died before an MR study could be performed and two patients who died in the 1980s, before MR imaging was available. We specifically looked for changes in the signal intensity and size of the basal ganglia and brain stem on both T1- and T2-weighted images, cerebral and cerebellar atrophy and focal lesions, and the stage of myelination. There was no disagreement between the two interpreters.

Results

Four patients had KSS/Pearson syndrome, three had MELAS, and eight had Leigh syndrome. Encephalomyopathy, with a wide range of symptoms, was present in seven patients. Two patients had myopathy and one had cardiomyopathy. The most common neurologic symptom was cognitive impairment, which ranged from severe mental retardation to mildly delayed development. Muscle hypotonia, ataxia, dystonic movements, and myoclonias were common. Only three children, one with cardiomyopathy and two with myopathy, had no neurologic symptoms at the time of the MR study. The imaging findings of the patients with KSS/Pearson and Leigh

TABLE 2: Imaging findings in patients with Pearson/Kearns-Sayre syndrome (cases 1–4) and Leigh syndrome (cases 5–12)

Patient/ Sex	MR/ CT	Age at MR/CT	Putamen	Nucleus Caudatus	Pallidum	Thalamus	Periaqueductal Gray Matter	Substantia Nigra, Red Nucleus	Pons and Tegmentum	Medulla Oblongata	White Matter	Supratentorial Atrophy	Cerebellar Atrophy
1/F	MR	2 y	—	—	—	—	—	—	—	—	+	+	+
	CT	2 y	—	—	—	—	?	?	?	?	—	—	—
	MR	3 y	—	—	—	—	—	—	+	—	+	+	+
2/F	MR	7 y	—	+	+	+	—	—	+	—	—	—	—
	CT	7 y	—	++	++	—	?	?	?	?	—	—	—
	MR	13 y	—	++	++	++	++	+	++	++	++	+	++
3/M	MR	12 y	—	—	+	—	—	—	—	—	—	—	—
	MR	13 y	—	—	—	—	—	—	—	—	—	—	—
4/M	MR	15 y	—	—	—	—	—	—	—	—	—	—	—
	MR	11 y	+	—	—	—	+	—	—	—	—	+	—
5/F	MR	14 y	++	—	—	—	+	—	—	—	—	+	—
	MR	1.5 y	++	—	—	—	+	+	—	—	+	—	—
6/F	MR	12 y	++	++	+	—	+	+	—	—	+	—	—
	MR	2 y	++	++	—	—	—	—	—	—	—	—	++
8/M	MR	5 y	++	++	+	+	—	—	—	—	—	+++	—
	MR	1.1 y	+++	+++	++	++	—	—	—	—	—	+++	—
10/F	MR	2 y	++	—	—	—	+	—	—	+	—	—	—
	CT	6 mo	++	++	—	—	?	?	?	?	—	++	—
11/F	MR	2 y	++	++	++	—	—	—	—	—	+++	++	—
	MR	2 y	++	++	++	—	—	—	—	—	+++	++	—

Note.— indicates normal finding; +, mild or nonspecific changes; ++, moderate changes; +++, severe changes; and ?, not seen.

syndromes (patients 1 through 12) are summarized in Table 2 and the results of patients 13 through 25 are presented in Table 3.

KSS/Pearson Syndrome

KSS is defined as a slowly progressive disease with onset before age 20. Symptoms include ataxia, ophthalmoplegia, retinitis pigmentosa, increased cerebrospinal fluid (CSF) protein, and various other symptoms, such as hearing deficit, endocrinologic dysfunction, and conductive heart block (25). Pearson syndrome, which can evolve into KSS with age (26), is characterized by hypochromic anemia and deficient exocrine pancreatic function in infants. Both syndromes are often associated with an mtDNA deletion.

All three patients with an mtDNA deletion had anemia as the first presenting sign in infancy or childhood, and should therefore be regarded as having Pearson syndrome. One of them died at the age of 6 years, the others started to acquire typical features of KSS at school age. The fourth patient, with slowly developing symptoms of KSS, did not have an mtDNA deletion.

The patient with the most severe clinical symptoms (anemia, pancreatic insufficiency, Fanconi type nephropathy, failure to thrive, and diabetes), leading to death at the age of 6 years (patient 1), had mild cortical atrophy and T2 hyperintensity of the frontal and temporal subcortical U fibers at the age of 3 years. No basal ganglia lesions were noted, but moderate brain stem atrophy was present. No calcifications were seen in the basal ganglia on CT scans.

In patient 2, who had transient anemia in infancy, progressive cognitive impairment, retinitis pigmentosa, short stature, ataxia, ophthalmoplegia, and diabetes, subtle symmetric T2 hyperintensities were

noted in the medial thalamic nuclei and tegmentum of the brain stem at the level of the peduncles when examined with MR imaging at the age of 7 years. A CT study at that time showed diffuse calcifications in the globus pallidi and caudate nuclei. An MR study at the age of 13 years showed hyperintensity of the globus pallidi and caudate nuclei as well as in the pulvinar and medial thalamic nuclei on both T1- and T2-weighted images. There was, however, no volume loss of these structures. The changes in the posterior brain stem had extended to the medulla oblongata, and pontine atrophy was also noted. Marked cerebellar atrophy was seen with hyperintensity of the cerebellar white matter. Deep cerebral white matter was hyperintense with sparing of the immediate periventricular layer. The subcortical U fibers were partially involved (Fig 1).

Patient 3, with transient anemia in infancy, slowly progressive hearing deficit and cognitive impairment, ptosis, diabetes, and short stature, had bilateral, symmetric punctate lesions in the globus pallidi, seen as areas of hyperintensity on T2-weighted images only, but otherwise normal findings. Patient 4, a clinically mildly affected boy with short stature, hearing deficit, cognitive impairment, ptosis, retinitis pigmentosa, and proteinuria, had two normal MR studies at 2-year intervals despite the slow progression of the cerebral symptoms.

Leigh Syndrome

The clinical presentation of Leigh syndrome is progressive impairment of cognitive and motor function, and, in the final stages, loss of respiratory control (27). The syndrome can be caused by various defects of the energy-producing pathways (28). The diagnosis of Leigh syndrome was made in eight patients. In two

TABLE 3: Imaging findings in patients with mitochondrial encephalopathy with lactic acidosis and strokelike episodes (MELAS) (cases 13–15), encephalomyopathy (cases 16–22), myopathy (cases 23 and 24), and cardiomyopathy (case 25)

Patient/Sex	MR/CT	Age at MR/CT	Focal Lesions	Supratentorial Atrophy	Cerebellar Atrophy	White Matter Changes	Other
13/F	MR	4 y	Cortical and thalamic, infarctlike	+++	++	+++	—
14/F	CT	6 y	Bilateral, parietal, infarctlike	—	—	—	—
15/F	CT	8 y	Parasagittal	—	—	—	—
	MR	8 y	Infarctlike	—	—	—	—
	MR	8 y	—	+	+	—	—
	MR	13 y	Parietooccipital, infarctlike	+	+	—	—
16/M	MR	7 y	Putaminal and thalamic, bilateral	—	—	—	—
17/M	MR	3 y	Frontal infarctlike	—	—	—	—
18/M	MR	5 y	—	—	—	+	Optic glioma
	MR	6 y	—	—	—	++	—
19/M	MR	8 mo	—	—	—	+	—
20/F	MR	6 y	—	+	—	—	—
21/M	CT	1 mo	—	++	—	—	—
22/F	MR	13 y	—	+	—	+++	—
23/F	MR	14 y	—	+	+	—	—
	MR	16 y	—	+	+	—	—
24/M	MR	1 mo	—	—	—	—	—
25/F	MR	1 y	Frontal infarctlike	—	—	—	—

Note.— indicates normal finding; +, mild or nonspecific changes; ++, moderate changes; and +++, severe changes.

siblings with a severe presentation leading to early death, the diagnosis was based on the presence of the T>G transversion at nucleotide 8993 of the mtDNA gene encoding subunit 6 of adenosine triphosphate (ATP) synthase. Both patients had a high proportion, over 90%, of the mutant mtDNA in all tissues. The clinical presentation of the remaining six patients was that of progressive neurologic deterioration. Defects of complex I were detected in three patients, complex IV in two patients, and complex III in one patient.

In all eight cases of Leigh syndrome the putamina were involved. In two, the lesions had an acute-subacute appearance with T2 hyperintensity and swelling with patchy T1 hyperintensity in one (Fig 2). In the remaining four cases, there was volume loss of the putamina with high intensity on T2-weighted images, low intensity on T1-weighted images, and a mixture of high and low intensity on proton density-weighted images. The anterior part of the putamen was most often involved, but in one patient there was bandlike T2 hyperintensity of the posterolateral putamen. The caudate nuclei were affected in three patients, with hyperintensity and volume loss evident along the entire length of the nuclei. The frontal horns of the lateral ventricles were dilated. In one patient, the nucleus accumbens was also involved. Two patients had involvement of the globus pallidus, and both these patients also had caudate lesions. Bilateral thalamic lesions were seen in one patient.

Involvement of the periaqueductal gray matter was seen in four patients. The red nuclei were involved in two patients, lesions within the pars compacta of the substantia nigra were seen in two. One patient had a small, asymmetric lesion in the medulla oblongata.

Subtle T2 hyperintensity was seen in the parietooccipital periventricular white matter in two patients. Mild to moderate cortical atrophy was seen in four

patients, and cerebellar atrophy was present in two others.

Of the two siblings with Leigh syndrome and the mtDNA T>G point mutation at nucleotide 8993, the girl who died at the age of 1 year (patient 11) only had a CT study, which showed bilateral, symmetric hypodensity in the putamina and caudate nuclei and moderate cortical atrophy. Her brother (patient 12), studied at the age of 1 year with MR imaging, had extensive CSF-like signal change of the entire temporal and frontal white matter, which was very hypointense on T1-weighted images and of intermediate to high intensity on T2-weighted images. The putamina and globus pallidi as well as the caudate nuclei showed hyperintensity and severe volume loss. Severe cerebellar atrophy was also present (Fig 3).

MELAS

MELAS is characterized by strokelike episodes often preceded by treatment-resistant partial seizures. Short stature, diabetes mellitus, and slowly progressive mental impairment leading to dementia are common features (29). The most common mtDNA point mutation occurring in this syndrome is an A>G transition at the tRNA Leu (UUR) 3243, causing a defect in the mitochondrial protein synthesis (30). Two of our patients had a high proportion, over 90%, of mutant DNA in the brain (31).

The findings in patient 13, who had a severe case of MELAS, have been described in detail elsewhere (32). Images taken 2 months before her death showed extensive infarctlike lesions, both acute and chronic, which were not confined to the vascular territories. Severe cortical atrophy was also noted. Patient 14 had only a CT study available, obtained in 1982 shortly before her death, that showed bilateral parietal hypo-

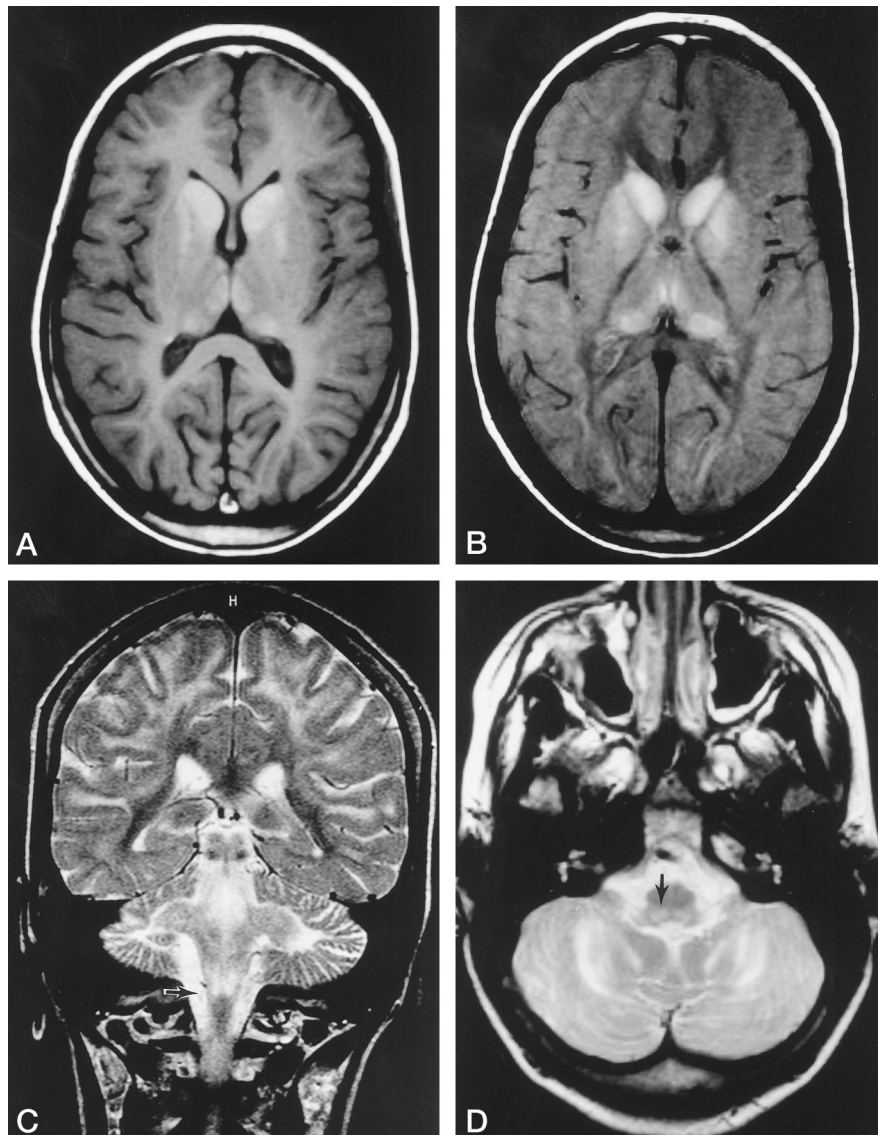


FIG 1. Patient 2: 13-year-old girl with Kearns-Sayre syndrome.

A and B, T1-weighted (A) and proton density-weighted (B) axial images show hyperintensity of the caudate nuclei, globus pallidi, and mediodorsal thalami.

C, T2-weighted coronal image displays white matter hyperintensity extending to the subcortical U fibers and involving the cerebellar white matter. High-signal lesions are seen within the posterior medulla oblongata (arrow).

D, T2-weighted axial image shows hyperintensity of the posterior columns of the medulla oblongata (arrow) and cerebellar white matter.

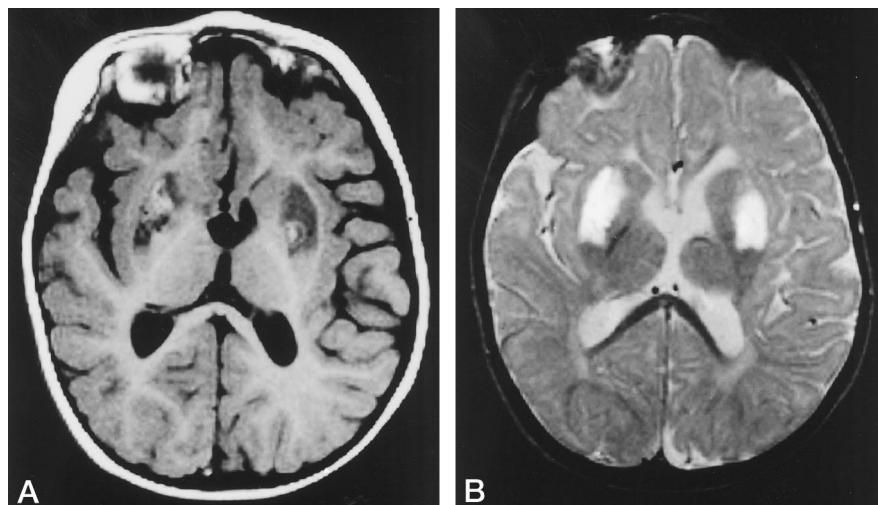


FIG 2. Patient 6: 1½-year-old girl with Leigh syndrome.

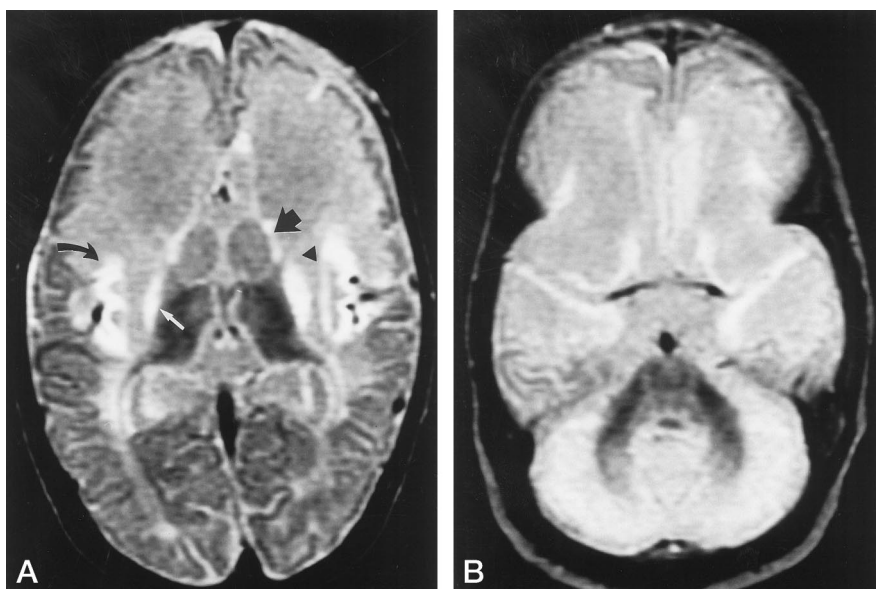
A, T1-weighted axial image shows swollen, hypointense putamina with areas of hyperintensity within the lesions.

B, T2-weighted axial image shows hyperintensity and swelling in the putamina. Myelination is severely delayed.

FIG 3. Patient 12: 2-year-old boy with Leigh syndrome and mtDNA mutation at 8993.

A, T2-weighted axial image shows hyperintense, shrunken putamina (white arrow) and caudate nuclei (large straight arrow), left claustrum (arrow-head), and bilateral insular cortices (curved arrow). The frontal and temporal white matter is isointense with CSF, whereas the cortical mantle is thin and there is absence of normal cortical signal within the depths of the sulci. The occipital cortex is spared, but there is no evidence of myelination.

B, The intensity of the thalami is similar to that of the brain stem, probably close to normal.



dense lesions with slight mass effect but without contrast enhancement. Patient 15, who presented with seizures and strokelike episodes, had infarctlike bilateral parasagittal lesions, hypodense on CT scans and hyperintense on T2-weighted MR images, with slight mass effect and no enhancement after administration of contrast material. On a follow-up study 2 months later, the lesions had disappeared except for mild cortical atrophy at the site of the previous lesions. This patient also had mild cerebellar and vermian atrophy. Two years later, she had an acute episode of partial status epilepticus, and new lesions were seen in the left parietal and parietooccipital regions (Fig 4).

Patients with an Undefined Encephalomyopathy

Seven children had encephalomyopathy with neurologic symptoms ranging from slow psychomotor development to ataxia or dystonia. Short, lean stature and slowly progressive cognitive impairment were common findings. The diagnosis was based on impaired oxygen consumption and deficient respiratory chain enzyme activities (complex I in five cases, complex IV in one case, and a combined complex I and IV defect in one case).

The findings in this group of patients were nonspecific. Among the patients, a 7-year-old boy (patient 16) with a severe cerebral palsy-like presentation, with spasticity and dystonia, had T2 hyperintensities in the posterolateral putamina and small lesions in the posteromedial thalami (Fig 5). A small infarctlike lesion was observed in the deep frontal white matter in a patient with developmental delay (patient 17). A 5-year-old boy (patient 18) had hyperintensity of the temporal subcortical white matter, consistent with delayed myelination or dysmyelination, but no change on the 1-year follow-up study. In addition, he had an enhancing optic pathway glioma, which showed progressive growth at follow-up. An 8-month-old boy

with severe hypotonia and arrested psychomotor development (patient 19) showed moderately delayed myelination on T1-weighted images. Patient 20, with developmental delay, had mild widening of the supratentorial CSF spaces.

A 1-month-old boy, a severely hypotonic and hypothermic infant with cytochrome oxidase deficiency (patient 21), was imaged soon after birth with CT and shown to have ventriculomegaly and temporal atrophy. A girl with progressive ataxia and both complex I and IV deficiency (patient 22) showed extensive hyperintensity and some volume loss of the entire white matter, including the internal and external capsules and white matter of the brain stem and cerebellum (Fig 6).

Myopathy or Cardiomyopathy without Central Nervous System Symptoms

A 14-year old girl with myopathy, Wolff-Parkinson-White syndrome, and cystic changes in the thyroid gland (patient 23) had only mild cerebral and cerebellar atrophy with no focal changes and no progression at follow-up. Patient 24, with severe muscle weakness, had normal imaging findings at the age of 4 weeks.

A patient with cardiomyopathy and myopathy (patient 25) had a small infarctlike lesion in the deep frontal white matter, but otherwise normal MR imaging findings.

Discussion

The clinical presentation of a mitochondrial disease in children is often nonspecific, comprising cognitive impairment, ataxia, and seizures associated with myopathy and involvement of other organs (6). The early clinical and neuroradiologic findings in patients with the well-characterized mitochondrial syndromes can be atypical, and a great many patients

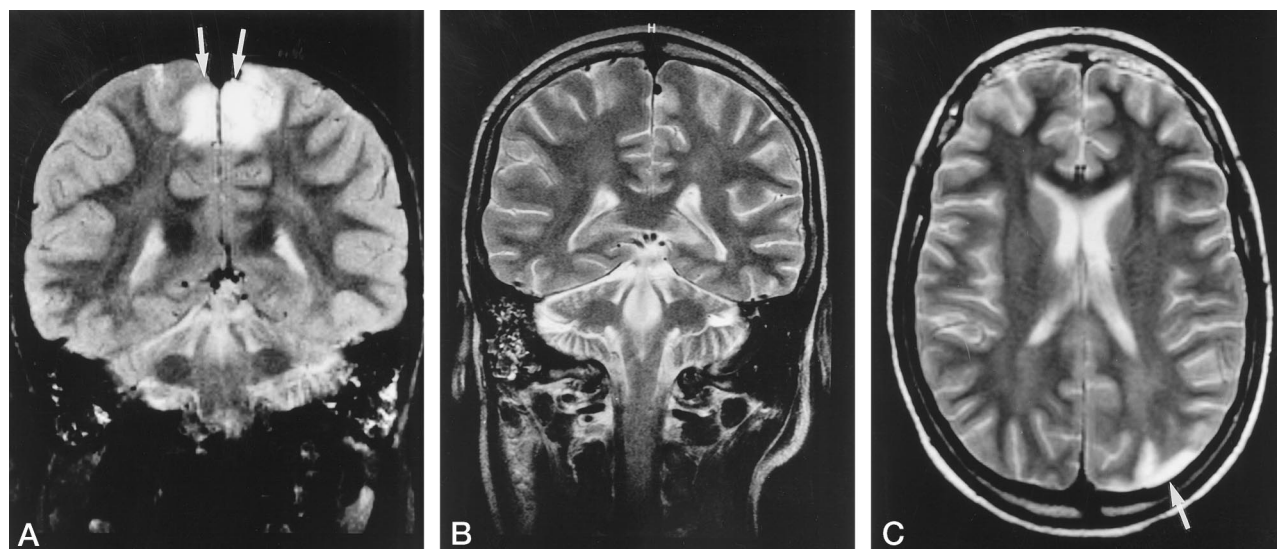


FIG 4. Patient 15: girl with MELAS at ages 8 and 13 years.

A, T2-weighted coronal image during an acute strokelike episode shows parasagittal bilateral hyperintense lesions (arrows) at the age of 8 years.

B, T2-weighted coronal image 2 months later shows that lesions have almost entirely resolved. Cerebellar atrophy is evident.

C, T2-weighted axial image 5 years later, during a prolonged seizure, shows a new hyperintense lesion in the left parietooccipital region (arrow).

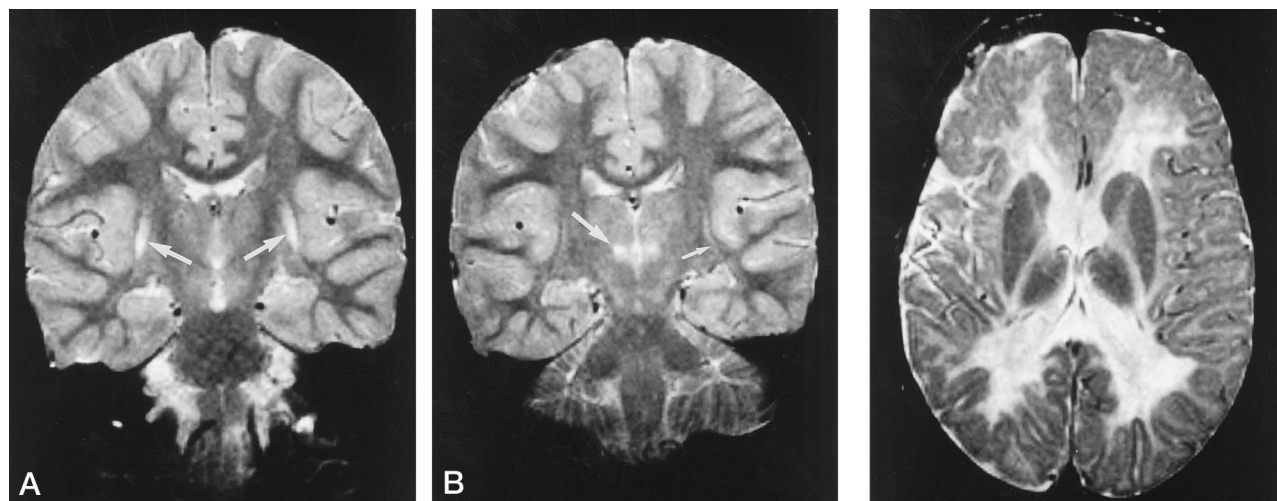


FIG 5. Patient 16: 7-year-old boy with complex I deficiency.

A, T2-weighted coronal image shows hyperintense and shrunken anterior putamina (arrows).

B, Hyperintense bands are noted along the lateral borders of the putamina posteriorly (small arrow) and within the posterior thalami adjacent to the third ventricle (large arrow).

FIG 6. Patient 22: 13-year-old girl with complex I and IV deficiency. T2-weighted axial image shows hyperintensity and volume loss of the white matter, more marked centrally and involving both the internal and external capsules. The subcortical U fibers show no myelin. Basal ganglia are hypointense relative to hyperintense signal of surrounding white matter structures.

remain without a specific diagnosis even after meticulous clinical, biochemical, and genetic workup.

Our subject population, unlike those in previous studies, was not limited to patients with the classical mitochondrial syndromes but included all pediatric patients in whom a mitochondrial disease had been diagnosed. Our series is also one of the largest published concerning the pediatric age group.

Typical imaging findings are the diagnostic hallmark of Leigh syndrome, which explains the uniformity of the MR findings. The diagnosis of Leigh

syndrome, which earlier could be made only by post-mortem examination, is characterized by vascular proliferation and demyelination, which lead to necrosis and cavitation in typical locations, including the basal ganglia, midbrain, pons, and posterior column of the spinal cord (27, 33, 34). MR lesions in corresponding locations therefore strongly suggest the presence of a defect in the energy-producing pathway (18–22). Putaminal involvement is reported to be a consistent feature in Leigh syndrome (22). The putamina were affected in all eight of our patients with

this disorder; in two of the patients, the putamina were swollen, and in one, high-signal foci were seen within the affected tissue on T1-weighted images, possibly indicating hemorrhage in an acute necrotizing process. Volume loss was evident in other cases as well as prolongation of T1 relaxation time, most likely representing cavitation, and also mixed signal intensity on the proton density-weighted images resulting from both cavitation and gliotic change. Lesions were also seen in the caudate nuclei, globus pallidi, and thalami, but never in the absence of putaminal lesions. The imaging findings of the two patients with the point mutation at nucleotide 8993 included symmetric putaminal and caudate nuclei lesions. Extensive changes in the temporal and frontal white matter, seen in one of the patients, were most likely related to microcystic cavitation after necrosis, which is characteristic of Leigh syndrome.

In KSS, the typical histopathologic finding is status spongiosus, a vacuolization of nervous tissue resulting in a sievelike appearance. Both gray and white matter are affected, most often the brain stem tegmentum, and the white matter of the cerebrum, cerebellum, and basal ganglia. Siderocalcific deposits are commonly seen in the basal ganglia (34). Involvement of the subcortical U fibers with sparing of the periventricular white matter is typical of KSS. This feature is characteristic of the spongy myelinopathies, and distinguishes the white matter involvement in KSS from that in the leukodystrophies, in which the central or "older" white matter is affected early in the course of the disease (13, 23, 35).

Of our four patients with KSS, only one had the typical imaging findings described in previous reports (9, 13, 16, 23). The clinical symptoms of the patients without MR changes were milder and progressed very slowly. Our patient with Pearson syndrome died before the typical clinical central nervous system symptoms of KSS developed, which might explain her minimal MR findings. T2 hyperintensities in the globus pallidi were seen in two patients.

Infarctlike, often transient lesions not confined to the vascular territories are the imaging hallmark of MELAS (10–14, 17). Focal necrosis and laminar cortical necrotic changes are the histopathologic correlates of this disease, together with neuronal degeneration and mineral deposits within the basal ganglia (34). The pathogenesis of the infarctlike lesions in MELAS is presumably deficient oxidative phosphorylation and also dysfunction of the endothelium of small pial arterioles and capillaries due to accumulation of abnormal mitochondria, the so-called mitochondrial microangiopathy (10–14, 36, 37). The imaging findings in our three patients with MELAS were characteristic of the disease.

The children with an undefined encephalomyopathy had a variety of imaging findings, including abnormal or possibly delayed myelination, atrophy, and minor focal parenchymal lesions, all of which are nonspecific and can be seen in many other conditions. There were, however, no normal findings in these

patients with cerebral symptoms, which is in concordance with the findings reported by Wray et al (16).

The MR manifestations in patient 22, with extensive T2 hyperintensity of the entire white matter, resembling the leukodystrophies and primarily considered as such, again show the wide range of findings in these patients. Extensive white matter changes, resembling leukodystrophy, have been reported in individual patients, but the pathologic mechanisms causing these lesions remain obscure (38–40).

Conclusion

Abnormal imaging findings were detected in all but one of our patients with central nervous system symptoms. Specific findings, such as changes in the basal ganglia and stroke-like cortical lesions, which influenced the direction of further investigations, were found in 15 of the 25 patients. In the remaining 10 patients, the findings were nonspecific or even misleading, as in the case of patient 22. Therefore, in light of this rather large sample population, we conclude that an atypical or nonspecific MR finding in a child with cerebral symptoms does not rule out mitochondrial disease. Further studies and long-term follow-up are needed to define the progression of neuroradiologic findings in these children.

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