Novel Infantile-Onset Leukoencephalopathy With High Lactate Level and Slow Improvement

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Objective: To describe a novel pattern of magnetic resonance imaging (MRI) abnormalities as well as the associated clinical and laboratory findings.

Design: The MRIs of more than 3000 patients with an unclassified leukoencephalopathy were systematically reviewed. Clinical and laboratory data were retrospectively collected.

Setting: University hospital.

Patients: Seven patients (3 male) shared similar MRI abnormalities and clinical features.

Main Outcome Measures: Pattern of MRI abnormalities and clinical and laboratory findings.

RESULTS

The MRIs showed signal abnormalities of the deep cerebral white matter, corpus callosum, thalamus, basal ganglia, brainstem, and cerebellar white matter between the ages of 9 months and 2 years. On follow-up, abnormalities gradually improved. Clinical regression occurred in the second half-year of life with spasticity and loss of milestones. From the second year on, clinical improvement occurred. So far, no second episode of regression has happened. Lactate levels were elevated during clinical regression.

Conclusion: These patients represent a single novel leukoencephalopathy, probably caused by a mitochondrial defect.


RESULTS

Early MRI Abnormalities

One MRI obtained in a patient at 2 months of age revealed no abnormalities. The MRIs made between the ages of 8 and 18 months...
showed confluent, symmetrical cerebral white matter abnormalities, predominantly affecting the deep white matter and corpus callosum. These structures had prominently increased signal on T2-weighted images and prominently decreased signal on T1-weighted images, indicating a lesion. Strikingly, a rim of periventricular white matter was preserved. The subcortical white matter had mildly elevated T2 as well as T1 signal, indicating lack of myelin deposition rather than a lesion (Figure 1A). Rarefaction of the affected cerebral white matter was seen in 1 patient. The posterior limb of the internal capsule was affected in 1 patient. The thalamus was affected in all pa-

Figure 1. Magnetic resonance imaging of patient 6. At age 11 months, T2 signal abnormalities are present in the deep cerebral white matter, thalamus, basal ganglia, brainstem, and cerebellar white matter (A-D). Restricted diffusion is indicated by high signal on diffusion-weighted images (E) and low signal on apparent diffusion coefficient maps (F). At age 3 years (G-I), the abnormalities have improved substantially.
tients (Figure 1B). The anterior part of the putamen, globus pallidus, and head of the caudate nucleus were mildly T2 hyperintense in all patients (Figure 1B) and in 3, this was in combination with focal lesions with a more prominent T2 hyperintensity. Infratentorially, the midbrain (n=6), dorsal part of the pons (n=5), medulla oblongata (n=6), and peridental cerebellar white matter (n=5) (Figure 1C and D) had high T2 and low T1 signal. No cerebro or cerebellar atrophy was seen. Restricted diffusion was observed, especially in the borders of the white matter lesions, corpus callosum, and brainstem (Figure 1E and F).

**EVOLUTION OF MRI ABNORMALITIES**

Around age 2 years, patients still had abnormalities of the deep cerebral white matter, thalamus, and brainstem (Figure 2A-C). The cerebellar signal alterations had improved. The degree of white matter involvement was variable. Three patients had some rarefaction.

After the age of 2 years, improvement of the cerebral white matter, brainstem, and thalamic lesions occurred (Figure 1G-I and Figure 2D-F). No new abnormalities developed. The basal ganglia lesions disappeared, but the mild T2 hyperintensity of the anterior part of the putamen, globus pallidus, and head of the caudate nucleus persisted (Figure 1H and Figure 2E). The mild T2 hyperintensity of the subcortical white matter faded, indicating further myelin deposition, but complete T2 hypointensity was not reached. There was mild white matter volume loss (Figure 1G-I and Figure 2D-F). Restricted diffusion disappeared.

Proton magnetic resonance spectroscopy at age 2 years showed elevated lactate levels in the affected white matter, which normalized on follow-up (Figure 3) (quantitative details for white matter and the basal ganglia in eTable 2).

**CLINICAL FINDINGS**

Clinical characteristics and ages at last examination are summarized in eTable 1. Two patients presented soon
after birth with feeding difficulties and failure to thrive. Five patients had delayed early development; development was initially normal in 2. All patients regressed in the second half-year of life, with loss of developmental milestones (n=3), irritability (n=2), axial hypotonia (n=6), limb spasticity (n=7), and feeding difficulties (n=3). In 2 patients, provoking factors were noticed: gastrointestinal illness and vaccination. At age 1 year, spasticity, especially of the legs, was the central feature. Muscle tone started to improve in the second year of life. All patients still displayed variable signs of spasticity at their latest examination (ages 1.3-10 years) (eTable 1) but much less than before. Four patients could walk without support and run (ages 3.3, 3.5, 5, and 9 years); 2 required support (ages 2.5 and 10 years). The youngest patient started to stand with support at the latest examination at 1.3 years of age. Initial language development was delayed in all patients except for 1 patient, who had normal language and lost it at disease onset. At the latest examination, 3 patients (ages 5, 9, and 10 years) could speak in simple sentences, 2 patients (ages 2.5 and 3.5 years) used single words, and 2 patients (ages 1.3 and 3.3 years) were nonverbal. Receptive language skills were better than expressive skills. None of the patients experienced further episodes of regression.

Less consistent neurological signs were mild cerebellar ataxia (n=3), dystonia (n=1), and seizures (n=2). The patients had no signs of dysfunction of other organs than the central nervous system. They had no signs of dysmorphism.

LABORATORY FINDINGS

Lactate levels in blood (n=6) and cerebrospinal fluid (n=5) were elevated in blood (3.1-8.6 mmol/L and 2.4-3.7 mmol/L, respectively). Follow-up measurements in blood (n=4) showed a decrease to normal values in 2 patients at ages 1.3 and 2.2 years and a steady elevation in the other 2 at ages 2.9 and 1.7 years. Cerebrospinal fluid lactate levels were not assessed again.

Respiratory chain enzyme activities in muscle (n=5), fibroblasts (b=2), and the liver (n=1) were normal. Lysosomal enzyme activities in leukocytes, especially arylsulfatase A (n=3) and galactocerebrosidase (n=3), were normal. Acylcarnitine profile results (n=5) and amino acid (plasma, n=6; urine, n=1), urinary organic acid (n=7), and very-long-chain fatty acid (n=4) levels were normal. Transferrin isoelectric focusing for congenital defects in glycosylation was normal (n=2). Chromosome analysis revealed no abnormalities (conventional technique, n=2; high-resolution technique, n=1). Sequencing of mitochondrial DNA (screening for deletions and duplications as well as analysis of the known genes, n=7; analysis of the entire mitochondrial genome [human mitochondrial resequencing array; Affymetrix], n=2) and nuclear genes encoding mitochondrial proteins (ie, PDSS1, SCO1, SCO2, COX10, SURF1, PDHA1, TYMP, POLG1, and SUCLA2 [n=2]) did not reveal mutations.

COMMENT

We present 7 patients with a similar pattern of MRI abnormalities. The most striking abnormalities were seen between the ages of 9 months and 2 years and consisted of selective involvement of the deep cerebral white matter, thalamus, and brainstem, especially in the midbrain. An MRI at 2 months of age was normal in 1 patient, suggesting that the abnormalities arose in the first year of life. After 2 years of age, MRI abnormalities improved and no new lesions were seen.

The clinical features are in line with the MRI abnormalities. Characteristically, there is a regression in the second half-year of life with loss of developmental milestones and progressive spasticity, often preceded by delayed early development. Gradual clinical improvement...
starts in the second year of life. So far, no second episode of regression has occurred.

The MRI abnormalities are reminiscent of those seen in Kearns-Sayre syndrome. Kearns-Sayre syndrome, a mitochondrial disorder caused by deletions in the mitochondrial DNA, also shows abnormalities of the cerebral white matter with sparing of a periventricular rim and abnormalities of the basal ganglia, thalamus, and brainstem. Kearns-Sayre syndrome, however, preferentially affects subcortical instead of deep cerebral white matter and MRI abnormalities increase over time. Kearns-Sayre syndrome was excluded in our patients by mitochondrial DNA analysis.

Rapid neurological regression around age 1 year, the MRI pattern, and the elevated lactate level are suggestive of a mitochondrial defect. The fact that analysis of respiratory chain function did not reveal abnormalities does not exclude a mitochondrial disorder. In leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate level in a subset of patients with neuropathy, ataxia, and retinitis pigmentosa syndrome, no abnormalities of respiratory chain activities in muscle are seen, although both are known mitochondrial disorders.

Although the patients described herein are sporadic cases from unrelated families and there is no known consanguinity between the parents, the disorder is probably genetic. We have initiated studies to identify the related gene.

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REFERENCES