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.


Childhood white matter disorders constitute a vexing problem, because causes are numerous and clinical signs are generally not discriminative. During the last 2 decades, multiple novel leukoencephalopathies have been identified. A considerable proportion of the patients, however, still remain without a specific diagnosis.

Individual leukoencephalopathies usually present with distinct and homogeneous patterns of magnetic resonance imaging (MRI) abnormalities, facilitating the diagnosis. In our search for novel disorders among the unclassified leukoencephalopathies, we use MRI pattern recognition as a primary tool. Patients sharing a distinct MRI pattern and clinical features are thought to have the same disease. Identification of associated genes has confirmed the validity of this approach. Herein, we present 7 children with a novel pattern of MRI abnormalities and their clinical and laboratory findings.

Methods

The MRIs of more than 3000 patients are part of our ongoing study on unclassified leukoencephalopathies. All MRIs were obtained for regular patient care. The study received institutional review board approval with waiver of informed consent. The MRIs included at least T1- and T2-weighted images; fluid-attenuated inversion recovery and diffusion-weighted images were available for some cases (eTable 1,  http://www.archneurol.com). The MRIs were assessed according to standard protocol.10 Evaluated items included presence, location, and appearance of white and gray matter lesions and stage of myelination. To minimize the effects of subjective rating, all items were only scored as present or absent.

Seven unrelated patients shared a distinct MRI pattern, dissimilar from known patterns. They had 18 MRIs (ages in eTable 1). Patient 1 underwent proton magnetic resonance spectroscopy 3 times (ages in eTable 2). Metabolite concentrations were calculated using LCModel11 and compared with age-matched control values. Clinical and laboratory data were obtained.

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

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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, glo-
bus 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 promi-
nent T2 hyperintensity. Infratentorially, the midbrain
(n=6), dorsal part of the pons (n=5), medulla oblongata
(n=6), and peridentate cerebellar white matter (n=5)
(Figure 1C and D) had high T2 and low T1 signal. No ce-
rebral or cerebellar atrophy was seen. Restricted diffu-
sion 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 brain-
stem (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 hyper-
intensity of the anterior part of the putamen, globus pal-
lidus, and head of the caudate nucleus persisted (Figure 1H
and Figure 2E). The mild T2 hyperintensity of the subcor-
tical white matter faded, indicating further myelin depo-
sition, 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

Figure 2. Axial T2-weighted images of patient 1. At age 2 years (A-C), abnormalities are seen in the deep cerebral white matter, thalamus, and brainstem. At age
10 years (D-F), the abnormalities have improved. Mild T2 hyperintensity of the putamen and caudate nucleus persists.
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 during regression (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, TYP, 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 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
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 lactate elevation, 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.\(^{8,14,15}\)

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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Author Contributions: Dr Steenweg had access to all the data. Dr van der Knaap was the principal investigator and had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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