Novel Hypomyelinating Leukoencephalopathy Affecting Early Myelinating Structures

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Objective: To describe 4 children with a novel hypomyelinating leukoencephalopathy, defined by a distinct pattern of magnetic resonance imaging (MRI) abnormalities.

Design: In our ongoing study on leukoencephalopathies of unknown origin, MRIs of patients are rated in a standardized manner. Patients are grouped according to their MRI abnormalities. The clinical and laboratory data are retrospectively reviewed.

Subjects: The MRIs of approximately 3000 patients with a leukoencephalopathy of unknown origin were initially evaluated. Four unrelated patients (all male, aged 1.8-7.4 years) displayed similar MRI alterations.

Results: Patients displayed mild T2 hyperintensity of the periventricular white matter. The posterior limb of the internal capsule showed alternating T2 hyperintense-hypointense-hyperintense stripes in 3 patients. The T1-weighted images showed hyperintensity, isointensity, or mild hypointensity of T2 hyperintense structures. The thalamus had a neonatal appearance with a mildly hypointense signal except for a darker lateral part. Clinically, patients presented with nystagmus between ages 6 and 20 months. Over time, cerebellar ataxia and mild spasticity developed. All achieved unsupported walking. Cognition and language were normal. Known causes of hypomyelination were excluded.

Conclusions: The patients share a striking pattern of MRI abnormalities and have a similar clinical picture, suggesting that they have the same disorder. The hypomyelination in this disorder specifically occurs in structures that normally myelinate early. We hypothesize that the disease is caused by a defect in a gene involved in early myelination.

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were available (eTable, http://www.archneurol.com). All MRIs included at least T1- and T2-weighted images. Clinical and laboratory data were retrospectively obtained.

**RESULTS**

**MRI FINDINGS**

All patients displayed mild T2 hyperintensity of the optic radiation and the frontoparietal periventricular white matter (Figure 1A, Figure 2B, and Figure 3A) with extensions into the white matter under the pericentral cortex in 3 patients (Figure 2A and Figure 4A). The T2 signal of the deep white matter was lower, but not as low as seen in normal, fully myelinated white matter. The directly subcortical white matter showed variable T2 hyperintensity, being most pronounced on earlier MRIs (Figure 1A). The posterior limb of the internal capsule showed alternating hyperintense-hypointense-hyperintense stripes on T2-weighted images (Figure 1B, Figure 2C, and Figure 3B), except for patient 4 in whom the posterior limb was hyperintense throughout (Figure 4B). Patient 4 was the only patient with T2 hyperintensity of the corpus callosum (Figure 4B). The brainstem, especially the caudal part of the pons (Figure 2D, Figure 3C, and Figure 4C) and medulla oblongata (Figure 1C), the hilus of the dentate nucleus (Figure 1C, Figure 2D, and Figure 3C), and peridiatal cerebellar white matter were mildly T2 hyperintense. The deep cerebellar white matter had a lower T2 signal. The T1-weighted images showed hyperintensity, isointensity (Figure 1D), or mild hypointensity of the T2 hyperintense white matter structures; the T2 hypointense white matter was T1 hyperintense. The thalamus had an appearance as seen in neonates with a mildly elevated T2 signal, except for the lateral part that had a low T2 signal (Figure 1B, Figure 2C, Figure 3B, and Figure 4B).

Follow-up MRIs in patients 1, 3, and 4 showed that the directly subcortical white matter became less T2 hyperintense than on earlier MRIs but did not become as dark as normal. Otherwise, MRI findings were essentially unchanged during the follow-up period available.

**CLINICAL DATA**

The clinical characteristics are summarized in the eTable. Patients had a normal neonatal period and early devel-
opment. They presented with nystagmus between ages 6 and 20 months, in 1 patient in combination with delayed walking. Over time, signs of cerebellar ataxia developed, including dysarthria and poor balance. The patients continued to show developmental progress, although it was slower than normal. They achieved unsupported walking, but patient 3 needed support for walking outside. Cognition and language were normal.

At their latest examinations, patients had a horizontal and rotatory nystagmus in all gaze directions. They had signs of cerebellar ataxia. Patients 1, 3, and 4 had mild spasticity, predominantly affecting the legs.

The patients were unrelated. Family history in patient 2 revealed a younger brother who was also affected. This boy presented with nystagmus and cerebellar ataxia at a similar age as his brother. In addition, 2 other male family members on the mother’s side were thought to be affected. Remaining family histories were negative.

ADDITIONAL INVESTIGATIONS

Routine hematology and chemistry panels revealed no relevant abnormalities. Levels of urinary organic acids and plasma or urinary amino acids were normal in all patients. Levels of very-long-chain fatty acids were normal in patients 1, 2, and 3. Levels of urinary oligosaccharides and sialic acid were normal in patients 1 and 3. Assessment of lysosomal enzymes in leukocytes, especially β-galactosidase (all patients), β-hexosaminidase (all patients), α-L-fucosidase (patients 2-4), arylsulfatase A (all patients), and β-galactocerebrosidase (all patients), revealed normal activities. Genetic testing showed a normal karyotype in patients 3 and 4 as well as no abnor-

Figure 3. Magnetic resonance images of patient 3 at age 3.0 years. The T2-weighted images show mild hyperintensity of the periventricular white matter (arrow) (A), mild hyperintensity of the thalamus except for the lateral part (black arrow) and alternating hyperintense-hypointense-hyperintense stripes in the posterior limb of the internal capsule (white arrow) (B), and mild hyperintensity of the hilus of the dentate nucleus (arrow) and pons (C).

Figure 4. Magnetic resonance images of patient 4 at age 7.4 years. The T2-weighted images show mild hyperintensity of periventricular white matter extending into the central subcortical white matter (arrow) (A), mild hyperintensity of the corpus callosum, posterior limb of the internal capsule (black arrow), and thalamus except for the lateral part (white arrow) (B), and mild hyperintensity of the hilus of the dentate nucleus, peridentate cerebellar white matter (arrow), and pons (C).
malities of the PLP1 gene (all patients) and GJC2 gene (patient 3). Electromyographic and nerve conduction velocity study findings were normal in patients 3 and 4.

COMMENT

The stable MRI pattern with mild T2 hyperintensity and variable T1 signal intensity of the white matter described here is indicative of hypomyelination. Unmyelinated white matter has long T1 and T2 relaxation times, resulting in low signal on T1-weighted images and high signal on T2-weighted images. With myelin deposition, T1 and T2 become shorter, leading to an increasing T1 signal and decreasing T2 signal. Because the change in T1 signal occurs before the change in T2 signal and is more pronounced, partially myelinated white matter structures have a mildly increased T2 signal and a T1 signal that varies between low, intermediate, and high depending on the amount of myelin deposited. This is true both for normal development and for defects in myelination such as hypomyelination. In contrast to normal development, the lack of myelin in hypomyelination is not age appropriate and is permanent. Only the directly subcortical white matter became less T2 hyperintense on follow-up, indicating that myelination of the subcortical white matter was delayed instead of permanently deficient.

Normal myelination follows a certain sequence. The brainstem starts to myelinate before birth in a caudorostral direction. At term birth, the lateral thalamus, pyramidal tracts in the posterior limb of the internal capsule, and tracts connected with the pericentral cortex also contain myelin. Soon after birth, the hilus of the dentate nucleus, peridendate white matter, posterior limb of the internal capsule, rest of the thalamus and basal nuclei, and the optic radiation acquire myelin. Subsequently, myelin spreads from the periventricular region toward the cortex. This fixed sequence of myelination implies a temporospatial regulation of gene expression.

Strikingly, in our patients, myelin is lacking in the brainstem, cerebellar white matter structures, optic radiation, periventricular white matter, and tracts connected with the pericentral cortex, which are the structures that normally myelinate early, whereas the structures that acquire their myelin later are better myelinated. This distribution of hypomyelination is in contrast with other hypomyelinating disorders, in which the early myelinating structures as a rule contain more myelin than the white matter that myelinates later.

The distinct and striking pattern of hypomyelination, the similar clinical picture, and the exclusion of known causes of hypomyelinating disorders suggest that these 4 patients have a single, novel disorder. Hypomyelinating disorders are generally genetically determined. We hypothesize that the disorder described here is caused by a defect in a gene involved in the regulation of early myelination. Because the 4 patients described as well as 3 affected family members are all male, the disorder could be X-linked. We propose that the disorder be called hypomyelination of early myelinating structures (HEMS).

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Author Contributions: Drs Steenweg and van der Knaap had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Steenweg and van der Knaap. Acquisition of data: Steenweg, Wolf, Schieving, Fawzi Elsaid, Friederich, and Østergaard. Analysis and interpretation of data: Steenweg, Wolf, Østergaard, Barkhof, Poulwels, and van der Knaap. Drafting of the manuscript: Steenweg and Fawzi Elsaid. Critical revision of the manuscript for important intellectual content: Steenweg, Wolf, Schieving, Fawzi Elsaid, Friederich, Østergaard, Barkhof, Poulwels, and van der Knaap. Administrative, technical, and material support: Wolf, Fawzi Elsaid, Østergaard, and Barkhof. Study supervision: Wolf and van der Knaap.

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Online-Only Material: The eTable is available at http://www.archneurol.com.

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