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Proton MR Spectroscopy in Pelizaeus-Merzbacher Disease

Jun-ichi Takanashi, Katsuo Sugita, Hitoshi Osaka, Mitsuko Ishii, and Hiroo Niimi

Summary: Proton MR spectroscopic findings in two patients with genetically defined Pelizaeus-Merzbacher disease revealed ratios of *N*-acetylaspartate/creatine and choline-containing compounds/creatine that were not significantly different from those found in a population of healthy subjects. These findings suggest that proton MR spectroscopy can aid in the diagnosis of Pelizaeus-Merzbacher disease.

Index terms: Magnetic resonance, spectroscopy; Pelizaeus-Merzbacher disease

Pelizaeus-Merzbacher disease (PMD) is a rare dysmyelinating disorder that affects the central nervous system. Despite convincing evidence that defects in the proteolipid protein (PLP) gene cause PMD (1, 2), sequential analysis of the entire PLP coding region has failed to reveal mutations in approximately 70% of these patients.

Magnetic resonance (MR) imaging in patients with clinically diagnosed PMD has shown diffuse T2 elongations in the white matter, reflecting the pathologic findings of dysmyelination (3, 4). These findings, however, are similar to those of other leukodystrophies, such as adrenoleukodystrophy, metachromatic leukodystrophy, and Alexander and Canavan diseases, and thus are not specific to PMD (5).

Proton MR spectroscopy is regarded as a good method by which to clarify any derangement of brain metabolism in vivo (6, 7). We evaluated the diagnostic value of proton MR spectroscopy in two patients with genetically defined PMD.

Case Reports

The two boys with PMD (patients 1 and 2, aged 5 and 6 years, respectively) have been described previously (4). Genetic analysis of their PLP genes by methods reported previously (8) revealed point mutations in exon 5 (Pro^{210}[CCA]→Leu[CTA]) in patient 1 and in exon 2 (Leu^{45}[CTA]→Arg[CGA]) in patient 2.

The hardware used for proton MR spectroscopy was the same as for MR imaging (1.5 T). The GE spectroscopic package (version 5.4.1) was used to acquire proton MR spectroscopic data, and the postprocessing was performed on a GE spectroscopic analysis station. Shimming was performed at less than 5 Hz full width at half-maximum intensity, based on the water signal. The point-resolved spectroscopic technique was used to acquire localized spectra (2000/136 [repetition time/echo time]) in the parietal white matter (volume of interest, 20 × 20 × 20 mm). In all patients, we used a spectral width of 2500 Hz, 2048 points, and 128 scans. The water signal was suppressed by a chemical-shift selective saturation pulse. The spectra were processed with standard techniques, including zero filling to 4096 points, 2 Hz exponential apodization, and no baseline correction. The peak areas of *N*-acetylaspartate (NAA) at 2.0 ppm, choline-containing compounds (Cho) at 3.2 ppm, and creatine (Cr) at 3.0 ppm, and the NAA/Cr and Cho/Cr ratios were calculated by using a lorentzian best fit.

Control subjects comprised 11 patients (4 to 15 years old) with headache and epilepsy who were also examined with proton MR spectroscopy. Informed consent was obtained in all cases. All control subjects had normal findings at neurodevelopmental and neurologic assessment and at cranial MR imaging.

Results

MR imaging showed diffuse T1 and T2 elongation in the bilateral white matter, with slight cerebral atrophy (Fig 1A and B). Proton MR spectroscopy (Fig 1C) revealed NAA/Cr ratios of 2.10 and 1.77, and Cho/Cr ratios of 0.93 and 0.88 in patients 1 and 2, respectively (Table). The NAA/Cr and Cho/Cr ratios in the control subjects were 1.75 ± 0.225 and 1.03 ± 0.182 (Table). Although the NAA/Cr ratio was slightly elevated and the Cho/Cr ratio was decreased on average in the PMD patients, the values are not

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From the Department of Pediatrics, Faculty of Medicine, University of Chiba (J.T., K.S., M.I., H.N.), and the Department of Pediatrics, School of Medicine, Yokohama City University (H.O.), Japan.

Address reprint requests to Jun-ichi Takanashi, MD, Department of Pediatrics, Faculty of Medicine, University of Chiba, 1–8–1 Inohana, Chuo-ku, Chiba-shi, Chiba 260, Japan.

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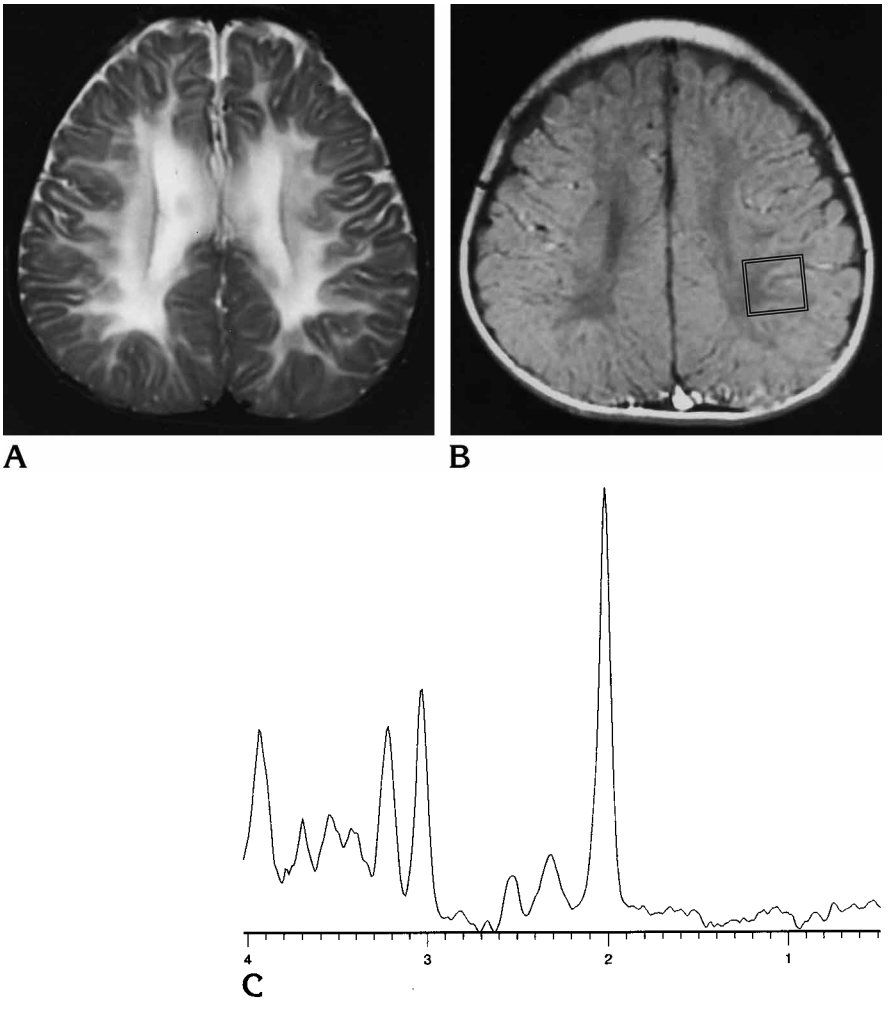

Fig 1. Patient 1.
A, Axial T2-weighted MR image (3000/100/2 [repetition time/echo time/excitations]) shows diffuse high signal lesions in the white matter.
B, T1-weighted MR image (300/17/2) also shows diffuse T1 elongations in the white matter; the parietal volume of interest is boxed.
C, At proton MR spectroscopy, the NAA (2.0 ppm)/Cr (3.0 ppm) ratio was 2.10 and the Cho (3.2 ppm)/Cr ratio was 0.93; there was no elevation of the lactic peak.

Proton MR spectroscopic data in two patients with Pelizaeus-Merzbacher disease and in 11 control subjects

	NAA/Cr	Cho/Cr
Patient 1	2.10	0.93
Patient 2	1.77	0.88
Control subjects	1.75 ± 0.225	1.03 ± 0.182

significantly different from the normal variance found in control subjects.

Discussion

Proton MR spectroscopy in our two patients with genetically defined PMD revealed normal values for NAA and Cho, an unusual pattern in a neurodegenerative disorder with diffuse T1 and T2 elongation in the white matter. A marked decrease in NAA is observed in many neurodegenerative disorders, such as adrenoleukodystrophy, metachromatic leukodystrophy, Alexander disease, Cockayne syndrome, and neuronal ceroid-lipofuscinosis (6, 7, 9). Van der Knaap et al (9) reported that the NAA/Cr ratio decreased in patients with grade 3 or 4 demyelination (grade 3, mild demyelination with more extensive involvement of the white matter; grade 4, severe demyelination affecting all or almost all of the white matter). The decrease in NAA in these leukodystrophies (demyelination) and in poliodystrophy may be regarded as a consequence of neuroaxonal degeneration and loss of functional brain parenchyma, since NAA is believed to be only present in neurons. In PMD, the axons are pathologically well preserved, as is the normal cortical cytoarchitecture (3), which might account for the normal value of NAA in this study. In addition, despite the onset of PMD in the first year of life, mental deterioration becomes evident only in the terminal stage of the disease

(2), also suggesting sparing of the cortical functions.

The in vivo Cho peaks might contain various compounds, such as phosphocholine and glycerophosphocholine, which are precursors and breakdown products of cell membranes. Therefore, elevation of Cho is observed in the period of accelerated myelination within the first few months and in that of myelin destruction in various demyelinating disorders (6, 7).

In our patients, the values for Cho and NAA in the white matter were normal. Neuropathologic examination showed a complete or nearly complete absence of subcortical and intracortical myelin, with no signs of active demyelination. In addition, biochemical studies revealed almost no severe alteration of the neutral phospholipid contents, including phosphatidylcholine (a nuclear MR-invisible macromolecule) (10), into which nuclear MR-visible choline residues are incorporated (11). It is therefore conceivable that the Cho peak remained within the normal range in the patients with PMD, reflecting no active demyelination and no alteration of precursor nuclear MR-visible choline.

An estimate of the usefulness of proton MR spectroscopy in the diagnosis of genetically defined PMD will require further studies with greater numbers of patients. However, on the basis of clinical and MR findings, we believe this technique will prove valuable in increasing the accuracy of PMD diagnosis, and will also be beneficial in clarifying the pathologic differences among myelination disorders, such as dysmyelination and demyelination.

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