Age-related changes in a patient with Pelizaeus-Merzbacher disease by repeated ^{1}H-MRS.

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Abbreviations

PMD	Pelizaeus-Merzbacher disease
MRS	magnetic resonance spectroscopy
PLP1	proteolipid protein 1
MRI	magnetic resonance imaging
CNS	central nervous system
GABA	γ-aminobutyric acid
ABR	auditory brainstem response
PRESS	**Point Resolved Spectroscopy**
CHESS	chemical shift-selective
TR	repetition time
TE	echo time
ROI	region of interest
NAA	N-acetyl aspartate
Glu	glutamate
%SD	percent standard deviation
STEAM	stimulated echo acquisition mode
Cho	choline-containing compounds
Cr	creatinine
Ins	myoinositol
Gln	glutamine
MD	myelin-deficient

・Abstract

Purpose:

In this report, we describe a patient with Pelizaeus-Merzbacher disease (PMD) who underwent repeated evaluations by ^{1}H-Magnetic resonance spectroscopy (MRS) .

Subject:

The patient was given a definitive diagnosis of PMD based on genetic testing, which showed overlap of the proteolipid protein 1 (PLP1) gene. The control subjects for ^{1}H-MRS consisted of healthy age-matched children.

Methods:

All measurements were performed with a clinical 3-tesla magnetic resonance imaging (MRI) system. For ^{1}H-MRS, the center of a voxel was positioned in the right parietal lobe. ^{1}H-MRS was performed when the patient was 2, 6, 14, and 25 months old.

Results:

The concentration of GABA in early childhood (2 months 1.72 mM, 6 months 2.15 mM) was increased compared with that in normal controls. However, his GABA concentration was normalized at 14 and 25 months. The concentrations of Ins were increased after 6 months. No remarkable changes were seen in the concentration of Cho at any time.

Conclusion

These results suggest that the changes in metabolite concentrations during growth may reflect the pathological state of PMD. Furthermore, the lack of a change in the Cho concentration may be useful for differentiating PMD from other demyelinating diseases.

・Introduction

Pelizaeus–Merzbacher disease (PMD) is a rare, X-linked dysmyelinating disorder of the central nervous system (CNS) that induces congenital nystagmus beginning in the first year of life, delayed achievement of motor and cognitive milestones, spastic paralysis, ataxia and seizures. In contrast to other demyelinating leukodystrophies, such as metachromatic leukodystrophy and adrenoleukodystrophy, in which myelin is formed but subsequently destroyed, PMD is characterized by a failure of myelin to form. PMD is caused by alteration of the gene that encodes proteolipid protein 1 (PLP1), one of the most abundant proteins in CNS myelin [1,2]. In PMD, magnetic resonance imaging (MRI) generally shows either diffuse or patchy (tigroid) T2 hyperintensity in the cerebellar, brain stem, and supratentorial white matter. This appearance is believed to be the result of the lack of formation of myelin (hypomyelination or dysmyelination) [3]. However, based on MRI findings alone, it is difficult to differentiate PMD from other forms of white-matter degeneration, such as leukodystrophy. ^{1}H-Magnetic resonance spectroscopy (MRS) may be useful for evaluating the degree of white-matter degeneration. However, there have been few reports on the use of ^{1}H-MRS in PMD, and the results have varied. To our knowledge, there has been no report on the application of ^{1}H-MRS to determine the γ-aminobutyric acid (GABA) concentration in PMD patients.

In this report, we describe a patient with PMD who underwent repeated ^{1}H-MRS for the evaluation of changes over time.

Case

At birth, the patient weighed 2178g and his gestational age was 38 weeks 3 days. There were no abnormal episodes in the perinatal period. There were no abnormalities by Guthrie testing or an acylcarnitine analysis. His family history was unremarkable. Horizontal nystagmus was noted beginning at one month after birth. This symptom persisted, and his parents consulted our hospital when he was 2 months old. In the auditory brainstem response (ABR), only a wave I was seen on both sides, and thus we suspected PMD.

At age 7 months, a clear delay of myelinization was observed in MRI(Figure), and the ABR abnormality persisted. Therefore, genetic testing was performed for the PLP1 gene. The results showed duplication of the PLP1 gene, and therefore he was given a definitive diagnosis of PMD.

The patient is currently age 2 year 9 months. He can maintain a seated position with the use of his own hands. However, he cannot pull himself up or speak any intelligible words.

Methods

^{1}H-MRS was performed when the patient was 2, 6, 14, 25 and months old. The control subjects for ^{1}H-MRS consisted of age-matched children (Group 1: 9 children, 2-11 months old (mean 5.9 months), Group 2: 10 children, 12-26 months old (mean 18.3 months)). All measurements were performed with a clinical 3-tesla MR imager (Signa 3T HD, GE Medical Systems, Milwaukee, WI, USA) using a standard quadrature head coil for MRI and ^{1}H-MRS measurements. All subjects were treated with triclofos sodium (Tricloryl; 0.5 ml/kg body weight) for sedation one hour before the MR examination. For ^{1}H-MRS, the center of a voxel was positioned in the right parietal lobe.

MEGA was incorporated into Point Resolved Spectroscopy (PRESS) consistent with the protocol established in previous reports [4,5]. Water suppression was carried out using conventional three chemical shift-selective (CHESS) pulses after manual optimization, and was achieved at a level of less than 1%. Gradient map shimming was conducted in the measurement location by the high-order shim program, and the full width at half maximum of the water peak was less than 7 Hz. The sequence parameters were as follows: repetition time (TR) = 1500 ms, echo time (TE) = 68 ms, region of interest (ROI) = 3×3×3 cm^3 (27 ml), summation = 128 signals for each spectrum, total acquisition time = 12 minutes. Measurements with and without frequency-selective pulses were conducted alternatively, i.e., J evolution for GABA was refocused during odd-numbered acquisitions, and was not refocused during even-numbered acquisitions. Phase correction was conducted for each spectrum. Differences in the acquired spectra provided an edited spectrum for GABA. The in vitro data for N-acetyl aspartate (NAA), glutamate (Glu), and GABA were acquired with MEGA-PRESS with the same parameters as for human measurements and set according to the LCModel basis set. The signals in the difference spectra obtained by MEGA-PRESS were analyzed by LCModel (version 6.1) with our original basis set for MEGA-PRESS, and the quantified concentration of GABA was confirmed in a phantom study with known concentrations of metabolites. The criteria for selecting reliable metabolite concentrations were based on the percent standard deviation (%SD) of the fit for each metabolite that reflected the Cramer-Rao lower bounds. Only results with a %SD <15% were included in the analysis.

The parameters of the conventional stimulated echo acquisition mode (STEAM) sequence were as follows: TR = 5000 ms, TE = 15 ms, ROI = 1.5×2.0×2.0 cm^3 (6.0 ml), total acquisition time = 6.8 minutes. We analyzed the metabolites, NAA, choline-containing compounds (Cho), creatinine(Cr), myoinositol (Ins), Glu, using the

external standard calibration method in LCModel Ver 6.1. The %SD value of the fit for each metabolite that reflected the Cramer-Rao lower bounds was less than 15%. The concentration of each metabolite was judged to be abnormal when the value was more than 2SD greater than or less than that in the control subjects.
Informed consent was obtained from the family members of all of the children.

・Results (Table 1, Table 2, Figure)

Metabolite concentrations in normal controls are shown in Table 1.

In the PMD patient (Table 2), the NAA concentration increased with age. At age 6 months, the NAA concentration was significantly higher than that in normal control subjects. At 6, 14 and 25 months, the Cr, Ins and Glu concentrations in the PMD patient were increased compared to those at 2 months. At 6 months, the Cr, and Glu concentrations were significantly higher than those in normal control subjects. At 6, 14, 25 months, the Ins concentrations were significantly higher than those in normal control subjects.

At each age, there was no change in the Cho, concentration, and there was no significant difference compared to that in normal controls.

The GABA concentration in the PMD patient was high at 2 and 6 months. However, at 14 and 25 months, the GABA concentration had decreased. The GABA concentration in the PMD patient was significantly different from that in normal controls at 2 and 6 months.

・Discussion

Table 3 shows ^{1}H-MRS findings in PMD patients that have been reported to date [6-13]. The results of ^{1}H-MRS in PMD are somewhat varied. These differences in ^{1}H-MRS findings may be due to ① the age at which testing was performed, ② the site of the examination, and/or ③ differences in the abnormality of the PLP1 gene. However, Takanashi and Hanefeld recently reported that increases of NAA, Ins, and Cr were observed in PMD patients. They also reported that there was either no change or a decrease in Cho in PMD patients. Since these findings are similar to ours, they may be pathognomonic for PMD.

In our PMD patient, the NAA concentration increased with age. At age 6 months, the NAA concentration was significantly higher than that in normal control subjects. Pouwels et al. reported that the density of NAA in childhood increased with age [14], which is consistent with our results regarding a change in NAA with age by 1H-MRS. However, this does not explain why a significant increase was only observed at 6 months. There have been several reports on the increase in the NAA concentration in PMD [6,8]. Two possible explanations for this increase have been proposed. First, this may be due to a disorder of axonal signal transduction as a result of myelination deficiency, which activates axonal metabolism. Second, this may be due to an increase in oligodendrocytic progenitor cells, which was confirmed in a murine model of PMD. In our case, a significant increase was only observed at age 6 months, which reflects the distinguishing pathological condition of PMD at that age (i.e., activation of axonal metabolism).

In our PMD patient, there was no change in the Cho concentration at each age, and there were no significant differences compared to the normal controls. The concentration of Cho is believed to increase during the process of myelination, and in demyelinating diseases [6]. In comparison to mature oligodendrocytes, oligodendrocytic precursor cells and astrocytes have moderately low concentrations of Cho [15]. This lack of a change in the Cho concentration may reflect the pathological condition of PMD, which is a failure to form myelin, rather than demyelination.

In our PMD patient, the Cr and Ins concentrations at 6 and 14 months were higher than those at 2 months. At 6 months, the Cr and Ins concentrations were significantly higher than those in normal control subjects. Furthermore, the Ins concentrations were significantly higher than those in normal control subjects at 14 and 25 months. The total Cr concentration is a marker for the concentrations of neurons and glia cells. An increased Cr concentration has recently been reported in the lesions of patients with multiple sclerosis (MS) [16]. The increased astrocytic activity associated with gliosis

was considered to be responsible for the elevated Cr concentration in MS. Ins has been shown to be a glia-specific marker, with a particularly high concentration in astrocytes [17]. The elevated Ins in MS has been speculated to be due to both the accumulation of myelin breakdown products during the acute phase and astrocytic gliosis in chronic lesions [6]. The former mechanism is not applicable to PMD because there is no active demyelination phase. Therefore, the elevated Ins and Cr concentrations may result from astrocytic gliosis caused by chronic damage to axons.

In our case, the Glu concentrations at 6 and 14 months were higher than that at 2 months. At 6 months, the Glu concentration was significantly higher than that in normal control subjects. In one study, the glutamine (Gln) concentration in white matter of a PMD patient was significantly higher than that in normal control subjects [8]. The increase in Glu in PMD may reflect an increase in neurotransmitter caused by the activation of signal transduction which compensates for disordered axons with myelination deficiency.

In our case, GABA concentrations were high up until age 6 months. However, at 14 and 25 months, the GABA concentration had decreased. The GABA concentration in PMD was significantly different from that in normal controls at both 2 and 6 months. To our knowledge, there has been no previous report on the use of MRS to determine the GABA concentration in PMD patients. A study in an animal model of PMD, the myelin-deficient (MD) rat, showed that it carries a point mutation in the PLP gene [18]. Histologic examination of the caudal brainstem in the MD rat showed fewer GABA(A) receptors on neurons in the nucleus tractus solitarius, hypoglossal nucleus, and dorsal motor nucleus of the vagus. In our case, the high GABA concentration by ^{1}H-MRS may be due to compensation for the disorder of the GABA nervous system.

Therefore, the changes in metabolite concentrations during growth may reflect the pathological state of PMD, such as a change in axonal signal transduction with myelination deficiency, an increase in oligodendrocytic progenitor cells, and astrocytic gliosis caused by axonal damage. Furthermore, the lack of a change in the Cho concentration may be useful for differentiating PMD from other demyelinating diseases. However, our study considered only one subject. To enhance the reliability of our findings, we must study a greater number of PMD patients.

References

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Table 1

Metabolite concentrations in normal controls by ^{1}H-MRS.

Group 1: 9 children, 2-11 months old (mean 5.9 months)

	NAA	Cr	Cho	Ins	Glu	GABA
average	7.1	6.8	2.9	4.9	8.1	1.05
standard deviation	1.2	1.4	0.7	1.4	1.4	0.22

Group 2: 10 children, 12-26 months old (mean 18.3 months)

	NAA	Cr	Cho	Ins	Glu	GABA
average	8.8	7.9	2.4	4.4	9.1	1.28
standard deviation	1.3	1.2	0.4	0.9	1.8	0.35

Table 2

Result of ^{1}H-MRS in the PMD patient.

more than 2SD greater or less than that in the control subjects.

A: 2 months old

	NAA	Cr	Cho	Ins	Glu	GABA
Concentration	5.5	5.6	2.3	4.8	6.5	#1.72
SD	-1.3	-0.9	-0.9	-0.1	-1.1	#3.0

B: 6 months old

	NAA	Cr	Cho	Ins	Glu	GABA
concentration	#9.7	9.4	2.7	#8.1	#12.0	#2.15
SD	#2.2	1.9	-0.3	#2.3	#2.8	#4.90

C: 14 months old

	NAA	Cr	Cho	Ins	Glu	GABA
concentration	10.2	8.9	2.7	6.7	10.7	0.95
SD	1.1	0.8	0.7	#2.6	0.9	-0.93

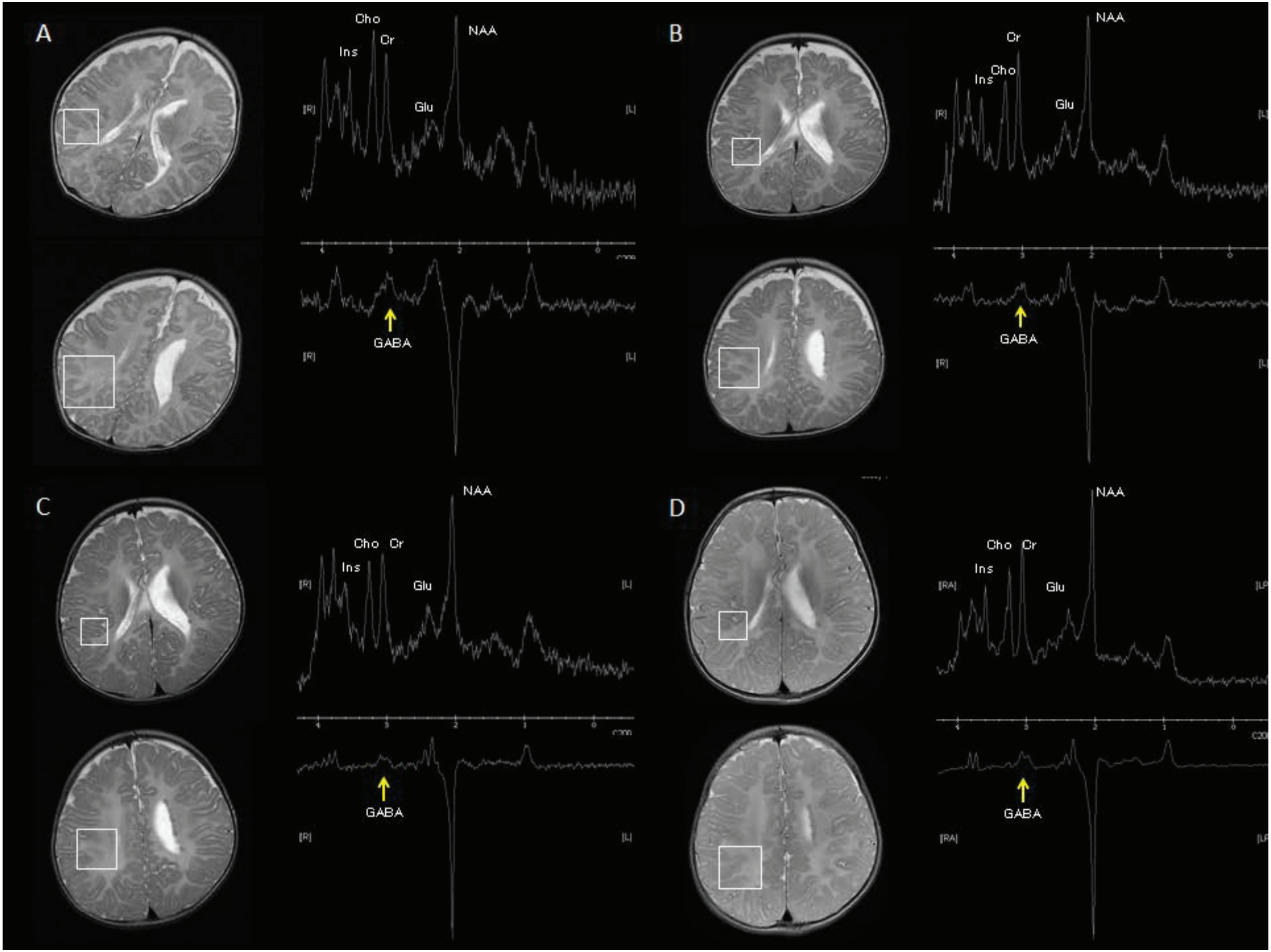
D: 25 months old

	NAA	Cr	Cho	Ins	Glu	GABA
concentration	10.1	8.8	2.3	8.0	10.5	0.98
SD	1.0	0.7	-0.3	#4.1	0.8	-0.84

Table 3

^{1}H-MRS findings in Pelizaeus-Merzbacher disease (PMD) reported to date.

	Number of patients	Age (year)	Comments
Takanashi J, et al. [6] Neurology 2002;58:237-241]	5	4-10	NAA (16% increase), Cr (43% increase), Ins (31% increase) Cho: no change
Takanashi J , et al. [7] AJNR 1997;18:533-535	2	5,6	Normal MRS results, creatine levels tended to be elevated
Hanefeld FA, et al. [8] Neurology 2005;65:701-706	5	0.6-6.8	Increased tNAA, Gln, Ins, creatine, and phosphocreatine levels, Decreased Cho level
Kurata K, et al. [9] No to hattatsu 2000;32:503-508	3	25-34	No reduction in the NAA concentration.
Pizzini F, et al. [10] AJNR 2003;24:1683-1689	3	2-7	Decreased NAA level Increased Cho and Cr levels
Grodd W, et al. [11] Radiology 1991; 181: 173–181.	4	0.7-5.7	Increased Cho level and decreased NAA levels
Spalice A, et al. [12] Pediatr. Radiol. 2000; 30: 171–175.	2	1.5, 6	Decreased Cho level
Bonavita S, et al. [13] Neurology 2001;56:785–788	9	6–43	Decreased NAA level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