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ORIGINAL RESEARCH

Correlation of MR Imaging and MR Spectroscopy Findings with Cognitive Impairment in Mucopolysaccharidosis II

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BACKGROUND AND PURPOSE: There are no reliable markers to predict neurologic outcome of patients with mucopolysaccharidosis (MPS) II. We hypothesized that brain MR imaging and MR spectroscopy are useful in depicting features related to cognitive impairment (CI) in MPS II.

MATERIALS AND METHODS: Nineteen male patients with MPS II were included in this study. They were evaluated through intelligence/developmental tests to be classified in 2 groups: patients with CI (group A) or patients without CI (group B). Brain MR imaging evaluated white matter (WM) lesions, hydrocephalus, and brain atrophy. Voxels from MR spectroscopy (point-resolved spectroscopy TE 30 ms) were positioned in the WM of the deep right frontal lobe and at the gray matter (GM) in the posterior occipital cortex across the midline. Comparison of MR imaging and MR spectroscopy findings between these 2 groups and a control group was performed.

RESULTS: The mean age of the patients was 9.6 years (group A, 7.08 years old, 12 patients; group B, 14 years old, 7 patients; $P = .076$). Brain atrophy and hydrocephalus were more frequently found in group A patients ($P = .006$ and $P = .029$, respectively); these patients also presented more severe WM lesions than patients from group B ($P = .022$). Patients from group A also had a higher myo-inositol (mIns)/creatine (Cr) ratio in the GM ($P = .046$) and in the WM ($P = .032$). The choline/Cr and *N*-acetylaspartate/Cr ratios were similar in both groups.

CONCLUSIONS: Our study showed that severe WM lesions, brain atrophy, hydrocephalus, and elevated mIns/Cr were more common in patients with MPS II and with CI.

Hunter disease, or mucopolysaccharidosis (MPS) type II, is a rare lysosomal storage disease caused by deficiency of iduronate 2-sulfatase which leads to incomplete degradation and progressive accumulation of glycosaminoglycans (GAG) in various organs, including the central nervous system (CNS). The cerebral manifestations of MPS II range widely from mild to severe disability; the reason for this heterogeneity is not well understood. Patients having neurologic compromise usually present severe disability and die before 15 years of age, whereas patients without cognitive impairment (CI) can present a normal life expectancy.[1,2] Despite the high morbidity and mortality of the disease, enzyme-replacement therapy (ERT) is a potential treatment for MPS II.[3]

Brain MR imaging is the prime imaging technique for detection of CNS abnormalities in patients with MPS II. White matter (WM) lesions, dilated perivascular spaces (DPVS), hydrocephalus, and spinal canal stenosis have been described in previous studies.[4-8] However, the relationship between neuroimaging findings and mental dysfunction is controversial. Data from Gabrielli et al[9] showed a correlation between WM alterations and mental retardation. Matheus et al[10] did not find an association between neuroimaging findings and clinical status. Some reasons for these discrepancies could be the inclusion of different types of patients with MPS as a unique study group, inclusion of patients with mild phenotype only, and subjective scores to graduate lesions on MR imaging.[9,10]

In metabolic and destructive brain disorders, MR spectroscopy imaging functions as a diagnostic tool for noninvasive analysis of biochemical tissue.[11-13] Regarding MPS, Takahashi et al[14] recently described the MR spectroscopy findings in patients with MPS before and after bone marrow transplantation (BMT). The authors found an abnormal resonance peak at 3.7 ppm in the brain and urine of patients with MPS, higher than the myo-inositol (mIns) in a small case report study. Until now, these findings have not been confirmed in other studies.

Given the wide spectrum of disease severity and progressive course, one of the challenges for managing the disorder is to accurately predict clinical phenotype. To date, there is no reliable marker to predict the onset of cerebral lesions and outcome. Adequate measure of MR imaging brain involvement and detection of cerebral lesions before clinical manifestations could be used to monitor lesion progression and select therapeutic interventions. The purpose of our study was to test which MR imaging and MR spectroscopy findings correlate with neurologic compromise in patients with MPS II.

Materials and Methods

We prospectively evaluated 19 male patients with MPS II from the MPS clinics of the Medical Genetics Service of our hospital. Each patient had typical clinical manifestations of the disorder, as well as a biochemical diagnosis of MPS II confirmed by a deficient activity of IDS in plasma or leukocytes, with a normal activity of at least one other sulfatase, to exclude multiple sulfatase deficiency. The patients had not been submitted previously to BMT or ERT.

All of the patients were submitted to age-appropriate development tests (Bayley for children younger than 42 months, Weschler for children between 43 months and 10 years, and Leiter for patients who

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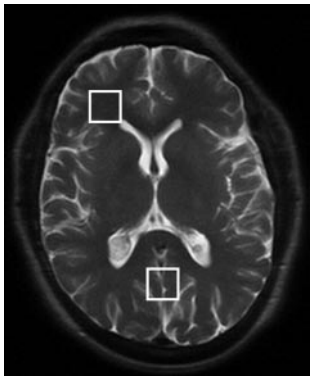

Fig 1. Example of the localization used for single-voxel imaging. Superimposed on an axial T2-weighted image, the *white square* shows the volume of brain tissue sampled by MR spectroscopy at the WM (right frontal lobe) and GM (posterior occipital cortex).

were 11 years or older) by a psychologist (A.P.P.) who was experienced in development neurology. According to the study protocol, patients were classified either as presenting CI (group A) or not (group B). CI was considered present when developmental tests or intelligence quotient (IQ) below 70 was found. Severely affected patients who could not respond to development tests were classified within the CI group. For MR spectroscopy, an age-matched control group was examined with the same protocol used to examine the patient group. This control group consisted of healthy children from the community without developmental delay or neurologic symptoms.

All of the MR imaging of the brain was performed on a 1.5T MR system and included axial fluid-attenuated inversion recovery (FLAIR)-weighted images (TR/TE/TI = 9000 ms/114 ms/2500 ms), axial and coronal T2-weighted images (TR/TE = 4000 ms/99 ms), and sagittal T1-weighted images (TR/TE, 522 ms/14 ms). WM lesions were defined as hyperintense on FLAIR and graded in 2 categories: mild (scattered and <5 WM lesions) and severe (extensive, confluent, and >5 WM lesions). Brain atrophy was considered present when dilated sulci were found as described by Lee et al.[4] For statistical analysis, hydrocephalus was calculated by a semiquantitative ratio measuring the maximum distance between the outer borders of the occipital horns divided by the maximum biparietal diameter [ventricular size = 10 − (occipital horns diameter/biparietal diameter)]. Although DPVS are common in patients with MPS II, this finding was not tested in this study.

Single-voxel proton MR spectra were acquired at the same 1.5T MR unit by using the point-resolved spectroscopy technique (TR/TE = 2000 ms/30 ms). Automated shimming and chemical shift selective water suppression were used. Voxels of 8 mL were positioned at 2 locations containing mainly WM tissue at the deep right frontal lobe and at the gray matter (GM) in the posterior occipital cortex across the midline (Fig 1). To reduce measurement variability, these locations are considered standard for research studies in our department. For MR spectroscopy analysis, we excluded patients with severe hydrocephalus. The data were postprocessed, and mIns was assigned at 3.56 ppm, choline (Cho) at 3.2 ppm, creatine (Cr) at 3.03 ppm, and *N*-acetylaspartate (NAA) at 2.0 ppm. Computer software designed by the manufacturer (Siemens, Erlangen, Germany) was used to measure peak areas. Imaging evaluation was performed by a single reader (L.V.) with a computerized data base, blinded to clinical findings or disease form.

For statistical analysis, descriptive summary statistics and univariate analysis were performed using the software SPSS for Windows 10 (SPSS, Chicago, Ill). For categoric variables (age, severity of WM lesions, and brain atrophy), the Fisher exact test was used. For continuous variables (degree of hydrocephalus and metabolite ratios on MR spectroscopy), we used the Student *t* test for independent samples. Significance level was set at .05.

The study was approved by the local institutional review board (number 03/066). Informed consent was obtained from the patients or their legal representatives before undergoing evaluations.

Results

Nineteen patients were included in the study. The mean age of the patients was 9.6 years (SD, 6.5 years; age range, 3–26 years). Based on IQ and development testing, 12 (63.2%) of 19 patients had CI (group A), whereas 7 (36.8%) of 19 did not (group B).

Table 1 lists imaging findings in both groups. Although the presence of WM lesions did not differ significantly between groups, WM lesion severity was significantly greater in patients with CI ($P = .038$). Most of these patients presented severe lesions diffusely involving the WM and usually affecting more than 3 cerebral lobes. Isolated involvement of periventricular or deep WM was uncommon. Hyperintense lesions were confluent in some patients but never caused mass effect. None of the evaluated patients had lesions involving the corpus callosum. Hydrocephalus and brain atrophy were more frequent in patients with CI ($P = .029$ and $P = .006$, respectively). Brain atrophy was diffuse and sometimes asymmetric, with frontoparietal regions usually more severely affected.

Examples of MR spectroscopy of patients with and without CI are shown in Figs 2 and 3. Table 2 shows MR spectroscopy findings in both groups. Patients presenting CI had a higher mIns/Cr ratio in the GM ($P = .046$) and in the WM ($P = .032$). The Cho/Cr and NAA/Cr ratios, in both WM and GM, were similar in both groups. Metabolite value differences between groups occurred independently of degree of WM lesions, hydrocephalus, or patient age ($P > .05$).

Discussion

Our data suggest that MR imaging and MR spectroscopy can be useful tools to assess the severity of brain compromise in patients with MPS II. We found a higher prevalence of brain atrophy, hydrocephalus, severe WM lesions, and elevated mIns in more severely affected children. These results confirm the high sensitivity of neuroimaging for characterization of brain involvement in MPS. In addition, MR spectroscopy findings could be useful to better understand the pathophysiology of brain response to GAG deposits.[15,16] Although our study group was composed of a highly selected population of patients with MPS II, and the extrapolation of these results for all of the patients with MPS should be done with caution, our preliminary results may be supported by using neuroimaging as a marker of disease severity in clinical trials.

Brain atrophy has been considered a common finding in MPS, though correlation with mental status is controversial in the literature.[9,10] As an imaging finding, atrophy was always diffuse and tended to involve more extensively both frontal and parietal areas. In some patients, asymmetry was found. We did not find an explanation for such asymmetry, because neurologic examination did not show focal motor or sensitive signs. As pointed out by Matheus et al,[10] one possible explanation could be an association of brain atrophy and asymmetric deposition of GAG or CSF entrapment in subarachnoid spaces. This association could explain why there is controversy regarding the correlation between dilated sulci and mental status.

Hydrocephalus is an important cause of morbidity in MPS

Table 1: Univariate analysis of MR imaging findings

Variable	All Patients ($n = 19$)	Children with CI ($n = 12$)	Children without CI ($n = 7$)	P
Mean age (SD)	9.63 (6.5)	7.08 (3.5)	14 (8.4)	.076
WML	Severe = 14 (73.7%); Mild = 5 (26.3%)	Severe = 11 (91.7%); Mild = 1 (8.3%)	Severe = 3 (42.9%); Mild = 4 (57.1%)	.038
Hydrocephalus	7.83 (0.44)	7.98 (0.46)	7.58 (0.26)	.029
Brain atrophy	11/19 (57.8%)	10/12 (90.9%)	1/7 (9.1%)	.006

Note:—CI indicates cognitive impairment; WML, white matter lesion. Age is expressed in years. Numbers between parentheses indicate SD or percentage.

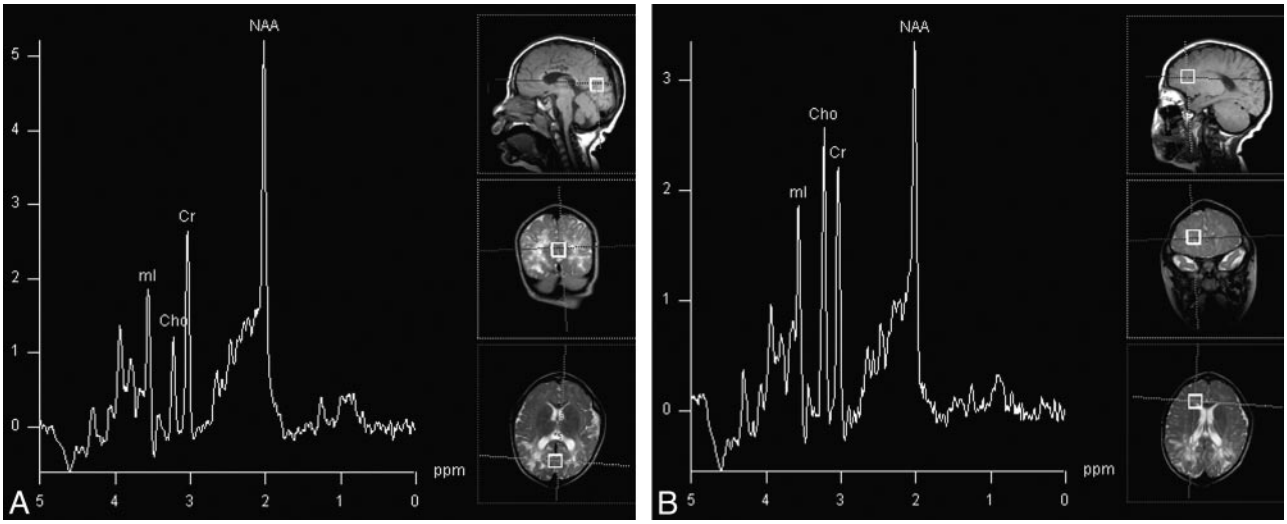

Fig 2. MR spectroscopy of a patient with MPS II and CI. There is elevation of the mIns/Cr ratio at the GM (*A*) and WM (*B*).

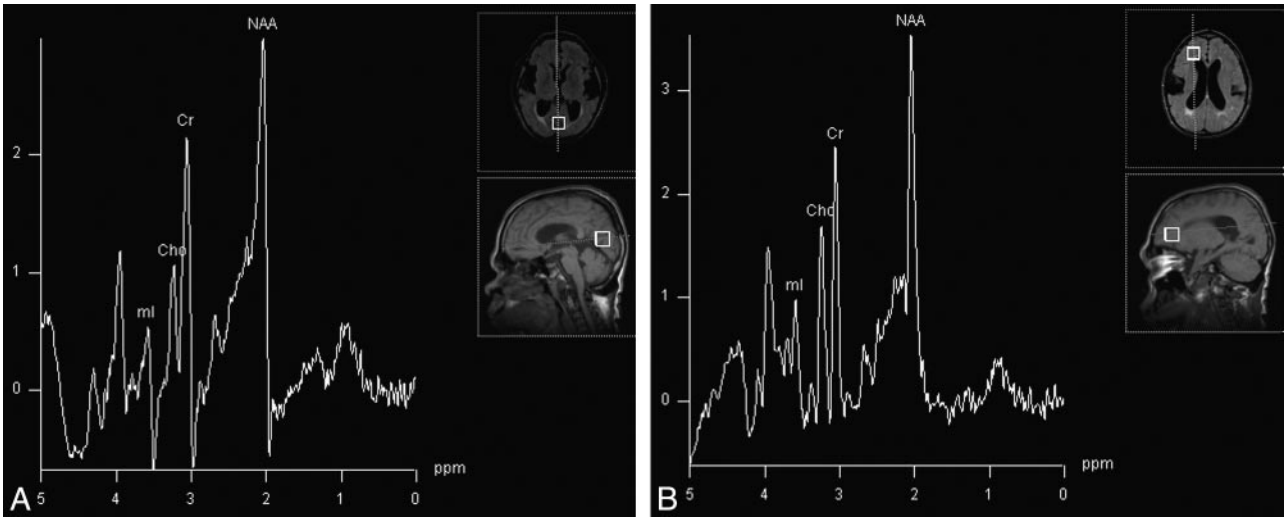

Fig 3. MR spectroscopy of a MPS II patient without CI. Compared with Fig 2, elevated mIns/Cr ratio at the GM (*A*) and WM (*B*) is no longer present.

II,[17,18] because chronic intraventricular high pressure can lead to behavioral disturbances, optic nerve lesions, and brain stem damage. Because of probable outcomes, different authors recommend neurosurgical intervention for patients with MPS, mainly types I, III, and VI. Experiences with such neurosurgical procedures in MPS II are limited. Because venous hypertension is a known cause of hydrocephalus, one hypothesis for the ventricular enlargement in these patients could be the reduced venous outflow through the skull base. New studies are necessary to confirm this association.

The pathophysiologic mechanisms causing hyperintensity on FLAIR-weighted images and their consequences are not fully understood. Intraneuronal deposition of GAG has been reported in the literature. Perhaps brain response to this deposition could be gliosis, resulting in a signal change on MR imaging. Knowledge of the patterns of WM lesions is important, because MPS can be mistaken for other leukodystrophies.[19-23]

There are limited data correlating WM lesions and clinical findings on MPS.[5,9,10] Gabrielli et al[9] found a linear correla-

Table 2: Univariate analysis of MRS findings

Metabolite Ratio	Children with CI ($n = 12$)	Children without CI ($n = 7$)	Control Group ($n = 10$)	P
WM				
NAA/Cr	1.94 ± 0.49	2.17 ± 0.26	2.11 ± 0.36	.450
Cho/Cr	0.94 ± 0.21	0.97 ± 0.12	0.83 ± 0.19	.301
mIns/Cr	0.57 ± 0.18	0.43 ± 0.12	0.40 ± 0.10	.032
GM				
NAA/Cr	2.05 ± 0.41	2.01 ± 0.50	2.12 ± 0.21	.842
Cho/Cr	0.45 ± 0.08	0.45 ± 0.07	0.48 ± 0.07	.668
mIns/Cr	0.47 ± 0.88	0.36 ± 0.11	0.45 ± 0.66	.046

Note:—CI indicates cognitive impairment; WM, white matter; NAA, *N*-acetylaspartate; Cr, creatine; Cho, choline; mIns, myo-inositol; GM, gray matter. Groups A and B indicate children with and without cognitive impairment, respectively.

tion between WM lesions and mental retardation in 20 patients with different forms of MPS. On the other hand, Matheus et al[10] described a broad spectrum of MR imaging findings but no relationship between the imaging and clinical manifestation in 18 patients with MPS types I and II. In our study, the severity of WM lesions was more commonly seen in patients with CI. This correlation may reflect the fact that our study group was composed of patients with a single type of MPS (MPS II) with a wide range of neurologic compromise. As far as we know, our study is the largest series of patients with MPS II studied through MR imaging and MR spectroscopy up to now.

Regarding MR spectroscopy findings, we found a statistically significant elevation of mIns in the GM and a trend for elevated mIns in the WM of patients with CI. The mIns peak contains contributions from various compounds, including mI, inositol monophosphate, phosphatidyl inositol, and inositol diphosphate. The main component, mIns, is synthesized primarily in glial cells and does not cross the blood-brain barrier.[24] Studies from primate models showed significant correlation between markers of astrogliosis and mIns/Cr ratios.[25-30] For these reasons, mIns is considered to be a glial marker, and an increase in its content is believed to represent glial proliferation or an increase in glial cell size. Because intraneuronal deposition of GAG and microglial activation in MPS models have been reported in the literature,[22,31] it is possible that cerebral GAG deposition is responsible for inducing the changes in glial cells that can be measured by MR spectroscopy as an elevation of mIns/Cr ratio.

mIns is also considered an organic osmolyte, playing a major role in the volume and osmoregulation of astrocytes.[11,13,27] For this reason, increased volume of cells in MPS II could also be responsible for the elevation of mIns. New studies are necessary to confirm these theories.

Finally, another potential explanation is that mIns could be an indirect marker of GAG deposition. An integrating correlation between in vitro GAG and abnormal MR spectroscopy resonance at 3.7 ppm in the brains of patients with MPS II, higher than the chemical shift of mIns peak in MR spectroscopy, was described recently by Takahashi et al.[14] The authors concluded that the presence of this peak could represent GAG molecules. Although the study has many limitations (eg, a small number of patients and a control group with known epilepsy history), if this correlation turns out to be confirmed in future studies, we could speculate that macromolecules (GAG) could be a major component of elevated mIns peak detected with MR spectroscopy. However, the precise measurement of GAG would require a different MR spectroscopy quantification approach that was not performed in our study.

We did not find differences in NAA/Cr between groups. This result is interesting, because we expected to detect a low NAA in patients who were more severely affected. One possible reason could be explained at the cellular level. In the MPS model, Walkley[30] did not find axonal spheroid formation (neuroaxonal dystrophy) despite widespread intraneuronal storage in neurons. In contrast, this cellular finding is abundant in gangliosidoses, a lysosomal storage disease with progressive psychomotor regression and low NAA at the MR spectroscopy, even in the normal-appearing WM.[31,32]

Because both Cho/Cr and mIns/Cr are considered markers of glial response, we also expected to find an increase in the Cho in neurologic patients. In addition, Takahashi et al[14] also found an elevated Cho/Cr ratio in the WM of patients with MPS. The fact is that correlation between mIns and Cho as glial markers is not universal. For instance, the elevated Cho/Cr ratio and normal mIns/Cr ratio is described in schizophrenic patients[33] and is the opposite in gliomatosis cerebri.[34] In addition, we must take into account the fact that the way we measured metabolite concentration allowed us to obtain only relative metabolite concentrations.

In conclusion, our data support the evidence that cerebral involvement is common in patients with MPS II. Because there is no specific treatment for neuronal involvement in patients with MPS, a better understanding of the pathophysiology of brain response to GAG is crucial. This study showed that severity of WM lesions, hydrocephalus, and elevated mIns could be markers of brain dysfunction in patients with MPS II. Further studies involving a larger sample and serial imaging are required to confirm our preliminary MR spectroscopy findings.

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