Brain MRI in mucopolysaccharidosis

Effect of aging and correlation with biochemical findings

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ABSTRACT

Objective: To investigate the influence of aging on conventional MRI and magnetic resonance spectroscopy (MRS) findings of mucopolysaccharidosis (MPS) patients and to test the correlation of enzyme levels, urinary glycosaminoglycans (GAG), and neuroimaging findings.

Methods: Sixty patients with MPS types I (n = 8), II (n = 31), IV-A (n = 4), and VI (n = 17) underwent T2, fluid-attenuated inversion recovery (FLAIR), and MRS of the brain. For analysis of MRI variables, we measured the normalized cerebral volume (NCV), CSF volume (NCSFV), ventricular volume (NVV), and lesion load (NLL) on FLAIR using semiautomated and automated segmentation techniques. For MRS, a point-resolved spectroscopy technique was used. Voxels were positioned at the white and gray matter. Statistical analysis involved Pearson or Spearman tests for correlation between neuroimaging, age, enzyme levels, and urinary GAG.

Results: The median age at onset of the disease was 20 months. Patients with longer disease duration had more NLL in the white matter ($r = 0.28$, $p = 0.03$), and this difference was more pronounced in MPS II patients ($r = 0.44$, $p = 0.02$). Metabolites ratios in MRS, NCV, NCSFV, and NVV did not correlate with disease duration or age of the patients ($p > 0.05$). MRI and MRS variables in either the white or the gray matter did not correlate with enzymatic activity or GAG levels. Patients with MPS II had a lower mean NCV ($p < 0.001$).

Conclusions: Our data showed that white matter lesion is more extensive as disease duration increases, especially in mucopolysaccharidosis type II patients. MRI and magnetic resonance spectroscopy findings did not correlate with either enzymatic or glycosaminoglycan levels.
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The mucopolysaccharidosis (MPS) are a group of inherited lysosomal storage disorders characterized by a deficiency in one of the lysosomal enzymes responsible to degrade glycosaminoglycans (GAG).[1] There are 7 types of MPS due to 11 different enzymatic deficiencies with a combined incidence of 1 in 25,000. In all types, partially degraded GAG accumulates in lysosomes of affected cells, leading to chronic and progressive deterioration of cells. The neurologic expression of the disease varies within each enzyme deficiency. Mental retardation is characteristic of MPS III, and severe forms of MPS I, II, and VII, and this condition is probably multifactorial.[1]

The management for MPS is changing, as new treatment options such as enzyme replacement therapy (ERT) and bone marrow transplantation undergo trials. For example, ERT is currently available for MPS I, II and VI.[2-4] However, to achieve a good long-term outcome, treatment options before the onset of irreversible clinical symptoms will be an important goal. Markers of disease activity will be needed for early diagnosis, for prognosis, and to monitor therapy in MPS.

MRI and magnetic resonance spectroscopy (MRS) have assumed an important role as tools to assist in the diagnosis of many metabolic disorders.[5-7] Also, quantitative assessment of brain lesions is becoming an important consideration in monitoring the clinical

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outcome and treatment effects. The reason is because recent considerable advances in MRI have allowed the study of brain morphometrics in vivo, which can provide accurate, reproducible, and quantitative measures for assessing imaging findings, such as brain atrophy, white matter (WM) lesion load, and ventricular size. Recent advances in neuroimaging and image postprocessing have enabled largely automated measurements of cerebral, ventricle, and CSF volumes. Besides, combining the results of imaging studies with the results of molecular genetics improves the genotype–phenotype correlation and has the potential to enable a better understanding of the pathophysiology of the disease.

Regarding neuroimaging in MPS, results of several studies involving MRI demonstrated that brain atrophy, WM lesions, and hydrocephalus are commonly observed in MPS patients.[8-12] Also, MRI techniques that demonstrated functional environment such as MRS have been used for the evaluation of MPS patients.[13]

Although such findings have been described for more than 20 years, evidence from these studies was based mostly on case reports or small series of cases, usually with a heterogeneous phenotype. Age-related changes of the magnetic resonance (MR) findings are controversial. Besides, the relationship between neuroimaging and biochemical findings has not been tested.

In this study, we sought to investigate the age-related changes through neuroimaging and to test the correlation of MRI, MRS, and biochemical findings in patients with MPS.

METHODS

Subjects. From August 2002 to August 2006, we selected all patients with MPS seen at the genetic department of our hospital. Of these, 70 patients with biochemical confirmed diagnosis of MPS were able to participate of this study. We excluded 10 individuals because of inadequate image quality for reliable postprocessing and/or patients who were unable to undergo the MRI (usually patients with respiratory compromise and clinically unstable). The remaining 60 patients were the study group (8 patients with MPS I, 31 with MPS II, 4 with MPS IV-A, and 17 with MPS VI). All patients with MPS I had MPS HIS or MPS IS. Of the MPS II patients, 17 had the severe form and 14 had the mild form. Forty-four patients were male and 16 were female. Each patient had typical clinical manifestations of the disorder, as well as a biochemical diagnosis of MPS confirmed by a deficient enzymatic activity (alfa-L-iduronidase for MPS I, iduronate sulfatase for MPS II, galactose 6-sulfatase for MPS IVA, and *n*-acetylgalactosamine 4-sulfatse for MPS VI) and increased urinary GAG. To exclude multiple sulfatases deficiency, a normal activity of at least one other sulfatase was necessary for MPS II, IV-A and VI. For MPS I and II, enzymatic deficiency was measured in leukocytes and plasma. Enzymatic deficiency for patients with MPS VI was measured in leukocytes. Thirty-one patients were receiving ERT (7 with MPS I, 16 with MPS II, and 8 with MPS VI; mean time of ERT treatment was 9.5 months).

Age at onset was defined as the age at which the first clinical symptom was noticed. Age and disease duration at the first MR examination was also measured. Because the values ranges of urinary GAG and enzymatic deficiency vary according to the MPS subtype and age, for measuring the GAG urinary level (first sample of the day), we standardized the result using the higher number of the normal value range as the standard reference and divided the patient's GAG from this reference. For measuring the enzymatic level, we used the same approach but choose the lower number of the normal value range. The study was approved by the local institutional review board. Informed consents were obtained from the patients or their legal representatives before undergoing evaluations.

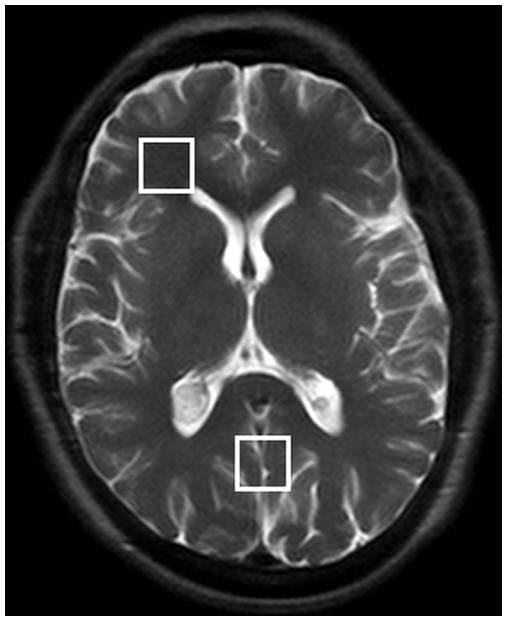
Data acquisition. All subjects were examined with a clinical 1.5-T MRI unit (Symphony, Siemens, Erlangen, Germany). The MRI protocol included acquisition of two transverse images obtained parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum: 1) fluid-attenuated inversion recovery (FLAIR) sequence with repetition time (TR) of 9,000 msec, echo time (TE) of 114 msec, inversion time (TI) of 2,500 msec; and 2) T2-weighted images with TR of 4,000 msec and TE of 99 msec. The slice thickness was 5 mm, the field of view ranged from 180 to 230, and pixel size ranged from 0.45 to 0.55 cm. No paramagnetic agent was used.

Single-voxel proton MR spectra were acquired at the same 1.5-T MR unit by using point-resolved spectroscopy technique (TR/TE: 2,000/30 msec). Automated shimming and chemical shift selective water suppression were used. Voxels of 8 mL were positioned at two 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 (figure 1). To reduce measurement variability, partial volume effects with CSF or other brain structures, these locations are considered standard to research studies in our department. Software designed by the manufacturer (Siemens, Erlangen) was used to analyze peaks of *N*-acetylaspartate (NAA) at 2.01, choline (Cho), creatine (Cr), and myoinositol (mI). Integral values of mI at 3.56 parts per million (ppm), Cho at 3.25 ppm, and NAA at 2.01 were expressed as ratios to the Cr resonance intensity at 3.05 ppm. MRS postprocessing was performed at a workstation by two researchers in agreement (L.V. and M.K.) They were blinded to the age, type, and clinical status of the patients.

Data analysis. For analysis of MRI variables, we measured the normalized cerebral volume (NCV), normalized CSF volume (NCSFV), normalized ventricular volume (NVV), and normalized lesion load (NLL) in the WM on FLAIR.

Superimposed on an axial T2-weighted image, the white square shows the volume of brain tissue sampled by magnetic resonance spectroscopy at the WM (right frontal lobe) and GM (posterior occipital cortex).

Figure 1 Example of the localization used for single-voxel imaging

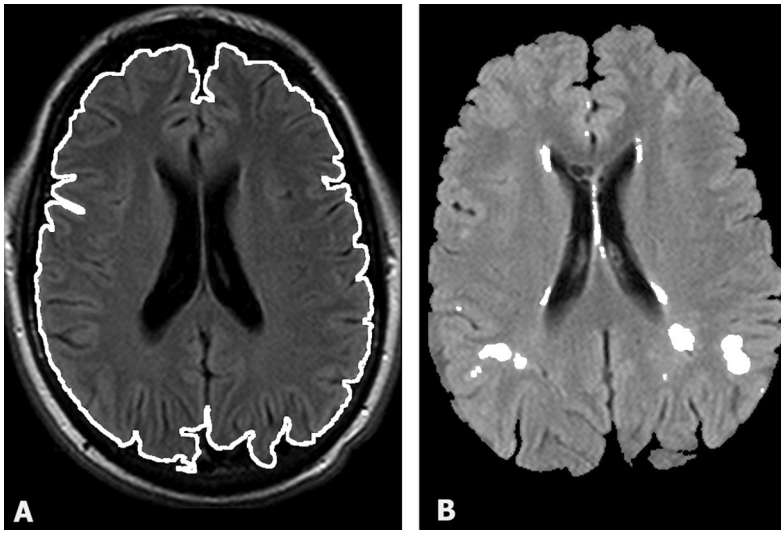


For preprocessing, segmentation and quantitative analysis, we used the ImageJ software (http://rsb.info.nih.gov/ij) from the NIH. This software has both semiautomated and automated segmentation tools (figure 2). Volumes were counted in voxels using the Voxel Counter plug-in of ImageJ software.

For normalization, the outer table of the skull was defined as the peripheral edge of the volume of interest. Normalized volumes, which are corrected for different skull sizes, were used for statistical analysis.

NCV was measured using a semiautomated segmentation technique. The method consists of an established seeded region growing algorithm in multiple regions of interest. The seeds are generated through manual specification of the structure of interest with a mouse. The borders of the skull and cerebral hemispheres were outlined using the Multi Cell Outliner plug-in (http://rsb.info.nih.gov/ij/plugins/multi-cell-outliner.html). We also apply a manual correction step to account for occasional misclassification of nonbrain areas. In some individuals with large skulls, the very superior or inferior regions (5 to 10 mm) were not included in the analysis volume. Importantly, because of normalization process, volumes are largely insensitive to incomplete coverage.

Figure 2 Results of semiautomated and automated segmentation of cerebral volume (A) and lesion load in the white matter (B)



NCSFV, NVV, and NLL were measured using an automatic segmentation technique. A two-step procedure was made. Using a local threshold technique, the analyzed structure was marked by a trained researcher (F.M.). For NCSFV and NVV, a transverse axial T2-weighted image was used. For NLL, a transverse FLAIR image was selected for measurement. The segmented structures were measured to obtain absolute total volumes. NVV measured only lateral ventricles values, so the III and IV ventricles were excluded.

Statistical analysis. Statistical analysis was performed by using the software SPSS for Windows 12 (SPSS, Chicago, IL). Descriptive statistics, including the mean, median, and standard deviations of the clinical, biochemical, and imaging data were calculated. Age-related effects on MRI, MRS, and biochemical variables were evaluated using the Pearson (r) or Spearman correlation coefficient (r_s), according to data distribution. For comparison between groups, analysis of variance with Tukey test for post hoc analysis or Kruskal–Wallis was performed, according to data distribution. The significance level for group comparisons and correlation tests was set to $p < 0.05$.

RESULTS Demographic characteristics, biochemical features, and MRI and MRS findings of the 60 patients are provided in table 1. Most had MPS II (51.7%). The median age at onset was 20 months (± 20.5). The age range of onset was 0 to 80 months, so all patients were younger than 7 years at the onset. The oldest patient was aged 38 years and had MPS IS. Half of the patients underwent the first MRI at age 10 years or older (percentile 50 = 121 months). There was no significant difference in age at onset or age at the first MRI between MPS types.

Table 2 shows correlation of MRI and MRS with age of the patients and disease duration. Patients with longer disease time had more NLL in the WM ($r_s = 0.28$, $p = 0.03$; figure 3). This difference was more pronounced in MPS II patients ($r_s = 0.44$, $p = 0.02$; figure 4) and did not change if ERT was or not used ($r_s = 0.37$, $p = 0.04$ for patients without ERT and $r_s = 0.39$, $p = 0.04$ for patients with ERT). NCV, NVV, and NCSFV did not correlate with disease duration and age of the patients ($p > 0.05$). There was no correlation of MRS metabolites (either WM or GM), GAG accumulation in the urine, or enzymatic level with disease duration or patient age.

To explore the relationship between neuroimaging variables with biochemical findings, we assessed the relationship of MRI and MRS findings

Table 1 Demographic, biochemical, and imaging findings in 60 patients with MPS

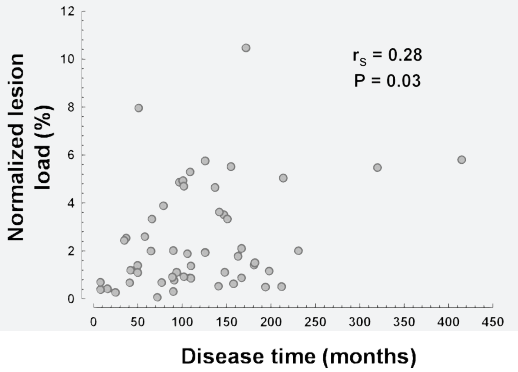
Age at onset	20 ± 20.5 (0–84)
Disease duration	102 ± 73.8 (8–415)
Age at first MRI	121 ± 78.8 (31–463)
Urinary GAG level	3.56 ± 1.86 (0.35–10.42)
Enzymatic level	0.06 ± 0.11 (0–8)
Normalized brain volume	50.8 ± 6.25 (35.4–69.5)
Normalized ventricular volume	2.5 ± 3.70 (0.2–22.4)
Normalized CSF volume	6.5 ± 3.55 (1.5–15.1)
Normalized lesion load	2.41 ± 2.17 (0.05–10.4)
GM NAA/Cr	2.19 ± 0.41 (1.10–3.57)
GM Cho/Cr	0.52 ± 0.11 (0.28–0.85)
GM mI/Cr	0.39 ± 0.10 (0.17–0.67)
WM NAA/Cr	2.22 ± 0.61 (1.47–4.69)
WM Cho/Cr	1.03 ± 0.19 (0.36–1.42)
WM mI/Cr	0.46 ± 0.16 (0.20–1.20)

Numbers are mean or median ± SD (range). Age at onset, disease duration and age at the first MRI values are expressed in month and median. Fractional cerebral, ventricular, cerebral spinal fluid (CSF) and lesion load volumes are expressed in % and normalized for skull size.
MPS = mucopolysaccharidosis; GAG = glycosaminoglycans; MRS = magnetic resonance spectroscopy; GM = gray matter; NAA = *N*-acetylaspartate; Cr = creatine; Cho = choline; mI = myoinositol; WM = white matter.

with urinary GAG and enzymatic level. MRI and MRS variables in either the WM or the GM did not correlate with degree of decrease of enzymatic level or GAG urinary level, even if the patient was on ERT or not.

Table 3 shows correlation of MRI and MRS findings between subtypes of MPS. Because of the small number of patients, the MPS IV group was excluded for subgroup analysis. Patients with

Figure 3 Scatterplot of the normalized lesion load volume vs disease duration in 60 patients with mucopolysaccharidosis



MPS II had a lower mean NCV ($p < 0.001$). There was no difference between the MRS metabolites, NVV, NCSFV, and NLSV and type of MPS (figure 5).

DISCUSSION The MPS represents a heterogeneous group of illnesses that frequently cause neuropsychomotor dysfunction in children.[1] The diagnosis is initially suspected through history and physical examination and confirmed by biochemical and genetic examinations. Even though laboratory analyses are necessary for diagnostic confirmation, MRI is important to characterize the brain lesions, especially hydrocephalus, spinal stenosis, and WM lesions.[8-14] In doubtful cases, MRI is also important to exclude other metabolic diseases.[15] Besides, the method can be used to monitor disease progression and therapeutic response, especially in clinical trials.[16]

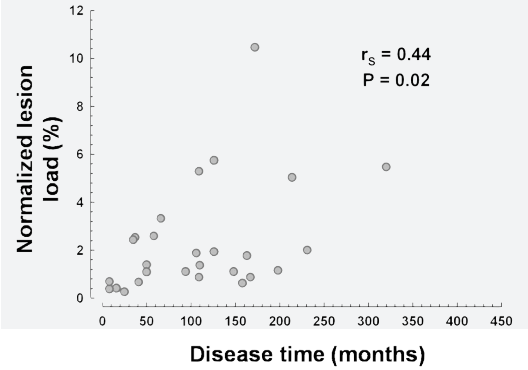
In spite of various descriptions regarding the

Table 2 Age-related changes on MRI and MRS in 60 patients with mucopolysaccharidosis

Variable	Disease duration	Age of the patient
Normalized cerebral volume	$r = -0.17, p = 0.19$	$r = -0.15, p = 0.24$
Normalized ventricular volume	$r_s = -0.05, p = 0.66$	$r_s = -0.10, p = 0.45$
Normalized CSF volume	$r_s = 0.08, p = 0.54$	$r_s = 0.09, p = 0.50$
Normalized lesion load	$r_s = 0.28, p = 0.03$	$r_s = 0.20, p = 0.13$
GM NAA/Cr	$r = -0.23, p = 0.10$	$r = -0.19, p = 0.17$
GM Cho/Cr	$r = 0.21, p = 0.12$	$r = 0.24, p = 0.08$
GM mI/Cr	$r = -0.24, p = 0.07$	$r = -0.17, p = 0.23$
WM NAA/Cr	$r = 0.01, p = 0.96$	$r = -0.06, p = 0.66$
WM Cho/Cr	$r = 0.18, p = 0.23$	$r = 0.21, p = 0.15$
WM mI/Cr	$r = -0.21, p = 0.16$	$r = -0.18, p = 0.22$

r and r_s indicate Pearson correlation coefficient and Spearman correlation coefficient; respectively.
MRS = magnetic resonance spectroscopy; MPS = mucopolysaccharidosis; GM = gray matter; NAA = *N*-acetylaspartate; Cr = creatine; Cho = choline; mI = myoinositol; WM = white matter.

Figure 4 Scatterplot of the normalized lesion load volume vs disease duration in 31 patients with mucopolysaccharidosis type II



MRI findings in patients with MPS, the evidence available are based on small series of cases, with heterogeneous samples of patients and without a serious criteria as to the appointment of subgroups.[10,11,17-23] Besides, most of the variables were analyzed subjectively and no study used MRI quantitative techniques. To date, the correlation between neuroimaging, biochemical alterations, and neurologic symptoms is controversial.

In this study, we evaluated MRI and MRS findings in 60 patients with MPS using semiautomated and automated segmentation techniques. As far as we now, this is the largest series describing such findings. The major conclusions are as follows: 1) WM lesion are more extensive as disease duration increases, especially in MPS II patients; 2) MRS metabolites, cerebral volume, ventriculomegaly, and CSF volume do not change with disease duration; 3) urinary GAG level and enzymatic level do not correlate with MRI or MRS findings; and 4) reduced brain volume is more pronounced in MPS II patients.

Regarding demographic data, two interesting findings were observed. First, all patients had a disease age at onset below age 7 years. So we can conclude that most or even all patients with MPS are diagnosed before that age, mainly because the somatic findings are usually evident in young children. An exception could be MPS III patients (a group that was not included in this study), who frequently present neurologic findings but usually do not have severe somatic compromise at least during the first years of the disease. Second, most of the patient underwent the first MRI examination at age 10 years, rather late in the course of the disease. This is an important point to discuss because if MRI is going to be used as a tool to monitor disease progression or as a marker of treatment response, we need to perform these examinations earlier. The reason for this delay is probably the origin of most of the patients who came from many regions or countries far away from our center.

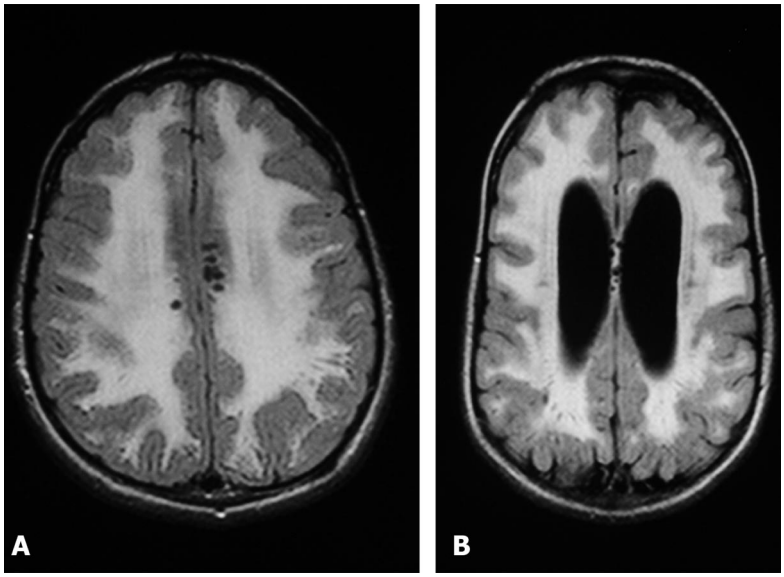
In contrast to previous findings,[24] our data showed a positive correlation of WM lesion and disease duration. The cause of this lesion is not fully understood. Histologic studies demonstrate gliosis, loss of axons, and myelin in the brain of MPS patients and animal models. Because extensive WM lesion is a frequent finding in many metabolic diseases, MPS should be differentiated from other leukodystrophies. Besides, because MRI variables including WM lesion seem to be a promising adjunct outcome measures in meta-

Table 3 Correlation of MRI and MRS findings with type of MPS

Variable	MPS I (n = 8)	MPS II (n = 31)	MPS VI (n = 17)	*p* Value
Normalized cerebral volume	54.4 ± 8.5	48.1 ± 5.9	52.9 ± 3.3	0.004*
Normalized ventricular volume	3.1 ± 4.8	2.6 ± 4.3	2.1 ± 1.4	0.807
Normalized CSF volume	7.2 ± 3.8	6.6 ± 3.6	5.8 ± 3.0	0.626
Normalized lesion load	2.7 ± 2.0	2.3 ± 2.3	2.4 ± 2.2	0.856
GM NAA/Cr	1.9 ± 0.15	2.1 ± 0.44	2.3 ± 0.41	0.126
GM Cho/Cr	0.52 ± 0.09	0.50 ± 0.12	0.56 ± 0.12	0.265
GM mI/Cr	0.38 ± 0.08	0.41 ± 0.11	0.35 ± 0.08	0.141
WM NAA/Cr	2.02 ± 0.21	2.15 ± 0.46	2.3 ± 0.9	0.514
WM Cho/Cr	1.12 ± 0.19	1.04 ± 0.18	0.94 ± 0.22	0.174
WM mI/Cr	0.45 ± 0.07	0.46 ± 0.11	0.39 ± 0.14	0.262

Numbers are mean ± SD. Fractional cerebral, ventricular, CSF, and lesion load volumes are expressed in % and normalized for skull size. Magnetic resonance spectroscopy (MRS) metabolites are expressed in ratio to creatine.
* Analysis of variance with post hoc analysis.
MPS = mucopolysaccharidosis; GM = gray matter; NAA = *N*-acetylaspartate; Cr = creatine; Cho = choline; mI = myoinositol; WM = white matter.

Figure 5 White matter lesions in mucopolysaccharidosis patients



Examples of extensive white matter lesions on fluid-attenuated inversion recovery in patients with mucopolysaccharidosis types II (A) and VI (B).

bolic disease trials, the potential progressive behavior of WM lesions with aging is an important issue to be aware of.

An increase of WM lesions with aging is also important because it shows that neuropathology in the WM could be a progressive phenomenon. Evidence from animal models showed progressive age-related changes. Current evidence suggests that ectopic dendritogenesis, neuroaxonal dystrophy, and death of neurons could be responsible for cellular dysfunction in MPS patients.[28-30] In addition to GAG deposition, gangliosides (GM2 and GM3) also accumulate in the brains of MPS patients. It is interesting that ganglioside accumulation has been found in the brain of the MPS forms that present mental retardation.[1] Although we cannot prove it in this study, we speculate that ganglioside accumulation could be involved in the appearing of WM lesions.

Our data showed that MRS ratios, cerebral, CSF, and ventricular volumes were not age-related variables. This conclusion was based on normalized and automated MRI techniques to reduce potential confounding effects. As far as we know, these results have never been described previously in the literature. They are important because they indicate that brain atrophy and hydrocephalus could not be a consequence of aging. Maybe other markers related to genotype could also play a role in the development of these neurologic entities. This could be important to plan potential forms of treatment and to search for the cause of these conditions.

Histologic studies showed that GAG accumulates in the meninges, and it is a potential cause of hydrocephalus.[1] Comparing the GAG level with ventricular and CSF volumes, we thought to test this correlation. However, our data showed that increased urinary GAG levels do not correlate either with ventricular or CSF volumes. Although this negative relationship does not exclude the correlation, it is possible that other features are responsible for ventricular and sulci enlargement in these patients. For instance, venous hypertension could be one of these causes. We did not measure hemodynamic parameters in this study, but obstruction in cerebral veins is thought to be a cause of communicating hydrocephalus in children with skull base abnormalities.[14] It has been postulated that ventricular enlargement results from diminished venous outflow through bone dysostosis of the skull base. Because skull base abnormalities and communicant hydrocephalus occur in MPS patients, this could be a potential cause of ventricular enlargement. New studies with measuring of venous flow (such as MR venography) could test this hypothesis.

In our data, a lower enzymatic level did not correlate with changes in MRI and MRS variables. Because there is evidence that a lower enzymatic level is considered a marker of disease activity, we expected a positive correlation with some neuroimaging variables such as extensive lesions in the WM, a low NAA/Cr, and elevated mI/Cr at the MRS.[24,25] However, we could not find such results. Correlations between patient genotype, amount of residual activity, and clinical presentation have been investigated for many lysosomal diseases, including MPS. Although residual enzymatic activity presents itself as a potential marker of disease, results from the literature are controversial.[26] We speculate that besides the residual enzymatic activity, other findings, such as the type of the substrate and genotype profile, must contribute to CNS pathology.[25-27] Brain atrophy is common in MPS, and the most compelling reason for measuring it is that it provides a marker of axonal loss, which, if progressive, is likely to result in irreversible disability.[9,10,13,14] It probably represents neuronal death and myelin loss, although other entities, such as ectopic dendritogenesis, neuroaxonal dystrophy, and microglial activation, have also been described in MPS.[28-30] Evidence suggests that brain atrophy is more common in MPS I, II, and III.[9,10] Our data confirm that cerebral volume is lower in MPS II patients. The results found in MPS I patients were probably caused by the prevalence of the subtypes

in our data. In this study, we included eight patients with the intermediate form (Hurler–Scheie) or the mild form (Scheie). None had the severe form of the disease (Hurler). A higher cerebral volume in patients with MPS VI is not surprising because mental compromise is not a frequent finding in this type of MPS.

Evidence from series of cases suggests that WM lesions and hydrocephalus are more prominent in MPS IH and II.[1,9,10] Comparing MPS subtypes, we did not find significant difference regarding WM lesions or ventriculomegaly in patients with MPS I or II from MPS VI patients. In some of the 17 patients with MPS VI, we found extensive WM lesions and ventricular enlargement. Although primary neurologic involvement has generally been considered absent, our data shows that severe WM lesions and hydrocephalus do occur in this subtype of MPS.

Discrepancy between neuroimaging findings and clinical phenotype is seen in other metabolic disorders, such as Alexander disease, megalencephaly leukoencephalopathy with subcortical cyst, and leukoencephalopathy associated with congenital muscular dystrophy.[13,14,31] Recently, Walkley et al.[32] described abnormal lysosomal storage in neurons and glial cells of a feline model of MPS VI. The authors also could prove an abnormal amount of gangliosides (GM2 and GM3) in such cells. Previously, this substrate was found in neurons of patients with the most common forms of MPS (I, II, and III) that present mental compromise.[1] Further studies are necessary to better understand the correlation of gangliosides, MRI findings, and neurologic compromise in children with MPS VI.

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