Journal of Pediatric Rehabilitation Medicine: An Interdisciplinary Approach 3 (2010) 109–118
DOI 10.3233/PRM-2010-0115
IOS Press

Clinical Review

Radiologic and neuroradiologic findings in the mucopolysaccharidoses

Ralph Lachman[a,*], Kenneth W. Martin[b], Sérgio Castro[c], Margarida Ayres Basto[c], Alexandra Adams[d] and Elisa Leão Teles[e]
[a]*Radiological Sciences & Pediatrics, UCLA School of Medicine, Los Angeles, CA, USA*
[b]*Children's Hospital & Research Center Oakland, Oakland, CA, USA*
[c]*Serviço de Neuroradiologia, EPE, Porto, Portugal*
[d]*Serviço de Neurocirurgia, EPE, Porto, Portugal*
[e]*Unidade de Doenças Metabólicas, Hospital de Sao João, EPE, Porto, Portugal*

Accepted 18 March 2010

Abstract. The mucopolysaccharidoses (MPS) represent a group of inheritable, clinically heterogeneous lysosomal storage disorders, in which progressive accumulation of glycosaminoglycans (GAGs) can affect organs and tissues all over the body. The current paper discusses the skeletal X-ray and neuroimaging findings in MPS patients, and the imaging techniques that can be used for diagnosing and monitoring abnormalities in the skeleton and central nervous system. Most MPS types show a typical radiologic expression, called dysostosis multiplex, which manifests as malformations of the skeletal system involving bones in the skull, thorax, spine, pelvis, long bones, and hands. Abnormalities of the spine and GAG deposits in the meninges surrounding the spinal cord can result in spinal cord compression, which, if untreated, can lead to compressive myelopathy. Magnetic resonance imaging (MRI) is the most powerful imaging technique for detecting spinal cord compression, but also radiography and computed tomography are useful. GAG deposits in the brain and surrounding tissues can result in brain anomalies, i.e. white matter lesions, brain atrophy, and hydrocephalus, which can be detected using MRI. Skeletal X-ray and neuroimaging findings can play an important role in diagnosis, follow-up, surgical or medical planning, and assessment of treatment response in MPS patients. There is a need for standardized procedures in evaluating and monitoring neurologic complications in these patients.

Keywords: Brain diseases, diagnostic imaging, dysostosis multiplex, mucopolysaccharidoses, spinal cord compression

1. Introduction

The mucopolysaccharidoses (MPS) represent a group of inheritable metabolic diseases, in which a deficiency of one or more of the enzymes involved in glycosaminoglycan (GAG) degradation results in the accumulation of undegraded or partly degraded GAGs in connective tissue. This accumulation progressively leads to widespread tissue and organ dysfunction, and ultimately results in premature death in the majority of patients [8]. Most MPS types are characterized by skeletal abnormalities and joint disease, the exception is the case of MPS III which is primarily central nervous system-related and has only mild dysostosis multiplex even in the most severely affected patients. Within the group that have moderate to severe dysostosis multiplex (ie MPS I, II, IV, VI and VII) the severity of the dysostosis multiplex is variable, even intrafamilially and is generally related to the phenotypic expression of the disease in each patient. It is not possible to accurately differentiate between MPS types based on specific skeletal X-ray or neuroimaging character-

*Address for correspondence: Ralph Lachman, Radiological Sciences & Pediatrics, UCLA School of Medicine, C/o International Skeletal Dysplasia Registry, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA. Tel.: +1 310 423 9915; E-mail: arleen.hernandez@cshs.org.

istics. Skeletal X-rays showing dysostosis multiplex are useful in suggesting MPS as a possible diagnosis or supporting the diagnosis when MPS is suspected. Diagnosis of MPS in general and determination of type requires demonstration of abnormal enzyme assay. Although not used in diagnosis of MPS or MPS type, MRI of brain and spine are critical for evaluating the complications of MPS (i.e. cervical spine compression and hydrocephalus) and the need for neurosurgical treatment. A genetic skeletal survey including skull (anteroposterior [AP], lateral), chest (AP), spine (AP and lateral), pelvis (AP), tubular bones (AP), and/or hands and feet (AP) showing dysostosis multiplex is useful in suggesting or supporting MPS as a possible diagnosis. Specific diagnosis of MPS disease and determination of subtype requires demonstration of an abnormal enzyme using enzyme assays. In addition, for patients with the diagnosis of MPS disease (particularly MPS I, II, IV, and VI), cervical spine instability should be evaluated shortly after diagnosis using lateral cervical spine X-ray with flexion and extension views. This exam is only repeated if clinically indicated or after enzyme replacement therapy or hematopoietic stem cell transplantation, which may increase joint or ligament flexibility. If the flexion/extension exam by skeletal X-ray is not adequate for evaluation, CT scan with flexion/extension may be helpful. Skeletal X-ray follow-up exams may be required to evaluate specific clinical problems such as hip pain, scoliosis/ kyphosis, or genu valgum (knock knees) or other bone-related clinical problems. Although not used in diagnosis of MPS, MRI of brain and spinal cord are critical for evaluating the complications of MPS (i.e. cervical spine compression and hydrocephalus) and the need for neurosurgical treatment. These evaluations should be initiated at diagnosis for baseline assessment and then only repeated every one to three years depending on clinical severity or specific neurologic findings.

Skeletal abnormalities can result in dysmorphism and severe growth retardation, with the severity of these abnormalities varying from patient to patient. Other common features that are characteristic for most but not all MPS types include coarse facial features, vision and hearing impairment, specific organomegaly, heart valve disease, breathing difficulties, and neurologic problems [8]. The latter include carpal tunnel syndrome, spinal cord compression, and brain abnormalities (which can result in intellectual deficit in some MPS types).

The current paper gives an overview of the skeletal X-ray and neuroimaging findings in patients with MPS and discusses how skeletal X-ray and neuroimaging techniques can be used for diagnosing and/or monitoring skeletal dysplasia, spinal cord compression, and brain anomalies in these patients.

Table 1
"Storage disorders" that manifest dysotosis multiplex

Mucopolysaccharidoses (*MPS*)
Hurler syndrome (MPS I-H)
Scheie syndrome (MPS I-S)
Hurler-Scheie syndrome (MPS I-HS)
Hunter syndrome (MPS II)
Sanfilippo syndrome (MPS III A,B,C)
Morquio syndrome (MPS IV A,B)
Maroteaux-Lamy syndrome (MPS VI)
Sly syndrome (MPS VII)
Mucolipidoses (*ML*)
I-Cell disease/Leroy (ML II)
Pseudo-Hurler Polydystrophy (ML III)
Other storage disorders
Multiple Sulfatase Deficiency
Carbohydrate-Deficient Glycoprotein Syndrome
GM I Gangliosidosis
Geleophysic Dysplasia

2. Dysostosis multiplex

Several MPS types and other storage disorders share characteristic skeletal features revealed by X-ray radiological examination that is described as dysostosis multiplex (Table 1). The occurrences of any and some of these typical radiologic manifestations can indicate the presence of one of these disorders and warrant further clinical examination. In MPS, dysostosis multiplex generally involves malformations of the skull, thorax, spine, pelvis, long bones and hands. The more features of dysostosis multiplex that are present, the more likely that it represents a case of MPS disease.

The *skull* of patients with MPS often shows an abnormal J-shaped sella turcica and a thickened diploic space (Fig. 1). The shape of the sella is characteristic, but not diagnostic of MPS disorders.

In the *thorax*, MPS often manifests as paddle-shaped (oar-shaped) ribs, which are widened anteriorly and tapered posteriorly (Fig. 2). Also common, but less characteristic for MPS, are the short and thickened clavicles (Fig. 2).

In the *spine*, dysostosis multiplex shows as multiple superiorly notched (inferiorly beaked) vertebrae, and often posterior scalloping, at the thoraco-lumbar junction (Fig. 3). A combination of superior notching and posterior scalloping is very typical for MPS. In MPS IVA (Morquio syndrome), vertebral bodies are more typically middle-beaked.

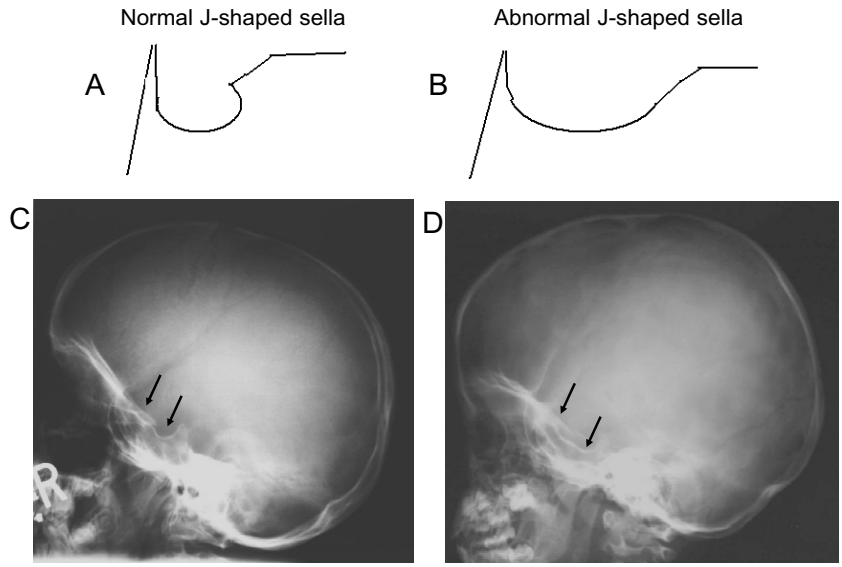

Fig. 1. Manifestations of dysostosis multiplex in the skull. (A) normal J-shaped sella turcica, (B) abnormal J-shaped sella typical for MPS. Radiographs showing (C) the skull of a patient with normal diploic plates and mildly abnormal J-shaped sella (arrows), and (D) the skull of a patient with thickened diploic plates and severe J-shaped sella (arrows)

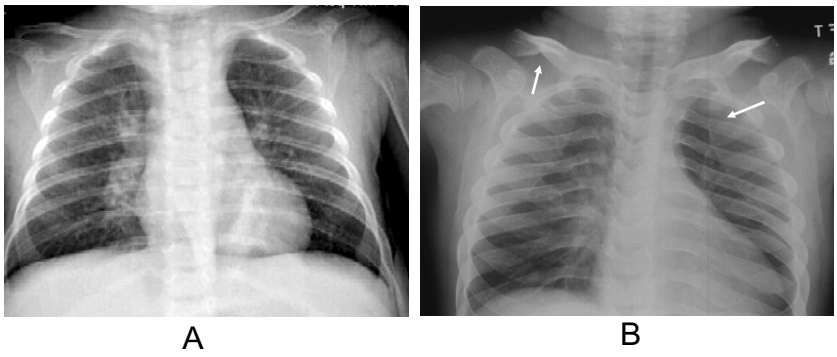

Fig. 2. Manifestations of dysostosis multiplex in the thorax. Radiographs showing (A) a normal chest and (B) a chest of an MPS patient showing paddle-shaped ribs and short thickened clavicles (arrows).

The *pelvis* of MPS patients is often characterized by rounded iliac wings and inferior tapering of the ilea (Fig. 4), with the lateral aspect of the ileum merging and tapering into the acetabular roof region. Inferior tapering is very typical for MPS disorders. A newly discovered finding in MPS patients is a double wall in the lower ileal lateral walls (Fig. 4).

The *long bones* of MPS patients often show mildly hypoplastic epiphyses (Fig. 5). Other long bone deformities include hypoplastic or fragmented capital femoral epiphyses, proximal humeral notching, long and narrow femoral necks that can be eroded on both the lateral and the medial sides, hypoplastic distal ulnae, and thickened short diaphyses.

The *hands* of MPS patients typically show proximally pointed metacarpals. Metacarpals can be short and thick with thin cortices, even if proximal pointing is not present. Nonspecific findings include hypoplastic and irregular carpal bones, and irregularly shaped tarsal bones (Fig. 6).

3. Skeletal X-ray and neuroimaging findings in the spine

In most MPS types, deformities of the spine and the skull base and GAG deposits in the tissues surrounding the spinal cord can result in spinal cord compression.

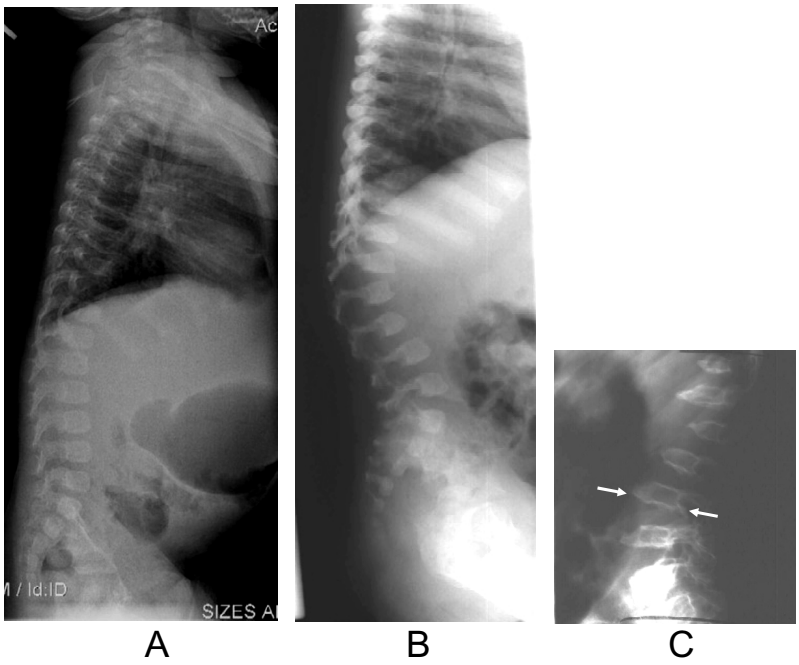

Fig. 3. Manifestations of dysostosis multiplex in the spine. Radiographs showing (A) a normal spine, (B) a spine of an MPS patient with several superior notched lumbar vertebrae, (C) vertebra showing middle beaking and posterior scalloping (arrows), as well as others which are superiorly notched.

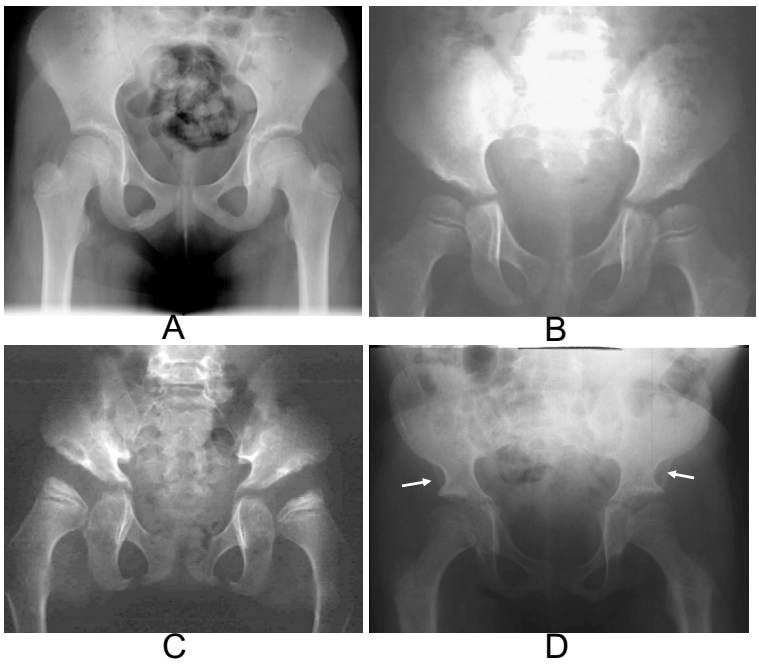

Fig. 4. Manifestations of dysostosis multiplex in the pelvis and hips. Radiographs showing (A) normal pelvis and hips, and pelvis and hips of MPS patients with (B) rounded iliac wings and mild ileal tapering, (C) capital femoral epiphyseal dysplasia and lower iliac wing tapering, (D) rounded iliac wings, double-contoured ileal lateral walls (arrows) and elongated femoral necks.

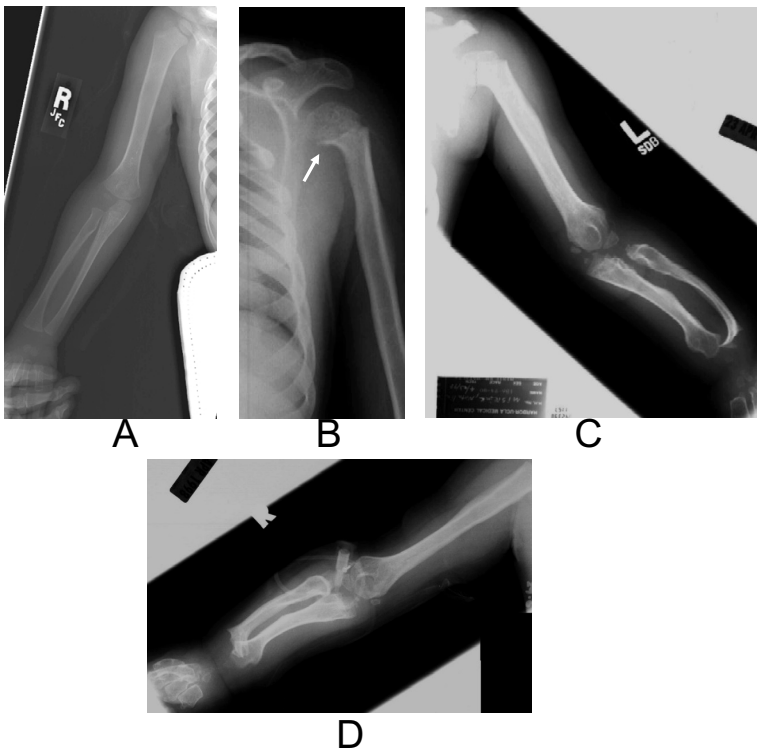

Fig. 5. Manifestations of dysostosis multiplex in long bones (humerus, radius and ulna). Radiographs showing normal humerus, radius and ulna (A), and humerus, radius and ulna of MPS patients with (B) proximal humeral notching (arrow), (C) humeral notching, distal radial and ulnar shortening with thick diaphyses (mesomelia), and (D) mesomelia and distal hypoplasia of the radius and ulna.

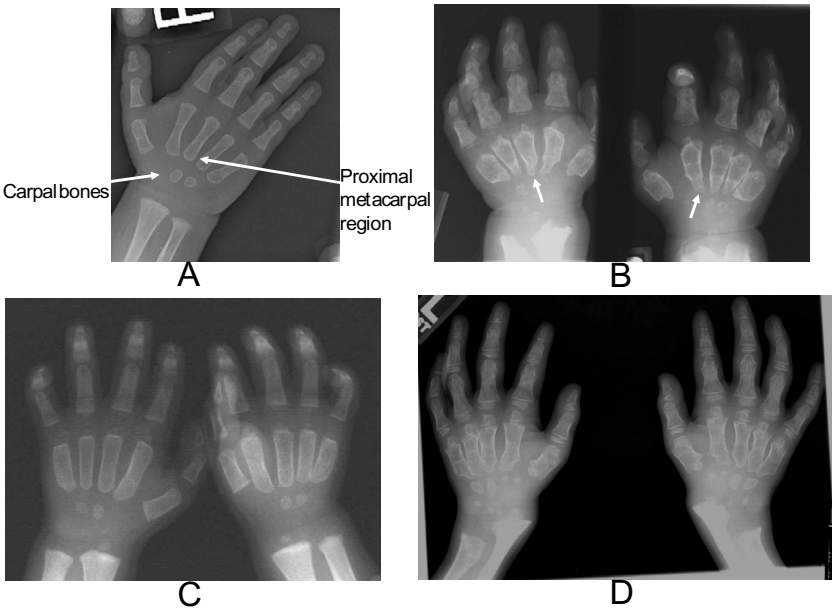

Fig. 6. Manifestations of dysostosis multiplex in the hands. Radiographs showing (A) a normal hand with arrows showing the regions that can be most severely affected in MPS, and the hands of MPS patients in (B) late infancy, with very severe proximal pointing, wide (expanded) short metacarpals and phalanges, and thin cortices (arrows), (C) early childhood, with moderately severe proximal pointing, and expanded metacarpals with thin cortices, (D) late childhood, with severe proximal pointing, thin cortices, small/irregular carpal bones, and ulnar hypoplasia.

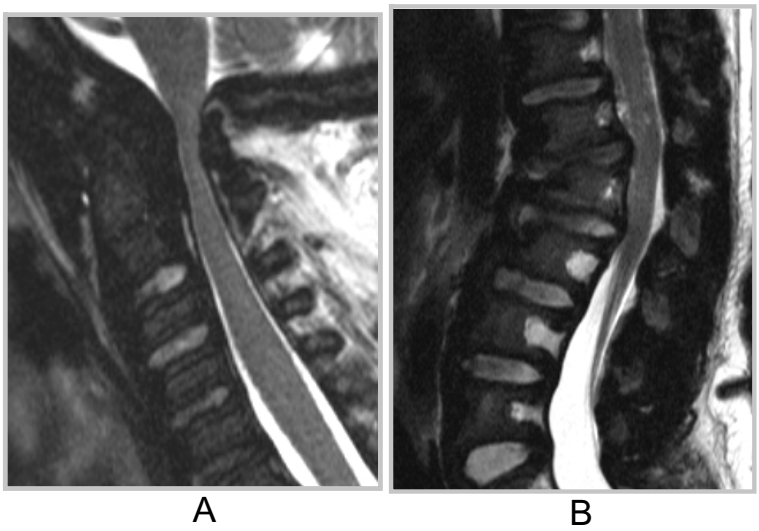

Fig. 7. Sagittal T2-weighted magnetic resonance imaging scans showing spinal cord compression in (A) the cervico-cranial region due to peri-odontoid soft tissue mass and (B) the thoraco-lumbar region due to beaked vertebrae.

If left untreated, spinal cord compression can lead to destruction of spinal cord tissue, also called compressive myelopathy, and in lumbar segment compression of neural roots. Spinal cord compression in MPS may involve multiple spinal cord levels, but is usually the result of spinal canal narrowing at the cervico-cranial or the thoraco-lumbar region (Fig. 7) [5,10,11,14–16]. Alterations of the spinal anatomy can be identified using imaging techniques such as skeletal X-ray, computed tomography (CT), and magnetic resonance imaging (MRI). These imaging tools can also be useful for surgical or medical planning, and for assessing the impact of treatment. Conventional radiography provides two-dimensional radiographic images of the skeleton and can be used to detect gross anomalies of the spine such as scoliosis, kyphosis (curvature of the upper spine or hunch back), abnormalities in cranio-cervical anatomy, spinal stenosis and spinal instability. It is particularly useful for helping to make an initial diagnosis. More subtle osseous anomalies can be identified using CT of the spine. This technique allows the generation of three-dimensional images from a large series of two-dimensional X-ray images. As is often done with cervical spine X-rays in extension and flexion positions, MRI and CT techniques can also be used for detecting dynamic instability and for surgical planning. When metal artefacts preclude high-quality MRI, then CT may be the preferred imaging technique. However, although CT is a powerful tool for imaging the bone, it is less potent when it comes to imaging soft tissue. The most powerful tool for imaging soft tissues such as the brain, the spinal cord, and the soft tissues including the meninges surrounding the cord is MRI, as it images the soft tissues more clearly and provides greater contrast between the different soft tissues in the body. It can be used for detecting the cause of spinal cord or nerve root compression, with the goal of planning surgical relief of these problems. In addition, it gives clues for practical and research purposes about disc disease and can be used for detecting abnormalities of the skull base and cranio-cervical instability. For routine imaging of the spine and the detection of spinal cord compression and injury in MPS patients, it is desirable that both T1 weighted axial and sagittal and T, weighted axial and sagittal MRI scans are performed. Steady State Free Procession (SSFP) is another useful tool for routine diagnosis in these patients. The latter technique produces MRI images with increased signal from fluid and can be used to detect cerebrospinal fluid with certainty. The detection of cerebrospinal fluid is particularly useful in patients where narrowing of the space between the spinal cord and the dura mater accelerates the movement of the cerebrospinal fluid. This acceleration causes a so called “dephasing” of the fluid, which shows black instead of white on T2 weighted sequence. In this case, it is impossible to distinguish whether the cerebrospinal fluid is either gone, which indicates spinal stenosis, or just dephased. The cerebrospinal fluid can also be imaged directly using contrast cisternography, or an MR phase contrast cerebrospinal fluid flow study can be performed to demonstrate the movement of the

fluid and infer from that whether or not there is complete stenosis.

When SSFP, cisternography, and the cerebrospinal fluid flow study cannot show the presence of cerebrospinal fluid, diffusion weighted imaging can be used to assess whether there is any restriction in the movement of water in the tissue [3]. Restriction of diffusivity in an area of spinal stenosis indicates tissue compression. An alteration in diffusivity might predict and correlate with early dysfunction of the cord, before the spinal cord is irreversibly damaged, and possibly even before the patient shows symptoms of spinal cord compression. Therefore, diffusion imaging might be useful as a tool for assessing the impact of surgical intervention or medical treatment. However, it yet needs to be elucidated whether this tool can also be used to measure improvements in diffusion after surgical or medical intervention. Other imaging techniques that can be useful for identifying alterations of the spinal cord include fluid-attenuated inversion recovery (FLAIR), and a number of dynamic techniques including dynamic flexion-extension, and possible diffusion tensor imaging (DTI).

4. Neuroimaging findings in the brain

Brain anomalies are common in MPS. Basically, the brain pathology in MPS is believed to be a consequence of complex mechanisms initiated by lysosomal accumulation of GAGs in neurons and microglia [9]. Common findings on brain MRI include brain atrophy, white matter lesions, and hydrocephalus (Fig. 8) [6,17,18]. Intellectual deficit is characteristic for MPS IH (Hurler syndrome), the severe forms of MPS II (Hunter syndrome) and VII (Sly syndrome), and all subtypes of MPS III (Sanfilippo syndrome). It can be due to brain atrophy, which provides a marker of axonal loss [12, 13]. Indeed, brain atrophy has been found to be more common in MPS I, II and III than in MPS VI [6,12, 17]. Intellectual deficit is also suggested to be related to the presence of extensive white matter lesions [4, 17]. However, although MPS VI patients are usually not intellectually challenged, they can still show white matter lesions [2]. The appearing of these lesions probably involves the deposition of gangliosides (GM2 and GM3) in the brain [17]. White matter lesions have been shown to become more extensive with time, especially in MPS II patients, suggesting that it is a progressive phenomenon [17].

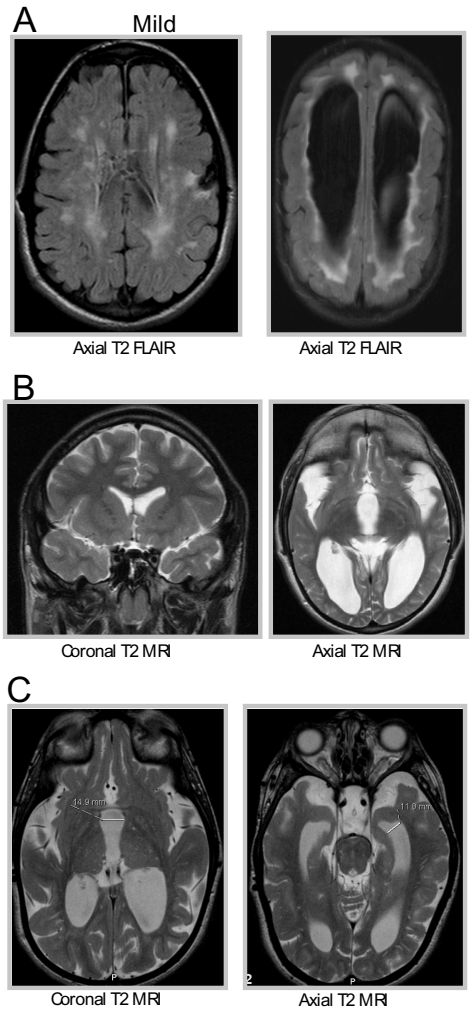

Fig. 8. Cerebral magnetic resonance imaging (MRI) scans showing (A) white matter (WM) lesions (hyperintense regions): periventricular + subcortical WM lesions (left), diffuse WM lesions (right); (B) mild (left) and severe (right) cortical atrophy (widening of the sylvian fissure and/or hemispheric fissure); (C) ventricular enlargement. FLAIR: fluid-attenuated inversion recovery.

Enlarged ventricles might be the consequence of either brain atrophy and white matter disease or hydrocephalus. Typical symptoms of hydrocephalus include enlargement of the head, headaches, and vomiting, but it can also result in sudden blindness due to optic nerve compression and injury. However, MPS patients usually do not show typical clinical symptoms of hydrocephalus or papillary oedema (unpublished observations). Therefore, ventricle enlargement may more commonly be due to brain atrophy in these patients.

Brain involvement in MPS is usually suspected on the basis of intellectual delay by certain age milestones. In patients with severe MPS II, for example, the ability

to sit, walk, and speak tend to occur later than in unaffected children [19]. However, as mentioned before, brain anomalies occurring in MPS patients are not limited to intellectual deficits in MPS patients; white matter lesions and ventricular enlargement have also been described for MPS VI patients who usually have normal intelligence [17]. The dysostosis multiplex finding of an abnormal J-shaped sella turcica appears to be also secondary to GAG accumulation with sella erosion.

Changes in brain morphology are generally assessed using MRI, which can provide accurate, reproducible and quantitative measures of brain atrophy, white matter lesion load, and ventricular size *in vivo*. It also allows monitoring of disease progression and therapeutic response as illustrated in Krabbe disease, which is another lysosomal storage disease characterized by central system degeneration [7].

5. Imaging problems in MPS patients

MPS patients are among the most difficult patients for performing advanced imaging studies for a variety of reasons. First, many of these patients are intellectually challenged and not very cooperative. Moreover, airway problems are common in these patients, which can be a problem for general anaesthesia, as well as the previously mentioned cervical spine instability. If patients are not generally anesthetized, the imaging studies are often compromised by claustrophobia and motion artefacts, especially in young children. CT and MRI imaging of the thoracic spine is complicated by both cardiac and respiratory motion. Sagittal images are most useful for looking for stenosis, but the presence of scoliosis or kyphosis makes sagittal imaging very difficult. Finally, metal artefacts, such as spinal rods, can considerably compromise MRI.

6. Assessing skeletal X-ray and neuroimaging severity for MPS patients

No international standards for evaluating radiologic/imaging findings in MPS currently exist. However, regular and systematic evaluation of MPS patients using a reproducible scoring system could be very useful for evaluating and monitoring these patients, for surgical planning, and for measuring the impact of treatment. In addition, standardized evaluation of radiologic findings might provide a better insight into the natural course of bone disease, and spinal cord and brain involvement in the different MPS types. Some issues remain when it comes to quantifying dysostosis multiplex. Particularly the great variety in bone shapes among individuals including even interfamilial variability makes it very difficult to quantify subtle skeletal changes. Due to these issues, the development of a scoring system for dysostosis multiplex remains a major challenge that warrants further insight into the exact mechanisms that cause these typical skeletal features of MPS.

Some efforts have been made to develop MRI scoring systems for spinal cord and brain disease in MPS. A study presented at the Annual Symposium of the Society of Inborn Errors of Metabolism (SSIEM 2008) used a scoring system for spinal cord involvement that was developed at the Hospital de São João (Porto, Portugal) [1]. This scoring system includes cervical MRI findings of odontoid hypoplasia, peri-odontoid soft tissue mass, posterior longitudinal ligament hypertrophy, subluxation of the C1-C2 articulation, and thoracolumbar findings of the beaked vertebra, concavity of the vertebral body posterior wall, kyphosis and spinal cord involvement as measures for the prognosis and monitoring of the MPS patients and for taking treatment decisions (Table 2). Another scoring system presented at SSIEM2008 was adapted from previous work for evaluating brain disease in MPS patients [2]. As measures of the brain involvement in MPS, this scoring system uses T2 weighted imaging hyperintense areas, cortical atrophy, enlargement of the supratentorial ventricles, enlarged periventricular spaces at the basal ganglia/thalamus, corpus callosum and white matter, optic nerve sheath enlargement and sella turcica enlargement (Table 3). In the past, comparable scoring systems have been used for clinical research in MPS patients [5,10, 12].

7. Conclusions

The MPS diseases are characterized by specific skeletal and CNS features that may be viewed by X-ray or advanced neuroimaging technology such as CT or MRI; the evaluation of which can make a large contribution to the diagnosis and follow-up of patients with MPS. These techniques can also be useful tools for surgical and medical planning and for assessing the impact of therapy. There is need for standardized procedures for evaluating and monitoring neuroimaging alterations in MPS patients, so that proper treatment can be offered before these alterations have caused irreversible damage.

Table 2
Scoring severity of spinal magnetic resonance imaging (MRI) findings [1]

Cervical MRI	
Odontoid hypoplasia	Not present Present
Peri-odontoid soft tissue mass	Not present Present
Posterior longitudinal ligament hypertrophy	Not present Present
Subluxation C1-C2	Not present Present
Intraspinal compromise	1 = Subarachnoid space involvement without spinal cord insult 2 = Spinal cord compression without signal changes 3 = Spinal cord compression with T2 hyperintense area
Thoraco-lumbar MRI	
Beaked vertebra	Not present Present
Concavity of the vertebral body posterior wall	Not present Present
Kyphosis	Not present Present
Intaspinal compromise	1 = Spinal canal narrowing without roots or medullary cone involvement 2 = Spinal canal narrowing with roots stretching due to bone changes

Table 3
Scoring severity of brain magnetic resonance imaging (MRI) findings. BG+T: basal ganglia/thalamus, CC: corpus callosum, PVS: perivascular spaces, WM: white matter [2]

T2 weighted imaging hyperintense areas	0 = No hyperintense lesions P1 = Hyperintense lesions confined to periventricular WM P2 = Hyperintese lesions at periventricular and subcortical WM
D = Hyperintense diffuse changes in WM signal	
Perivascular spaces enlargement at the WM, BG+T, and CC	0 = None 1 = PVS number $<$ 10 and PVS size $<$ 3 mm 2 = PVS number $\geqslant$ 10 and PVS size $<$ 3 mm 3 = PVS number $\geqslant$ 10 and PVS size $\geqslant$ 3 mm
Cortical atrophy	0 = None 1 = Mild widening of the sylvian fissure and/or the interhemisferic fissure $\leqslant$ 3 mm 2 = Moderate widening of the sylvian fissure and/or the interhemisferic fissure $>$ 3–$<$ 5 mm 3 = Severe widening of the sylvian fissure and/or the interhemisferic fissure $\geqslant$ 5 mm
Supratentorial ventricles enlargement	0 = None 1 = Width of III ventricle $<$ 5 mm, without temporal horn dilatation 2 = Width of the III ventricle between 5 and 10 mm and temporal horn dilatation 3 = Width of the III ventricle $>$ 10 mm
Sella turcica enlargement	Not present Present
Optic nerve sheath enlargement	0 = Nerve sheath diameter $\leqslant$ 5.7 mm 1 = Unilateral nerve sheath diameter $>$ 5.7 mm 2 = Bilateral nerve sheath diameter $>$ 5.7 mm

Acknowledgments

This manuscript was developed as the result of a meeting of experts entitled "Promoting Bone Health in MPS VI: Framing New Therapies" held in Oakland, California in October, 2008. Editorial assistance in the development of this manuscript was provided by Ismar Healthcare NV-SA, Belgium, and was paid for by BioMarin Pharmaceutical Inc., Novato, CA. BioMarin reviewed the manuscript, but had no control in the content presented and discussed at the meeting. All authors participated in the development and writing of the manuscript and are fully responsible for its content.

Conflicts of interest

Ralph Lachman has received consulting payment from BioMarin Pharmaceutical Inc. Elisa Leão Teles, Sérgio Castro, Margarida Ayres Basto, Alexandra Adams and Kenneth Martin acknowledge no conflicts of interest.

References

[1] S. Castro, M. Ayres-Basto, E. Rodrigues, M.M. Campos, J. Guimaraes and E. Leão-Teles, Vertebro-medular imaging findings in mucopolysaccharidosis types II and IV, *J Inherit Metab Dis* **31**(Suppl 1) (2008), 109.

[2] S. Castro, M. Ayres-Basto, E. Rodrigues, J. Guimaraes, A. Magalhães and E. Leão-Teles, Cerebral imaging findings in mucopolysaccharidosis types II and IV, *J Inherit Metab Dis* **31**(Suppl 1) (2008), 110.

[3] D. Facon, A. Ozanne, P. Fillard, J.F. Lepeintre, C. Tournoux-Facon and D. Ducreux, MR diffusion tensor imaging and fiber tracking in spinal cord compression, *AJNR Am J Neuroradiol* **26** (2005), 1587–1594.

[4] O. Gabrielli, G. Polonara, L. Regnicolo, V. Petroni, T. Scarabino, G.V. Coppa and U. Salvolini, Correlation between cerebral MRI abnormalities and mental retardation in patients with mucopolysaccharidoses, *Am J Med Genet A* **125A** (2004), 224–231.

[5] D.G. Hughes, R.D. Chadderton, R.A. Cowie, J.E. Wraith and J.P.R. Jenkins, MRI of the brain and craniocervical junction in Morquio's disease, *Neuroradiology* **39** (1997), 381–385.

[6] C. Lee, T.E. Dineen, M. Brack, J.E. Kirsch and V.M. Runge, The mucopolysaccharidoses: characterization by cranial MR imaging, *AJNR Am J Neuroradiol* **14** (1993), 1285–1292.

[7] P. McGraw, L. Liang, M. Escolar, S. Mukundan, J. Kurtzberg and J.M. Provenzale, Krabbe disease treated with hematopoietic stem cell transplantation: serial assessment of anisotropy measurements-initial experience, *Radiology* **236** (2005), 221–230.

[8] E.F. Neufeld and J. Muenzer, The mucopolysaccharidoses, in: *The metabolic and molecular bases of inherited disease*, C.R. Scriver, A.L. Beaudet, W.S. Sly and D. Valle, eds, McGraw-Hill Medical Publishing Division, New York, 2001, pp. 3421–3452.

[9] K. Ohmi, D.S. Greenberg, K.S. Rajavel, S. Ryazantsev, H.H. Li and E.F. Neufeld, Activated microglia in cortex of mouse models of mucopolysaccharidoses I and IIIB, *Proc Natl Acad Sci USA* **100** (2003), 1902–1907.

[10] V.J. Parsons, D.G. Hughes and J.E. Wraith, Magnetic resonance imaging of the brain, neck and cervical spine in mild Hunter's syndrome (mucopolysaccharidoses type II), *Clin Radiol* **51** (1996), 719–723.

[11] A.O. Ransford, H.A. Crockard, J.M. Stevens and S. Modaghegh, Occipito-atlanto-axial fusion in Morquio-Brailsford syndrome. A ten-year experience, *J Bone Joint Surg Br* **78** (1996), 307–313.

[12] T. Seto, K. Kono, K. Morimoto, Y. Inoue, H. Shintaku, H. Hattori, O. Matsuoka, T. Yamano and A. Tanaka, Brain magnetic resonance imaging in 23 patients with mucopolysaccharidoses and the effect of bone marrow transplantation, *Ann Neurol* **50** (2001), 79–92.

[13] Y. Takahashi, K. Sukegawa, M. Aoki, A. Ito, K. Suzuki, H. Sakaguchi, M. Watanabe, K. Isogai, S. Mizuno, H. Hoshi, K. Kuwata, S. Tomatsu, S. Kato, T. Ito and N. Kondo, Evaluation of accumulated mucopolysaccharides in the brain of patients with mucopolysaccharidoses by ^{1}H-magnetic resonance spectroscopy before and after bone marrow transplantation, *Pediatr Res* **49** (2001), 349–355.

[14] N. Tamaki, N. Kojima, M. Tanimoto, T. Suyama and S. Matsumoto, Myelopathy due to diffuse thickening of the cervical dura mater in Maroteaux-Lamy syndrome: report of a case, *Neurosurgery* **21** (1987), 416–419.

[15] V. Tandon, J.B. Williamson, R.A. Cowie and J.E. Wraith, Spinal problems in mucopolysaccharidosis I (Hurler syndrome), *J Bone Joint Surg Br* **78** (1996), 938–944.

[16] J.A. Thorne, M. Javadpour, D.G. Hughes, E. Wraith and R.A. Cowie, Craniovertebral abnormalities in Type VI mucopolysaccharidosis (Maroteaux-Lamy syndrome), *Neurosurgery* **48** (2001), 849–852.

[17] L. Vedolin, I.V. Schwartz, M. Komlos, A. Schuch, A.C. Azevedo, T. Vieira, F.K. Maeda, A.M. Marques da Silva and R. Giugliani, Brain MRI in mucopolysaccharidosis: effect of aging and correlation with biochemical findings, *Neurology* **69** (2007), 917–924.

[18] L. Vedolin, I.V.D. Schwartz, M. Komlos, A. Schuch, A.C. Puga, L.L.C. Pinto, A.P. Pires and R. Giugliani, Correlation of MR imaging and MR spectroscopy findings with cognitive impairment in mucopolysaccharidosis II, *AJNR Am J Neuroradiol* **28** (2007), 1029–1033.

[19] I.D. Young and P.S. Harper, The natural history of the severe form of Hunter's syndrome: a study based on 52 cases, *Dev Med Child Neurol* **25** (1983), 481–489.