# Imaging findings of mucopolysaccharidoses

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Learning objectives

The aim of this exhibit is to describe clinical features and imaging findings of mucopolysaccharidoses (MPS).

We discuss briefly several clinical properties of these metabolic disorders, reporting many epidemiological and pathophysiological data from old and recent literature.

We describe radiological and neuroradiological findings encountered in patients with MPS, to help radiologists in their diagnosis and management.

Background

MPS represent a heterogeneous group of inheritable lysosomal storage diseases, in which a deficiency of one or more enzymes involved in glycosaminoglycan (GAG) degradation results in the accumulation of undegraded GAGs in lysosomes. The storage of incompletely broken down GAGs - dermatan sulphate (DS), heparan sulphate (HS), keratan sulphate (KS) and chondroitin sulphate (CH) - leads to a progressive damage of affected tissues, including heart, respiratory system, bones, joints and central nervous system [1].

Seven types of MPS have been described in literature, caused by 11 different enzymatic deficiencies, with a rare incidence for single disease but a considerable overall incidence of 1 in 25000 live births. They are transmitted in an autosomal recessive fashion, except for MPS II, which is X-linked.

The ubiquitous nature of GAGs within the connective tissue of the body results in a wide range of clinical effects. The type of GAGs stored and the classification of diseases depend on the specific enzyme deficiency [2]. The table outlines (Fig. 1 on page 3) show the latest classification, with details of the accumulating compounds and enzymes deficiencies, as well as the eponym used for each condition.

Like most genetic disorders, there is a continuous spectrum of phenotype from the very severe to the most mildly affected; many mutations are responsible for these phenotypic differences. The typical symptoms include organomegaly, dysostosis multiplex, mental retardation and developmental delay; hearing, vision and cardiovascular function may also be affected. MPS are usually fatal diseases (especially neuronopathic forms of MPS), with average expected life span of one or two decades, though patients with milder forms can survive into adulthood [1-2].

MPSs are recognized through the combination of the clinical picture and the analysis of urinary GAGs, but this method cannot distinguish subgroups; definitive diagnosis is
usually possible through enzymatic assays of the defective enzyme in cultured fibroblasts or leukocytes [1].

Therapy of MPS consists mainly of symptomatic/supportive treatments, such as decompression of the cranio-cervical narrowing, tracheostoma insertion or corneal transplantation. In recent years there has been development of novel therapies including enzyme replacement therapies and substrate inhibition therapy [3].

Images for this section:

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Fig. 1: Figure 1. Summary of epidemiological, pathophysiological and clinical features characterizing different types of MPS.
Radiological and neuroradiological imaging findings have been described. Most important radiological findings occur in the skeletal system with multiplex dysostosis (Fig. 2 on page 20, a complex of anomalies involving several bones: skull, thorax, spine, pelvis, long bones, hands and feet [4]. Skeletal involvement dominates the clinical picture in MPS IV and MPS VI. Patients can also show hepatomegaly and splenomegaly [4-5].

Among neuroradiological features, MRI is able to detect abnormal signal intensity in the white matter, dilatation of periventricular spaces, widening of cortical sulci, brain atrophy and enlargement of extraventricular spaces; GAGs storages in the meningeal layers may lead to spinal cord compression. Central nervous system involvement is a prominent feature of MPS I, II, III and VII [5-6].

"Radiological Imaging Findings"

Dysostosis multiplex is the constellation of radiographic malformations classically seen in MPS. The development of such skeletal malformations correlates with the pathogenesis of the disease, and particularly with the reduced resistance of the bone matrix caused by a deficit in metabolism of GAGs [5].

Because the clinical presentation and the development of the disease may range within and between the seven major types of MPS, the distribution and the extent of bone alterations are not always encountered with the same morphological appearance; nevertheless, a certain uniformity of signs can be recognized in radiological images.

The skull of patients with MPS is often characterized by an abnormal "J-shaped" conformation of sella turcica (Fig. 3 on page 21) - usually wide with long clinoid apophyses and horizontal orientation.
Fig. 3: Figure 3. Magnified views of lateral skull radiographs. Normal skull, presenting a regularly shaped sella (Figure 3A). Skull of a 2-year-old patient affected by MPS VI; the abnormal J-shaped sella (white arrow), is clearly recognizable (Figure 3B).

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY
The cortical bone of the skull is thickened. The premature closure of the sagittal suture is responsible for the development of macrocephaly with dolicocephaly, plus the metopic perisutural hyperostosis causes a vertical frontal crest.

The most important facial anomalies are represented by the lack of pneumatization of mastoid cells and paranasal cavities; in addition, prognatism is due to an obtuse mandibular angle and the widely spaced teeth.

The most important thoracic anomaly concerns ribs, which can be "paddle-shaped" or "oar-shaped" (widened anteriorly and tapered posteriorly). Another feature that can also be found is the short and thickened aspect of the clavicles (Fig. 4 on page 22) [7].
**Fig. 4**: Figure 4. Frontal radiographs showing a normal chest in a 10-year-old girl (Figure 4A) and a chest of a 10-year-old girl affected by MPS IV (Figure 4B), the later presenting ribs (white arrowheads) tapered proximally and wider distally; broad and short clavicles (white arrow) are also appreciated. Scapulae are small with poorly formed glenoid cavities (Figure 4B).

**References**: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY

Issues involving the spine are extremely common ([Fig. 5 on page 23](#) and [Fig. 6 on page 24](#)) and are the basis of important complications due to compressive effects on the spinal cord and emerging nerve roots.
Fig. 5: Figure 5. Sagittal T2-weighted fast spin-echo image (Figure 5A); sagittal T1-weighted fast spin-echo image (Figure 5B). The figures show the entire spine of a 14-year-old female with MPS VI: narrowing of the craniocervical junction (white arrow), vertebral bodies deformities (curved white arrow) and nucleus pulposus hypotrophy (white arrowhead) are well depicted; gibbus at thoracolumbar region is also seen.

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY

At the cranio-vertebral junction level, the following abnormalities can be found:

- odontoid process displasia-hypoplasia;
- atlantoaxial instability or subluxation;
- periodontoid tissue and ligaments thickening;
- spinal stenosis.

These features represent a critical aspect in MPS (particularly in MPS IV), causing cervical stenosis and cord compression with resultant myelopathy. MRI is more appropriate to the evaluation of spinal cord alterations.
Malformations involving the shape of vertebral bodies, flattened and rounded, are usually observed (Fig. 7 on page 25; in the thoraco-lumbar tract the vertebral body can be deficient in its anterosuperior corner: as a consequence, the apparent prolongation of the anteroinferior corner results in an "anterior beaking" aspect (Figure 7C). When hypoplasia of both anterior corners occurs, the vertebral body is wedge-shaped (Figure 7D).

Fig. 7: Figure 7. X-ray of multiplex dysostosis of the spine. A 4-year-old child with Hurler syndrome shows vertebral bodies rounded (white arrow, figure 7A and figure 7B). The "anterior beaking" aspect (white arrowhead, figure 7C) with posterior scalloping and the platyspondyli with "wedge-shaped" deformity (curved white arrow, figure 7D) are observed in other radiographs of different MPS patients.

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY
These vertebral morphologic changes may progressively evolve to gibbus deformity (Fig. 8 on page 26) - particularly in MPS I.
Fig. 8: Figure 8. 45-year-old female suffering from MPS IV (Morquio disease). Sagittal MRI T2-weighted (Figure 8A) and T1- weighted (Figure 8B) fast spin-echo acquisitions of the cervico-thoracic spine show severe kypho-scoliosis with narrowing of the spinal canal.

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY
In the pelvis, X-ray examination often shows rounded iliac wings and inferior tapering of the ileum (Fig. 9 on page 27). Hip dysplasia MPS-related is very common with poorly developed acetabulum, underdevelopment of the medial portion of the proximal femoral epiphysis and coxa valga [8]. This alteration has not been shown to respond to medical therapy, so for these children surgical reconstruction is often required; the target of this treatment is the optimization of hip mechanics [4].
Fig. 9: Figure 9. X-ray of pelvis in a healthy child (Figure 9A). Images of pelvis of MPS patients (Figures 9B-D), showing typical imaging findings of disease: rounded iliac wings, inferior tapering of the ilia with a poorly developed acetabulum, underdeveloped medial portion of the proximal femoral epiphysis, increased coxofemoral joint space and coxa valga are well depicted into figures 9B-D.

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY

Knees can also be involved, developing genu valgum (Fig. 10 on page 28).
Fig. 10: Figure 10. 8-year-old boy with MPS IH. Anteroposterior femoral x-ray image (Figure 10A) showing bilateral genu valgum; proximal and distal epiphyses are flared and irregular. Diffuse cortical thinning and osteopenia are also observed (Figure 10B).

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY

In MPSs patients, the long bones are often characterized by mildly hypoplastic epiphyses. Other anomalies that can be found are the notching of the proximal part of the humerus and the long and narrow aspect of the femoral neck (Fig. 11 on page 29).
Fig. 11: Figure 11. 6-year-old boy with MPS II. Radiographs show several morphological appearances of multiplex dysostosis in long bones, with proximal humeral notching (white arrow, figure 11A), long and narrow femoral neck (curved white arrow, figure 11B), frayed and flared tibial metaphyses (Figure 11C). All segments, particularly those of the upper limb, are short and squat; they also have hypoplastic epiphyses, cortical thinning and flaring of the diaphyseal canal.

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY

Almost all forms of MPSs show distortion of the hand (Fig. 12 on page 30) and foot structure. Carpal and tarsal bones are hypoplastic and irregularly shaped; the metacarpal bones are proximally pointed and a "claw hand" can also be found due to the failing of digits to extend completely. The subcutaneous tissues on the surface of the hands are thickened, contributing to the poor function of the digits. Distal ulna and radius can be hypoplastic and have a "V-shaped" appearance; this oblique deformity of both bones at their terminal ends results in the alteration of the carpal angle.
Fig. 12: Figure 12. Dysostosis multiplex of hands and wrists in a 5-year-old boy (Figure 12B) and in a 15-year-old female (Figure 12D), both affected by MPS VI (radiographs are compared with normal hands and wrists belonging to subjects of the same age, respectively figure 12A and figure 12C). The main imaging findings encountered in these areas are reported: the V-shaped hypoplastic distal ulna and radio (white arrow), the presence of small irregular carpal bones (curved white arrow), the broad and proximally pointed short metacarpals (white arrowhead), and the bullet-shaped phalanges (empty white arrow).

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY
Abnormal storage of mucopolysaccharides and glycosaminoglycans causes liver and spleen enlargement; it also damages cartilage layers and synovial recesses in the joints. On MRI images, growth plate is irregularly enlarged, with multiple defects and erosions well depicted on coronal fast spin-echo proton-density weighted images (Fig. 13 on page 31).
Fig. 13: Figure 13. 15-year-old female affected by MPS VI. Coronal MRI fast spin echo image (Figure 13A) and spoiled gradient echo image (Figure 13B) show irregularly enlarged growth plate, with multiple defects and/or erosions.

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY

"Neuroradiological Imaging Findings"

Neurological involvement in MPSs is very common; the MRI abnormalities show a large spectrum of severity, from negligible to severe. Main neuroradiological features observed are:

- Abnormal signal intensity in the white matter;
- Dilatation of periventricular spaces;
- Widening of cortical sulci, brain atrophy and enlargement of extraventricular spaces;
- Spinal cord compression;
A typical neuroradiological imaging finding is represented by **focal or diffuse white matter lesions**, detected as high intensity areas on T2-weighted sequences.

**Diffuse white matter lesions** are located symmetrically in the periventricular white matter ([Fig. 14 on page 32](#)), although also seen as patchy lesions in the subcortical region. They derive from the delay of myelination in young children and on progressive demyelination in the course of the disease; these lesions can also reflect gliosis [9-10].

![Fig. 14](image)

**Fig. 14**: Figure 14. 12-year-old female affected by MPS VI. Axial T2-weighted fast spin-echo (Figure 14A), T2-weighted FLAIR (Figure 14B) and coronal T2-weighted fast spin-echo (Figure 14C) images of the brain show symmetrical diffuse increased signal intensity of periventricular white matter, with enlargement of subarachnoid spaces in the middle cranial fossa and ventriculomegaly. Midsagittal T2-weighted scan shows dilated perivascular spaces within the corpus callosum (figure 14D).

**References**: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY

**Focal white matter lesions** consist of multiple small spot-like areas isointense to the cerebrospinal fluid (CSF): they are represented by perivascular lacunae due to the accumulation of GAG at the Virchow-Robin spaces ([Fig. 15 on page 33](#)). Corpus callosum, best depicted on sagittal images, can be the only location of these lesions, but
usually they are also encountered in the parietal and occipital lobe, in the basal ganglia, at the grey-white matter junction level and in the thalamus [9-10].

**Fig. 15**: Figure 15. 15-year-old female affected by MPS VI. Axial T2-weighted fast spin-echo images (Figure 15A and figure 15C) and T2-weighted FLAIR acquisition (Figure 15B) show cribriform focal lesions of periventricular white matter (due to enlarged perivascular spaces), with ventricular enlargement. White matter lesions in the corpus callosum are well depicted by the mid-sagittal T2-weighted fast spin-echo acquisition (white arrowheads, figure 15D).

**References:** S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY

In addition, multifocal variable-sized hyperintense areas with a signal intensity which does not follow that of CSF may be detected on T2-weighted and on Fluid Attenuated Inversion Recovery (FLAIR) T2-weighted images; these areas may become extensive and confluent, probably reflecting gliosis.

**Communicating hydrocephalus** is a common finding caused by impaired circulation of CSF through the subarachnoid spaces or dysfunction of the arachnoid granulations, caused by thickening of the leptomeninges; the ventricular enlargement could be found with or without enlargement of subarachnoid spaces (Figures 13 and 14). A cystic-
appearing enlargement of the cerebellomedullary and/or suprasellar cisterna has been described. Ventricular enlargement might be the consequence of either brain atrophy and white matter disease or hydrocephalus [10].

**Brain atrophy** - seen as widened subarachnoid spaces and enlargement of the cortical sulci - is due to neuronal death and myelin loss. The atrophy of the brain occurs with white matter changes earliest in types I, II, III and VII, usually becoming visible during the first few years of life. In MPS types IV and VI, the white matter changes and atrophy may not become apparent until the second decade of life: these patients typically have normal intelligence and present for medical care with myelopathy.

**Macrocephaly** is commonly reported in patients with MPS: it results from a combination of hydrocephalus and mucopolysaccharide deposition within the brain, meninges, and skull. Other dysmorphic features, such as frontal prominence, scaphocephaly, short neck end enlarged tongue can be observed.

**Spinal cord compression** is most frequently located at the atlanto-axial (C1-C2) joint ([Fig. 16 on page 34](#)), and is particularly seen in patients with MPS type IV and MPS type VI. Atlanto-axial subluxation may occur in these patients as a result of several causes: laxity of the transverse ligament, dural thickening resulting from deposition of collagen and GAGs, hypoplasia or absence of the odontoid, anterior soft tissue mass of the odontoid (representing a combination of unossified fibrocartilage and reactive change), indentation of the posterior arch of C1. Ligamentous hypertrophy may develop in response to chronic subluxation at the C1 to C2 level, causing additional compression on the upper cervical spinal cord. Another cause of cord compression in these patients is gibbous formation in the thoracic spine, resulting from the malformations of vertebral bodies (most common in Morquio disease) [5,9-10].
Fig. 16: Figure 16. Sagittal T2-weighted fast spin-echo MRI acquisitions at the craniocervical junction in patient affected by MPS VI (the same patient as figure 15), before (Figure 16A) and after (Figure 16C) decompressive surgical procedure. Magnifications (Figure 16B and figure 16D) show a T2 hypointense lesion surrounding the odontoid process (white arrowhead, figure 16B) with marked narrowing of the foramen magnum and cord compression; the stenosis is moderately improved after surgery. Note also the abnormal J-shaped sella (white arrow, figure 16D).

References: S. Palmucci; Radiodiagnostic and Oncological Radiotherapy Unit, Catania, ITALY
Several orbital abnormalities can be found: thickening of the sclera and of the optic nerve sheath, optic canals narrowing, optic nerve atrophy (Fig. 17 on page 35).
Fig. 17: Figure 17. Optic nerve involvement in the same MPS patient as figure 15. Axial (Figure 17A), coronal (Figure 17B) and sagittal (Figure 17C) T2-weighted fast spin-echo acquisitions show widening of optic nerve sheath, with enlargement of perineural CSF space; angulation of right optic nerve is also observed.

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**Fig. 6:** Figure 6. MRI of the spine of a 12-year-old female with MPS VI. Sagittal T2-weighted (Figure 6A), sagittal T1-weighted (Figure 6B) and coronal T2-weighted (Figure 6C) fast spin-echo MRI acquisitions demonstrate marked kypho-scoliotic deformation of the spine, with disc hernias and vertebral bodies deformities.
Fig. 7: Figure 7. X-ray of multiplex dysostosis of the spine. A 4-year-old child with Hurler syndrome shows vertebral bodies rounded (white arrow, figure 7A and figure 7B). The "anterior beaking" aspect (white arrowhead, figure 7C) with posterior scalloping and the platyspondylia with "wedge-shaped" deformity (curved white arrow, figure 7D) are observed in other radiographs of different MPS patients.
**Fig. 8**: Figure 8. 45-year-old female suffering from MPS IV (Morquio disease). Sagittal MRI T2-weighted (Figure 8A) and T1- weighted (Figure 8B) fast spin-echo acquisitions of the cervico-thoracic spine show severe kypho-scoliosis with narrowing of the spinal canal.
Fig. 9: Figure 9. X-ray of pelvis in a healthy child (Figure 9A). Images of pelvis of MPS patients (Figures 9B-D), showing typical imaging findings of disease: rounded iliac wings, inferior tapering of the ilia with a poorly developed acetabulum, underdeveloped medial portion of the proximal femoral epiphysis, increased coxofemoral joint space and coxa valga are well depicted into figures 9B-D.
**Fig. 10**: Figure 10. 8-year-old boy with MPS IH. Anteroposterior femoral x-ray image (Figure 10A) showing bilateral genu valgum; proximal and distal epiphyses are flared and irregular. Diffuse cortical thinning and osteopenia are also observed (Figure 10B).
**Fig. 11**: Figure 11. 6-year-old boy with MPS II. Radiographs show several morphological appearances of multiplex dysostosis in long bones, with proximal humeral notching (white arrow, figure 11A), long and narrow femoral neck (curved white arrow, figure 11B), frayed and flared tibial metaphyses (Figure 11C). All segments, particularly those of the upper limb, are short and squat; they also have hypoplastic epiphyses, cortical thinning and flaring of the diaphyseal canal.
**Fig. 12:** Figure 12. Dysostosis multiplex of hands and wrists in a 5-year-old boy (Figure 12B) and in a 15-year-old female (Figure 12D), both affected by MPS VI (radiographs are compared with normal hands and wrists belonging to subjects of the same age, respectively figure 12A and figure 12C). The main imaging findings encountered in these areas are reported: the V-shaped hypoplastic distal ulna and radio (white arrow), the presence of small irregular carpal bones (curved white arrow), the broad and proximally pointed short metacarpals (white arrowhead), and the bullet-shaped phalanges (empty white arrow).
Fig. 13: Figure 13. 15-year-old female affected by MPS VI. Coronal MRI fast spin echo image (Figure 13A) and spoiled gradient echo image (Figure 13B) show irregularly enlarged growth plate, with multiple defects and/or erosions.
Fig. 14: Figure 14. 12-year-old female affected by MPS VI. Axial T2-weighted fast spin-echo (Figure 14A), T2-weighted FLAIR (Figure 14B) and coronal T2-weighted fast spin-echo (Figure 14C) images of the brain show symmetrical diffuse increased signal intensity of periventricular white matter, with enlargement of subarachnoid spaces in the middle cranial fossa and ventriculomegaly. Midsagittal T2-weighted scan shows dilated perivascular spaces within the corpus callosum (figure 14D).
**Fig. 15:** Figure 15. 15-year-old female affected by MPS VI. Axial T2-weighted fast spin-echo images (Figure 15A and figure 15C) and T2-weighted FLAIR acquisition (Figure 15B) show cribriform focal lesions of periventricular white matter (due to enlarged perivascular spaces), with ventricular enlargement. White matter lesions in the corpus callosum are well depicted by the mid-sagittal T2-weighted fast spin-echo acquisition (white arrowheads, figure 15D).
Fig. 16: Figure 16. Sagittal T2-weighted fast spin-echo MRI acquisitions at the craniocervical junction in patient affected by MPS VI (the same patient as figure 15), before (Figure 16A) and after (Figure 16C) decompressive surgical procedure. Magnifications (Figure 16B and figure 16D) show a T2 hypointense lesion surrounding the odontoid process (white arrowhead, figure 16B) with marked narrowing of the foramen magnum and cord compression; the stenosis is moderately improved after surgery. Note also the abnormal J-shaped sella (white arrow, figure 16D).
Fig. 17: Optic nerve involvement in the same MPS patient as figure 15. Axial (Figure 17A), coronal (Figure 17B) and sagittal (Figure 17C) T2-weighted fast spin-echo acquisitions show widening of optic nerve sheath, with enlargement of perineural CSF space; angulation of right optic nerve is also observed.
Conclusion

X-ray or CT/MRI may show specific skeletal and neurologic features in MPS patients, although it is not possible to accurately differentiate between MPS types based on radiological and neuroradiological characteristics. The evaluation of these imaging findings is useful for suggesting and supporting MPS as a possible diagnosis, for monitoring the chronic and progressive course of the disease, for surgical and medical planning and for assessing the impact of therapy.

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