Mucopolysaccharidoses: brain and spinal MRI findings.

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Learning objectives

-To know the different types of mucopolysaccharidosis (MPS), as well as its broad manifestations in cerebral and spine MRI.

-To know the evolution of the image findings with the passage of time, as well as to know the effectiveness of the current treatments that condition a greater or lesser radiological progression of the disease.
Background

Mucopolysaccharidoses are chronic diseases of lysosomal deposit, progressive and multisystemic, caused by deficiency of enzymes that degrade mucopolysaccharides, which causes a deposit in multiple tissues, including brain tissue, as well as causes alterations in the spine.

Through a review of cases of children with MPS from our hospital, typical images are described, mainly from the MPS type I (Hurler).
Findings and procedure details

Mucopolysaccharidoses (MPS) are chronic, progressive and multisystemic disorders whose pathological basis is an alteration in the lysosomal deposit due to deficiency of the enzymes that degrade the mucopolysaccharides, which causes an accumulation of them at the visceral level, musculoskeletal alterations and an abnormal urine elimination of these substances.

Clinical suspicion is essential to make the diagnosis, and radiological imaging methods and the determination of mucopolysaccharides in urine will establish a solid diagnosis, although the definitive diagnosis requires specific molecular and enzymatic studies. Prenatally, it is possible to diagnose this spectrum of diseases by analyzing the amniotic fluid.

At birth the children are apparently normal, and when the children begin to show abnormal phenotypes it means that the disease is probably progressing. The affection presents a multisystem distribution (musculoskeletal system, central nervous system, cardiovascular, digestive system, eyes and skin).

In mucopolysaccharidosis type 1 (which is where we are going to focus) there is a deficit of alpha-L-iduronidase, with a pathological accumulation of dermatan and heparan sulfate. The phenotypic spectrum has 3 clinical forms according to the age of presentation and the severity of the clinical expression:

- Hurler syndrome: the most common form and at the same time also the most severe form.
- Hurler-Scheie syndrome, a disease with an intermediate spectrum between the most severe and milder forms.
- The Scheie syndrome, which represents the mildest form (the diagnosis is made late, when children are practically prepubertal or adolescents, i.e., between 10 and 20 years old, with a normal life expectancy.

There are seven distinct types of MPS (I, II, III, IV, VI, VII, and IX; MPS type V and VIII are no longer used), which are divided further into subtypes according to the deficient enzyme and severity of the clinical picture (It has already been pointed out that the findings of all known entities will not be described, only the most typical and common findings). The overall estimated incidence is 1/25,000 individuals, although the incidence of each MPS type separately is much lower, on the order of one in 100,000 to one in 200,000 individuals.
CLINICAL MANIFESTATIONS

Cognitive impairment: MPS types I, II, III and VII. MPS type II can also be divided into severe (neuropathic) and mild (nonneuropathic) forms.

Mild or absence of manifestations: MPS type III.

Multisystemic abnormalities, especially skeletal involvement: MPS types I, II and VII.

No cognitive impairment but with neurologic disorders often secondary to bone changes, and myelopathy like the main clinical manifestation: MPS types IV and VI.

MPS type IX are very rare, and the main clinical feature reported is joint involvement.

Measurement of urinary glycosaminoglycans (GAGs) concentration is the screening method performed in a patient clinically suspected of having MPS, and if it is positive -- indicative of MPS. Thus, a negative test result is not sufficient to exclude a diagnosis, especially in a suggestive clinical setting. So the final diagnosis of MPS is confirmed with the help of an enzyme assay, in which the deficient enzymatic activity is determined, allowing identification of the particular type of MPS.

IMAGING FINDINGS

DYSOSTOSIS MULTIPLEX:

Bone dysplasia of mucopolysaccharidoses is one of the most prominent characteristics of these disorders. These dysplasias are secondary to the accumulation of GAGs in the growing cartilage, which will lead to abnormal osteoclastic activity, with the consequent reduction in cartilaginous reabsorption, and giving rise to the characteristic image findings of these entities.

Skull findings:

Sella turcica: The morphology of the normal sella turcica is rounded and saddle-shaped. However, in people with MPS the sella turcica suffers a widening along with a flattening of the tuberculum sella, which gives a form in J (figures 8 and 10). Although this finding is suggestive of MPS it is not pathognomonic, since it can appear as a variant of the normality (and in this case without clinical significance) in patients with neurofibromatosis and in patients with low-grade and slow-growing tumors that settle in the optic chiasm and that cause a remodeling of the sella turcica.
Dolichocephaly can also appear as a result of an early closure of the sagittal suture, as well as macrocephaly is a relatively frequent finding, both due to hydrocephalus and to the accumulation of GAGs in brain parenchyma, meninges and cranium.

The cortical bone of the calvarium may also appear thickened.

**Spine findings:**

The involvement of the spine by mucopolysaccharidosis includes a spectrum of developmental abnormalities and degenerative changes that affect both the intervertebral discs and the vertebrae and adjacent soft tissues. All this leads to a deformity of the spine and compression of the medullary cord.

Three major abnormalities in the craniocervical junction contribute to the stenosis of the spinal canal and compression of the spinal cord, and do not have to occur all 3 at once:

- Hypoplasia or odontoid aplasia.
- Atlanto-axial instability or subluxation of the transverse ligament and laxity of the alar ligament, as well as odontoid hypoplasia.
- Thickening of periodontoid soft tissue, dural and paraspinal ligaments caused by the accumulation of glycosaminoglycans and collagen (figures 6 and 7).

The instability of the cervical spine is more frequent in mucopolysaccharidosis IV. It is best evaluated with T2-weighted sagittal MRI in neutral, flexion and extension, which offers the advantage of evaluating the spinal cord for compressive myelopathy. The spine can also be evaluated more routinely with dynamic radiographs in neutral, bending and extension. Typically, stenosis of the spinal canal of the spine and cord compression worsen in flexion and decrease in extension.

An anterior atlanto-dental interval greater than 5 mm is abnormal at any age.

If the atlanto-dental joint is not well visualized, the diameter of the spinal canal between the posterior surface of the odontoid process and the posterior arch of C1 (the posterior atlantodental interval) is measured. A difference of more than 2 mm between flexion and extension implies instability. Compression of the untreated spinal cord leads to permanent cord cord damage.

The surgery consists of decompression with or without stabilization. The current accepted recommendations are for the decompression and fusion of asymptomatic patients when the space available for the spinal cord is less than 14 mm or when there is cervical instability> 8 mm.
Magnetic resonance plays an important role since it shows the degree of compression of the cord and its status in successive MR controls.

Several morphological abnormalities of the vertebral bodies are typical of mucopolysaccharidosis and are secondary to the failure of the ossification of the peripheral centers of secondary ossification of the vertebral bodies due to the accumulation of glycosaminoglycans. The vertebral platforms are weak in these regions, leading to a progressive spinal deformity.

These deformities include:
- Flattening of the vertebral bodies referred to as platyspondyly (vertebrae planae: flattened vertebral bodies throughout the entire skeleton). This appearance is normal until 12-14 months of age.
- Rounded or bullet-shape vertebral bodies (figures 9 and 12)
- Wedge-shaped vertebral bodies.
- Anterior inferior beaking of the thoracolumbar vertebrae because of deficient ossification of the anterior superior aspect of the vertebral body, which can lead to kyphosis. Thoracolumbar junctional kyphosis is a hallmark clinical feature of mucopolysaccharidosis, specially with MPS type I.
- Accelerated degeneration of the intervertebral discs with decreased height, dehydration and bulging of the discs (figures 5 and 11).

CENTRAL NERVOUS SYSTEM FINDINGS

Enlarged perivascular spaces:

The perivascular spaces of Virchow-Robin are spaces that contain interstitial fluid and act as a pathway for cerebral lymphatic drainage, and do not communicate with the subarachnoid space and that surround the vessels through their passage through the cerebral parenchyma. In the MPS, these spaces are distended with a mixture of CSF, interstitial fluid and GAG. It has been suggested that enlarged perivascular spaces are a sensitive marker of abnormal CSF circulation and represent its initial phase, which will result in ventriculomegaly in later stages of MPS.

Enlarged perivascular spaces have been described in patients with MPS I, II, III or VI and are more accentuated in patients with MPS I or II. They appear as numerous and small cystic lesions that usually measure between 2-8mm (figures 2 and 3). The periventricular white matter is the most common site of involvement, although dilated perivascular spaces can be found in the corpus callosum, the basal ganglia, the subcortical white matter, the thalamus or the brainstem, and its presence in the white matter is not impossible cerebellar.
2 important facts regarding perivascular spaces in MPS: They are accompanied by alteration of the surrounding white matter (this does not occur in healthy people). In healthy people, dilated perivascular spaces do not usually appear in the corpus callosum (fig.1).

**White matter lesions:**

White matter lesions (demyelination and dismyelination) are one of the most common findings reported in patients with MPS and are related to the deposition of partially degraded GAGs in neurons and oligodendrocytes in the CNS. In types I, II, III, and VII of MPS, white matter lesions appear in the first years of life.

At MR imaging, these lesions are nonspecific findings and appear as focal or confluent areas of T1 hypointensity and T2-FLAIR hyperintensity. Periventricular white matter is the most common site of involvement (fig.4), but these lesions can occur anywhere in the brain, including the subcortical white matter and the white matter in various brain lobes.

White matter lesions may coalesce and become larger and more diffuse, simulating the involvement pattern of leukodystrophy. Furthermore, enlarged perivascular space and white matter lesions do not necessarily occur in combination.

**Brain atrophy:**

Cerebral atrophy is a frequent finding in children with mucopolysaccharidosis and is probably secondary to neuronal death, loss of myelin and gliosis. Neuronal death can take place in two ways: due to the deposition of glycosaminoglycans in the neurons or in the walls of the vasa nervorum (which causes a secondary neuronal ischemic injury). The atrophy is predominantly cortical and can be symmetrical or not, and we will see a widening of the ventricular system and the subarachnoid spaces. Cerebral atrophy develops early during the first years of life in mucopolysaccharidoses I, II, III, and VII. In contrast, children with mucopolysaccharidosis IV and VI usually have normal intelligence and show no signs of atrophy until the second decade of life.

**Hydrocephalus:**

Hydrocephalus in patients with MPS is more common and more pronounced in patients with MPS I or II, and may be explained by:

1. The systemic accumulation of GAGs also affects the meninges, which may impair the function of arachnoid granulations, decreasing CSF reabsorption.
2. It has been hypothesized that abnormal bone proliferation at the skull base decreases cerebral venous outflow.

**Functional MRI:**
With respect to spectroscopy, an elevation of myoinositol can be seen in both the white and gray matter of children with MPS.

TREATMENT

There are some studies, such as that of Yoshiko Matsubara et al, in which they conclude that ventricular dilation and brain atrophy might represent useful markers for diagnosing the severity of MPS on imaging studies. While the effectiveness of enzyme replacement therapy in MPS patients with central nervous system symptoms has been reported to be poor, we found it to be effective with respect to imaging changes in MPS I patients. Because no new lesions developed after the start of ERT in patients with MPS II, early introduction of enzyme replacement therapy appears to be useful. For these reasons, radiological diagnosis is essential, or at least suggesting a mucopolysaccharidosis, in view of the described findings.
Fig. 1: Sagittal TIWI. Enlarged perivascular spaces that also affect the corpus callosum.

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Fig. 2: Axial T2WI. Enlarged perivascular spaces.

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Fig. 3: Axial 3D-T1WI with enlarged perivascular spaces.

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Fig. 4: Axial FLAIR. White matter periventricular lesions.

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Fig. 6: Thickening of periodontoid soft tissue, dural and paraspinal ligaments caused by the accumulation of glycosaminoglycans and collagen

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Fig. 7: Thickening of periodontoid soft tissue, dural and paraspinal ligaments caused by the accumulation of glycosaminoglycans and collagen.

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**Fig. 8:** Flattening of the tuberculum sella, which gives a form in J.

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**Fig. 10:** Flattening of the tuberculum sella, which gives a form in J.

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Fig. 9: Bullet-shape vertebral bodies.

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Fig. 5: Accelerated degeneration of the intervertebral discs with decreased height, dehydration and bulging of the discs.

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**Fig. 11:** Accelerated degeneration of the intervertebral discs with decreased height, and bulging of the discs.

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Fig. 12: Alteration of the architecture in all the vertebral bodies included in the study with discrete decrease in height and loss of the square morphology of the same. At the level of L2, there is a defect in the segmentation with wedging and anterior notch that gives rise to bullet-shape morphology with posterior displacement that produces a thoracolumbar kyphosis in the sagittal plane.

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Conclusion

MPS present a wide range of radiological manifestations in neuro-MRI, some of them typical (enlarged perivascular spaces, leukodystrophy, delay in myelination, hydrocephalus, cerebral atrophy and stenosis of the cervical spinal canal by soft tissue material around the atlanto-axoid joint, with or without compression of the spinal cord).

Radiology plays a fundamental role in the diagnosis and the follow-up of the disease (possible complications such as worsening stenosis of the craniocervical hinge, hydrocephalus or compression of the cord and can be treated quickly to avoid permanent damage).
References

