

# Mucopolysaccharidosis (MPS) and the Spine

## A patient guide

**In brief:** Mucopolysaccharidosis (MPS) is the name for a group of rare, inherited metabolic disorders in which the body lacks one of the enzymes needed to break down large sugar molecules called glycosaminoglycans, also known as mucopolysaccharides or GAGs. When the responsible enzyme is missing or deficient, these molecules accumulate inside cells and within connective tissue throughout the body, including bone, cartilage, ligaments and the membranes around the spinal cord. The several subtypes — including MPS I (Hurler, Hurler-Scheie and Scheie), MPS II (Hunter), MPS IV (Morquio) and MPS VI (Maroteaux-Lamy) — differ in the enzyme involved, the sugar that accumulates and the pattern of organs affected, but they share a characteristic effect on the skeleton known as dysostosis multiplex. From the point of view of the spine, two themes recur across the spectrum: a flexible thoracolumbar kyphosis or gibbus that appears early in childhood, most prominent in Hurler MPS I, and a far more serious instability and narrowing at the top of the neck, most prominent in Morquio MPS IV, where an underdeveloped peg of the second vertebra and thickened soft tissue can press on the spinal cord. The central idea is that MPS is a disease of stored sugar in the tissues, and the spine is one of the places where that storage produces its most consequential structural problems.

## What mucopolysaccharidosis is, and why it reaches the spine

The body constantly remodels its connective tissues, building up and breaking down the long sugar chains, the glycosaminoglycans, that give cartilage, bone, skin and ligaments their structure. This breakdown happens inside small recycling compartments within cells called lysosomes, and it depends on a sequence of enzymes, each performing one step. In mucopolysaccharidosis one of those enzymes is absent or works poorly because of an inherited fault in its gene. The result is that partly broken-down glycosaminoglycans cannot be cleared and accumulate, both inside cells and in the surrounding tissue.

The spine is affected because so much of it is built from precisely the tissues in which this storage occurs. The vertebral bodies form from cartilage that must mature into bone, the discs and growth plates are cartilage, the ligaments holding the vertebrae together are connective tissue, and the dura, the tough membrane sheathing the spinal cord, is connective tissue too. When stored glycosaminoglycans interfere with the growth and quality of all of these at once, the spine develops in an abnormal way and, in places, becomes mechanically vulnerable.

The different subtypes are distinguished by which enzyme is missing and which sugar accumulates. MPS I (Hurler at the severe end, Scheie at the milder end) involves a deficiency of alpha-L-iduronidase. MPS II (Hunter) involves iduronate-2-sulfatase. MPS IV (Morquio) involves enzymes affecting keratan and chondroitin sulfate. MPS VI (Maroteaux-Lamy) involves arylsulfatase B and the accumulation of dermatan sulfate. The clinical pictures differ — Hunter and the severe form of Hurler often involve the brain, whereas intelligence is typically preserved in Morquio and Maroteaux-Lamy — but the skeletal signature, dysostosis multiplex, runs through them all.

## Dysostosis multiplex and the shape of the MPS spine

Dysostosis multiplex is the collective term for the constellation of bone changes seen across the mucopolysaccharidoses. It is often present at, or shortly after, birth and tends to progress. Beyond the spine it includes shortened and thickened long bones, broad oar-shaped ribs, short wide collarbones and an abnormally shaped pelvis. Within the spine it produces a recognisable set of appearances that a radiologist can often identify on a plain X-ray.

The vertebral bodies in MPS are typically flattened, a feature called platyspondyly, and rounded or oval rather than the usual rectangular block shape. At the thoracolumbar junction, where the chest spine meets the lower back, the front of one or two vertebrae is characteristically underdeveloped, with the upper-front corner failing to grow properly. This produces an elongated lower-front lip, the so-called anterior beaking, that is one of the classic radiological hallmarks of MPS. Because the front of these vertebrae is deficient while the back is comparatively normal, the spine tends to bend forward at that point, producing the kyphosis described below.

These appearances are described as part of the natural pattern of the condition. They reflect the way stored glycosaminoglycans disturb the orderly conversion of cartilage to bone during growth, and they explain why the spinal problems of MPS are, at root, problems of abnormal development rather than of wear and tear.

## **The thoracolumbar gibbus and kyphosis, especially in Hurler MPS I**

The most visible spinal feature across much of the MPS spectrum, and the defining one in Hurler MPS I, is a forward angulation at the thoracolumbar junction known as a gibbus or thoracolumbar kyphosis. It arises directly from the underdevelopment of the anterior-superior part of one or two vertebrae, usually in the upper lumbar region. With the front of the vertebra failing to grow while the back continues, the spine hinges forward at that level, producing a sharp, often palpable, prominence of the back.

The gibbus frequently appears very early, sometimes within the first year of life, and it tends to progress. Natural history studies in MPS I have described a markedly larger kyphotic angle in children with the severe Hurler form than in those with attenuated disease, together with a steady progression over the years of childhood. In its early stages the deformity is often flexible, meaning it can be partly corrected by position, and only later does it tend to become more fixed.

A recognised concern with a progressive thoracolumbar kyphosis is that, in addition to the deformity itself, a sharply angled segment can in some circumstances place the spinal cord or the nerves at the apex under strain. The literature on MPS I has therefore concentrated on understanding which curves progress and which remain stable, and an international consensus process has been undertaken specifically to describe how thoracolumbar kyphosis in MPS I is assessed and considered. The reported surgical experience, where deformity correction has been undertaken, includes posterior fusion with instrumentation and, in the growing child, growing-rod techniques designed to allow continued spinal growth; published series describe substantial correction of the kyphotic angle in selected patients. These are descriptions of what has been reported in the literature, not recommendations.

## **The craniocervical junction: odontoid hypoplasia and instability, especially in Morquio MPS IV**

If the thoracolumbar gibbus is the signature of Hurler MPS I, the defining spinal concern of Morquio MPS IV lies at the opposite end of the spine, at the junction between the skull and the upper neck. Here two problems combine. First, the odontoid process — the upward-pointing peg of the second cervical vertebra around which the first vertebra and the head rotate — is characteristically underdeveloped, a feature called odontoid hypoplasia. Second, the ligaments that would normally restrain movement at this level are lax, partly because of the stored glycosaminoglycans within them.

The combination of a small, poorly formed peg and loose ligaments produces instability at the atlantoaxial joint, the joint between the first and second cervical vertebrae. This instability can allow excessive movement between the bones, which in turn can narrow the space available for the spinal cord. In Morquio MPS IV this craniocervical instability is recognised as a leading cause of disability and is regarded as a defining surgical concern of the condition, frequently developing from early childhood. It is one of the principal reasons the upper neck receives such close attention in this subtype.

Because the cord can be compromised slowly and intermittently, the literature describes the use of imaging of the craniocervical junction, including flexion-extension views and magnetic resonance imaging, to characterise both

the bony instability and the state of the cord. Scoring systems have been developed specifically to grade the severity of craniocervical cord compression in Morquio. The reported surgical experience, where intervention has been undertaken, centres on stabilisation of the upper neck, often by posterior fusion extending from the skull or upper cervical spine, sometimes combined with decompression, and these accounts emphasise that function is more readily preserved when the cord is addressed before severe weakness becomes established.

## Cervical myelopathy from soft-tissue thickening and GAG deposition

Across the mucopolysaccharidoses, and particularly in MPS I, MPS IV and MPS VI, the spinal cord in the neck can be compressed not only by unstable bone but by thickened soft tissue. The dura, the membrane around the cord, and the ligaments around the odontoid become infiltrated and thickened by stored glycosaminoglycans and associated material. This periodontoid and dural thickening encroaches on the canal, narrowing the channel through which the cord runs, a process distinct from, though often coexisting with, the bony instability.

When the cord is compressed in this way, the resulting condition is a cervical myelopathy — a disturbance of cord function that the literature describes as developing gradually and sometimes subtly, with features such as reduced stamina, changes in walking, clumsiness of the hands, or altered sensation. Because affected individuals, particularly children, may have short stature, joint stiffness and breathing difficulties from other aspects of the condition, the early signs of myelopathy can be difficult to disentangle from the background of the disease, which is one reason structured assessment and imaging feature so prominently in the literature.

The important structural point is that this is compression of the cord by stored material in the soft tissues, layered on top of, and sometimes independent of, the bony narrowing. Magnetic resonance imaging is described as the means of demonstrating the soft-tissue thickening, the narrowing of the canal and any change within the cord itself, and it is regarded in the consensus literature as the standard investigation for this purpose.

## Scoliosis and other spinal features

In addition to the forward-bending kyphosis at the thoracolumbar junction and the problems at the top of the neck, sideways curvature of the spine — scoliosis — and an exaggerated inward curve of the lower back — lordosis — are described across the MPS spectrum. The oval, flattened vertebral bodies and the abnormal growth that characterise the condition predispose the growing spine to curve in more than one plane, so that kyphosis, scoliosis and lordosis may coexist as a combined kyphoscoliotic deformity. In Morquio MPS IV in particular, a high proportion of severely affected children develop kyphoscoliosis along with chest-wall deformity within the first few years of life.

These deformities are described as part of the developmental skeletal disease rather than as separate conditions. Their assessment in the literature relies on serial imaging to judge whether a curve is progressing, and management considerations are weighed against the wider picture of the individual's overall health, growth and the demands of any surgery.

## Why enzyme replacement therapy and transplantation do not reverse the spinal skeletal disease

Two disease-modifying treatments have transformed the outlook in several mucopolysaccharidoses: enzyme replacement therapy, in which the missing enzyme is given by regular infusion, and haematopoietic stem cell transplantation, in which donor cells provide a source of the enzyme. These approaches can have substantial benefits for many soft-tissue and organ aspects of the conditions.

A consistent and important theme in the literature, however, is that neither enzyme replacement therapy nor stem cell transplantation reliably corrects or prevents the skeletal disease, including the spinal deformities and instability. The reason given is largely one of access: bone and cartilage are poorly supplied with blood, so the infused or cell-derived enzyme reaches them in only limited amounts, and the dense, avascular cartilage of the growth plates and discs is especially hard to penetrate. As a consequence, the bony and cartilaginous changes of

dysostosis multiplex — the vertebral underdevelopment, the kyphosis, the odontoid hypoplasia — tend to persist and progress despite treatment that helps other systems.

This is the principal reason the spine remains a focus of orthopaedic and neurosurgical attention even in individuals receiving modern medical therapy. The understanding expressed across the literature is that disease-modifying treatment and the structural care of the spine address different aspects of the same condition and are complementary rather than alternatives.

### **Surgical considerations: decompression, fusion and anaesthetic risk**

Where the spine in MPS is considered for surgery, the literature describes two broad situations. The first is correction of deformity, principally the thoracolumbar kyphosis of MPS I, where reported approaches include posterior instrumented fusion and, in growing children, growing-rod systems. The second, and the one most emphasised across the spectrum, is the management of cervical cord compromise, where the reported experience centres on decompression of the cord and stabilisation by fusion, frequently at the craniocervical junction in Morquio MPS IV and at the upper or mid cervical spine in the other subtypes.

A theme running through all of this literature is that surgery in MPS carries particular hazards that set it apart from spinal surgery in other conditions. Anaesthesia is recognised as high-risk: airway obstruction, restrictive lung disease and the difficulty or even impossibility of placing a breathing tube are repeatedly described, and the cervical instability that affects many patients restricts how the head and neck can be positioned, since extending the neck can itself threaten the cord. The literature describes the use of awake fibre-optic techniques and careful airway planning, the involvement of experienced anaesthetic teams, and intra-operative neurophysiological monitoring of cord function during complex spinal procedures. Because of these combined risks, the consistent message in the consensus literature is that decisions about spinal surgery in MPS are made by experienced multidisciplinary teams weighing the potential benefit against considerable risk, and are highly individualised.

### **Assessment and monitoring**

The assessment of the spine in mucopolysaccharidosis rests on a combination of clinical observation and imaging followed over time. Clinical and neurological examination is described as the cornerstone for detecting the early signs of cord involvement, watching for changes in walking, stamina, hand function and bladder or bowel control, against the backdrop of the individual's baseline.

Plain X-rays, including flexion and extension views of the neck, are used to demonstrate the characteristic vertebral shapes, the thoracolumbar kyphosis and any instability at the craniocervical junction. Magnetic resonance imaging is regarded as the standard means of showing soft-tissue thickening, narrowing of the spinal canal and any change within the cord, and is central to the assessment of both the upper neck and, where relevant, the thoracic cord. Computed tomography characterises the bony anatomy in detail. Neurophysiological tests, such as evoked potentials, are described both in assessment and, importantly, during surgery as a way of monitoring the cord. The literature emphasises serial, structured surveillance because the spinal problems of MPS evolve over years and can do so quietly.

## Outlook

The outlook for the spine in mucopolysaccharidosis depends heavily on the subtype, the severity of the underlying enzyme deficiency, and which part of the spine is involved. The thoracolumbar kyphosis of MPS I, while often visible and sometimes progressive, is in many individuals a deformity that is monitored, and where it has been corrected surgically the reported results describe meaningful improvement in alignment. The craniocervical instability and cord compression of Morquio MPS IV and the other subtypes are regarded as more serious, because they place the spinal cord at risk, and the literature stresses that function is more readily preserved when the cord is addressed before severe and established weakness develops.

Several themes run consistently through the field. The spinal disease of MPS is, at heart, a developmental consequence of stored sugar in the tissues of the spine. It is not, in general, corrected by enzyme replacement or transplantation, so structural surveillance of the spine remains relevant even with modern medical treatment. Surgery, where considered, carries particular anaesthetic and neurological risk that shapes every decision. And any individual outlook is a matter for assessment by an experienced multidisciplinary team familiar with the condition, rather than something that can be read from a subtype or a single measurement alone.