

ORTHOPEDIC DISORDERS IN CHILDREN WITH MPS AND RELATED DISEASES

A PARENTS' GUIDE

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The term *dysostosis multiplex* means “multiple bad bones”, and is the grouping of skeletal abnormalities classically seen with MPS and related diseases. Dysostosis multiplex occurs when bones do not form correctly at cartilage growth centers throughout the body. The unusual problem of joint stiffness and looseness of ligaments seen in children with MPS and related disorders only compounds the problem. Although the biology of these problems is yet to be understood, surgical procedures for the hips, knees, hands and spine can be helpful in reducing the associated pain, stiffness and disability. Mesenchymal stem cell transplants and gene therapy offer future alternatives to surgery, but at this point remain unviable options. Unfortunately, enzyme replacement therapy and stem cell transplant from bone marrow, cord blood or peripheral stem cell sources provide only mild benefit in this area, and families are left contending with deformities of the spine, hip, knees and hands. Many families and treating doctors are unfamiliar with the orthopaedic challenges faced by children with MPS and related diseases and how to contend with them. If left untreated, these problems usually become functionally limiting and often painful, creating the need for continued physical therapy, and oftentimes surgery. Given the large number of musculoskeletal issues in children with MPS, parents must be aware of what to anticipate in order to provide their children the best chance of a fulfilling, functional life. Although the orthopedic problems are primarily addressed here in the context of MPS I, these discussions may be generalized across the spectrum of MPS and related diseases.

Spinal Column

Issues involving the cervical spine (neck) are extremely common in children with MPS, and may be potentially life threatening. Changes to the cervical spine occur due to poor bone formation (flattening of the spine bones called vertebrae) and impaired growth of the *odontoid process*. The odontoid process is a peg-like axis at the base of the skull, on the second vertebra, which stabilizes the motion between the first and second vertebral bodies just below the skull. When this structure is small or absent, the spine can become unstable. With a successful stem cell transplant, growth of the odontoid can normalize, but soft tissue accumulation of mucopolysaccharides continues. Thus, spinal instability and spinal cord compression may still occur, although it is less common.

Spinal cord compression or instability of the neck may result in progressive spinal cord injury known as myelopathy. A combination of weakness, clumsiness, pain in the hands, arms, shoulders or legs and decreased exercise tolerance may be present with myelopathy. Continued accumulation of mucopolysaccharides in the spinal column, even after transplant, can make the problem worse. Very rarely, spinal instability can result in quadriplegia (loss of use the arms and legs). This is more common in MPS IV and has only been reported in two children with MPS I. There are, however, no reports of sudden quadriplegia happening in any post-transplant children, possibly due to the beneficial effects of transplant. Consequently, parents should be cautious about manipulation of the cervical spine. It is recommended that all children with MPS and related diseases should avoid “high risk” activities such as contact sports, gymnastics and the like. In addition, these children should be

treated with caution when undergoing positioning for anesthesia. Surgery to decompress and/or stabilize the spine is common in children with MPS IV, but is uncommon in children with MPS I post-transplant. The need for surgery in children with a transplant may become more common as the children get older. Children with other MPS disorders usually fall somewhere in between, and treatment should be tailored to individual needs. If instability develops, an “instrumentation and fusion” surgery (see description below) is generally performed under these circumstances. Some surgeons may elect to simply decompress the spinal cord without a fusion.

The single most common orthopedic feature of severe MPS I is the gibbus deformity. Gibbus refers to the bump in the child’s back, which is actually an abnormal curvature of the spine. This forward bend, or *kyphosis*, in the lower spine occurs in about 90% of children with severe MPS I, and is commonly found in other MPS and related diseases. The orthopedic term for a gibbus deformity is *thoracolumbar kyphosis*. Thoracolumbar kyphosis develops from poor bone growth in the upper front-most part of the vertebrae, which results in a wedging of the vertebrae (bones are smaller in the front than in the back). Prior to the advent of stem cell transplant, spine surgery for gibbus deformities was not performed on children with MPS I, due to their limited life expectancy and the detrimental effect on their quality of life. Now with stem cell transplant available and an extended life expectancy, a large number of gibbus deformities will eventually require surgical stabilization to halt the progression of the kyphosis. Following stem cell transplant, it seems that about a third of children will have their kyphosis progress and require early surgery (before age 9), a third will not progress, but may require surgery at some point in their life, and a third will actually improve, depending on the gene mutations of each child. Experience from other diseases, such as MPS IV and achondroplasia (dwarfism), indicate that myelopathy (nerve damage mentioned above) and respiratory problems can occur later in life if the kyphosis is left untreated.

Some children with MPS and related diseases may also have *scoliosis* of the spine. Scoliosis occurs when the spine curves from side-to-side, as opposed to front-to-back. Scoliosis may also require surgery, however this is less common. When not treated, scoliosis can progress to the point that children have difficulty expanding their chest wall for breathing. Occasionally, children may suffer from both kyphosis and scoliosis, making surgical intervention more likely and more complex. Bracing may slow the progression of both spinal kyphosis and scoliosis, delaying surgery, but not preventing surgery. Bracing can be uncomfortable for children, and they rarely tolerate it, especially young children. Consequently, bracing is usually not recommended. Indications for surgery vary, depending on the needs of the child and the desires of the family. Generally, a kyphosis of more than 70° or scoliosis greater than 40° indicates the need for surgery. The presence of myelopathy is also an indication for surgery. Surgery for kyphosis or scoliosis may be necessary as young as two years of age, and usually before adolescence. Published reports put the average age at about eight years. Current experience suggests that, if possible, delaying spinal surgery to the latter ages mentioned above allows maximal growth of the spine and further development of already thin and brittle bone.

Surgery to correct spinal deformities involves an incision in the back and sometimes from the front (through the flank or ribcage). The procedure is called an instrumentation and fusion. Surgery for scoliosis usually involves an incision from the back, while surgery for kyphosis almost always requires incisions from the front and back. Early experience suggests that treatment of kyphosis only from the back frequently results in failure and the need for re-operation, especially in children with MPS I. The “fusion” is actually the placement of bone from the pelvis or ribs, over the spine on the backside, or between vertebrae on the front side. The “instrumentation”, or metal hardware, is typically stainless

steel or titanium, and provides temporary support to the spine until the fusion heals. Once placed, it is not usually removed unless there is a complication related to its presence, such as an infection. Most children will require some combination of a cast or brace for anywhere from three months to a year following surgery. With proper surgical technique, instrumentation, and postoperative casting/bracing, the extra bone heals to form a strut between the vertebrae, which prevents progressive curvature of the spine. An unsuccessful fusion can be painful and may necessitate a repeat surgery. For the more common “run-of-the-mill” teenage scoliosis, surgery is successful in excess of 95% of the time, however it is unclear whether children with MPS and related diseases have the same frequency of success.

Hips/Pelvis

Like the spine, the hip joint suffers from altered bone formation. The hip is a ball-and-socket joint situated at either side of the pelvis. The “ball” is the head of the femur (thigh bone) and the “socket” is the cupped part of the pelvis (the acetabulum) that surrounds the ball. In abnormal formation of the hip, or *hip dysplasia*, there is a shallow acetabulum, underdevelopment of the femoral head, and *coxa valga* (straightening of the top of the thigh bone at the femoral neck). This combination of bone defects results in hip instability, and sometimes dislocation, where the ball and socket are no longer congruent.

Hip dysplasia to some degree is found in nearly all children with severe MPS I, and can also be found in children with mild MPS I, MPS VI, MPS II and MPS IV less often. In unaffected children, hip dysplasia is responsive to bracing 95% of the time, particularly with early intervention. Bracing in MPS and related diseases has not been studied, but is likely ineffective and can actually result in worsening muscle weakness and delay of physical development. Hip dysplasia is not responsive to stem cell transplant or enzyme replacement therapy, and most children with hip dysplasia eventually require corrective hip surgery, even with successful stem cell transplant. Surgery on the hips is done more easily at a younger age, around age 5-7, for an optimal outcome. Successful surgery becomes much more difficult at older ages. If the hips have already dislocated and the “cow is out of the barn”, so to speak, the surgery becomes technically very difficult, and the outcomes of surgery are much less predictable.

Hip surgery for dysplasia is a combination of precise bone cuts, or osteotomies, which allow the surgeon to reposition the bones and optimize hip mechanics. Cuts are made in the pelvis and sometimes the femur. The surgery on the bones may be performed in conjunction with tightening the soft tissues around the hip. Without hip surgery, there is progressive pain and stiffness, and eventually frank dislocation of the hips, with a dramatic reduction in walking ability. Thus far, the results of hip surgery in MPS are promising, resulting in improved motion and independent walking.

Knees

Almost all children with MPS IV, and about 50% of children with MPS I post-transplant, develop *genu valgum* (knock-knees) severe enough to require surgery. Children with MPS VI as well as the attenuated forms of MPS I, can also develop knock-knees severe enough to warrant surgery. The indication for surgery is a knee deformity greater than 15°. During this surgery staples are placed in the bone on the inner side of the knee through a relatively small incision. These staples prevent bone growth on the inner side of the knee, allowing the outer side to catch up. As a result, the knees straighten over time, and usually, the staples are removed with a second surgery. Occasionally, the staples can dislodge. When this happens, they are typically removed, and if necessary, new ones

replace them. In children too small for staple placement, osteotomies (bone cuts) in the large bones around the knee may be required. Although osteotomies are more invasive and painful, staples will not work in children who are too small, and experience has shown that children with MPS and related diseases heal well.

Children with MPS also suffer from stiff knees, which prevent full straightening and result in a crouched gait. This is probably improved with stem cell transplant, and perhaps by enzyme replacement therapy, but most children still require continued physical therapy to optimize knee motion and walking function.

Summary

Even with stem cell transplant or enzyme replacement therapy, children with MPS and related diseases continue to have significant muscular and skeletal disabilities, most commonly involving the spine, hips, knees and hands. These are rarely catastrophic or life threatening, but frequently limit a child's function, activity and quality of life. Surgical intervention is often required, to optimize long-term function. The timing and type of surgery may vary among children and among surgeons. Regardless, early evaluation is critical in determining what treatments will be necessary to optimize the quality of life for a child with MPS and related diseases.