Musculoskeletal Manifestations of Sanfilippo Syndrome (Mucopolysaccharidosis Type III)

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Background: The most pronounced symptom in mucopolysaccharidosis type III (MPS III, Sanfilippo Syndrome) is the severe neurocognitive deterioration of the central nervous system. The effects of MPS III on the musculoskeletal system are less severe than those caused by other forms of MPS, however, it is our experience that many families seek orthopaedic attention for perceived musculoskeletal discomfort, particularly about the hip and spine. The purpose of this study is to report musculoskeletal findings in a case series of patients with MPS III.

Methods: This study represents a retrospective case series of all records available from 2 institutions on patients with MPS III. Chart and radiographic review was performed and outcomes tabulated. Our hypotheses are: (1) Musculoskeletal abnormalities are prevalent in children with MPS III and (2) Musculoskeletal deformities in children with MPS III may require surgical intervention.

Results: Eighteen patients were identified (10 female and 8 male) with an average age of 10.3 years. Three had significant scoliosis (21 to 99 degrees) and 2 others had L1 hypoplasia. Four patients had osteonecrosis of the femoral heads. One patient required a carpal tunnel release, and another a trigger thumb release. There were no cases of cervical instability.

Conclusions: In our study with these patients, we have observed several unreported musculoskeletal manifestations of MPS III. Osteonecrosis of the hips can be a source of severe discomfort for these children. Although uncommon, operative intervention for orthopaedic conditions is sometimes warranted. Operative indications in this cohort include progressive scoliosis of large magnitude, carpal tunnel syndrome, and trigger digits.

Level of Evidence: Level IV; case series.

Key Words: mucopolysaccharidosis, sanfilippo syndrome, scoliosis, osteonecrosis, foot deformities

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The mucopolysaccharidoses (MPS) are a family of genetic disorders in which the lysosomal enzymes responsible for the degradation of normally produced glycosaminoglycans are nonfunctional. MPS is found in approximately 1 in every 25,000 live births.[1] MPS III, or Sanfilippo Syndrome, is an autosomal recessive disorder, characterized by the absence of 1 of 4 enzymes essential in the metabolism of heparan sulfate: heparan N-sulfatase, α-N-acetylglucosaminidase, acetyl-coenzyme A α-glucosaminide-N-acetyltransferase, and N-acetylglucosamine-6-sulfatase.[2] The lack of each of these enzymes creates 4 subcategories of MPS III, known as types A, B, C, and D, respectively.[3] The incidence of MPS III (all 4 types combined) is estimated to be 1 in 70,000 births.[4] Phenotypically, these types are essentially indistinguishable. The most pronounced symptom in MPS III is the severe deterioration of the central nervous system. This is manifested in the form of aggression and sleep disturbances. Visual changes, difficulty in breathing and swallowing, respiratory infections, heart disease, enlarged liver and spleen, and hernias are also present.[1–3] The average life expectancy of a patient with MPS III is late teens to early twenties.[3]

Dysostosis multiplex, the constellation of radiographic abnormalities classically seen in MPS, results from defective endochondral and membranous growth throughout the body, including the hips, knees, and spine.[5–7] Skeletal disease manifestations in MPS range from mild platyspondyly with or without epiphyseal dysplasia to severe, life-threatening spinal deformities, and crippling hip deformities.[5,8] Both joint stiffness and ligamentous laxity are associated with MPS disorders, compounding the problems associated with the skeletal deformities. The effects of MPS III on the musculoskeletal system are less severe than those caused by other forms of MPS, however, it is our experience that many families seek orthopaedic attention for perceived musculoskeletal discomfort, particularly about the hip and spine. In our study with these patients, we have observed several unreported musculoskeletal manifestations of MPS III, and believe that this information will prove extremely useful to those who treat these children. The purpose of this study is to report musculoskeletal findings in a case series of patients with MPS III (Sanfilippo Syndrome).

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METHODS

This report represents a case series of patients, which is drawn from the medical records at 2 institutions. An Institution Review Board-approved retrospective chart review of patients identified with a diagnosis of MPS III at these institutions was performed. Available clinical data including age, age at diagnosis, sex, and ambulatory status were recorded. Specific notation regarding the presence or absence of musculoskeletal abnormalities was made, including: height and weight, foot deformity, wrist pathology, scoliosis, cervical spine deformity, hip dysplasia, and femoral head osteonecrosis. For available x-rays, the cobb angle, acetabular index, and center edge angle of Wieberg were determined and recorded. Acetabular dysplasia was defined as an acetabular index >20 degrees or center edge angle <20 degrees. Orthopaedic surgery interventions were tabulated including surgery for spinal deformity, hip deformity, carpal tunnel syndrome, and lower extremity deformity.

RESULTS

Eighteen patients with a diagnosis of MPS III were identified at the 2 participating institutions (Table 1). Ten were female and 8 were male. Stature was recorded in 15 patients, of which 5 were $<5\%$ for their age. Thirteen of the 18 patients had cervical spine radiographs in which there were no identified abnormalities, including cervical instability and odontoid hypoplasia. Thirteen patients had scoliosis films taken, of which 6 were found to have identifiable abnormalities (Table 2). These included severe scoliosis (1), scoliosis with thoracolumbar kyphosis (1), and hypoplastic/misshapen vertebral bodies (4) (Fig. 1). Hip abnormalities were identified in 10 patients. Osteonecrosis of the femoral heads was identified in 4 patients and was bilateral in all 4 (Fig. 2). Hip dysplasia was identified in 8 patients (2 patients had both dysplasia and osteonecrosis) and 1 of these patients was treated with proximal femoral derotation osteotomies (Fig. 3). Foot and ankle deformities were identified in 3 patients, 1 with straight equinus contractures and 2 with equinovarus deformities. Hand and wrist abnormalities were reported in 6 patients including carpal tunnel syndrome, Madelung deformity, trigger thumb, dorsal ganglion, and scaphoid avascular necrosis.

Surgical procedures were performed on 4 patients. The following procedures were performed on different patients: trigger finger release, carpal tunnel release, split posterior tibial tendon transfer with tendoachilles lengthening, and plantar fascia release for an equinovarus foot deformity, posterior spinal fusion and instrumentation for scoliosis, and proximal femoral varus osteotomies for hip dysplasia. No complications were noted in the charts for these procedures.

TABLE 1. Demographic Data of Eighteen Patients Identified With MPS III

Patient No.	Sex	Age at Diagnois (y)	Age at Follow-up (y)	Height	Weight
1	Female	4	12.3	5%	10%
2	Female	6	9.6	25%	25%
3	Female	14	18	25%	50%
4	Male	2	8.1	50%	90%
5	Male	5	7.9	< 5%	< 5%
6	Male	4	7.3	50%	90%
7	Female	9	18	< 5%	< 5%
8	Male	8	9.25	50%	90%
9	Male	4	18	< 5%	< 5%
10	Female	5	8.25	10%	50%
11	Female	—	15.1	< 5%	< 5%
12	Female	3.5	16	< 5%	< 5%
13	Male	2	7.6	—	—
14	Male	—	10.5	—	—
15	Female	5	5.5	33%	64%
16	Male	0.9	1.2	36%	72%
17	Female	2	3	90%	50%
18	Female	—	11	—	—

DISCUSSION

The natural history for children with MPS III is a relentless neurodegeneration.[1–3] These patients tend to stop walking as early as their mid-teens, with the remainder walking only into their late twenties. Furthermore, there seems to be some discrepancy among the subtypes of MPS III. MPS IIIA seems to be much more aggressive than MPS IIIC for instance, with a median age for death at 15 years compared with 34 years in MPS IIIC.[3,9] In addition to the issues of longevity and ambulatory potential, is the aggressive and destructive behavior seen in these children. At present there is no effective therapy for MPS III. Unlike other forms of MPS, hematopoietic stem cell transplant has not proven to be an effective treatment for the neurodegenerative aspects of Sanfilippo syndrome.[10] When considering treatment options for these patients, this natural history should be understood.

Although musculoskeletal pathology is a well-recognized component of other MPS disorders, this is the first study, to our knowledge, to specifically address the musculoskeletal findings in MPS III. Indeed, review of several exhaustive clinical reviews of MPS III, do not even mention musculoskeletal abnormalities in this disorder.[2,3,9] We were able to identify 2 articles that discussed skeletal findings in MPS III.

In a general review of the skeletal manifestations of MPS, Chen et al[11] report mild radiographic findings of dysostosis multiplex in MPS III. This review does not address deformities of surgical relevance. Rigante and Cardonna[12] evaluated serum markers for bone metabolism and bone mineral density in MPS III by dual-energy x-ray absorptiometry. Three patients with MPS III, aged 11, 15, and 24 years were reviewed in this study, and all 3 were found to be vitamin D deficient, with 25-hydroxy vitamin D levels <15 ng/mL. Mild secondary hyperparathyroidism and high serum levels of osteocalcin, alkaline phosphatase, and crosslaps, indicative of high bone

TABLE 2. Radiographic Findings in Patients With MPS III

Patient No.	Cervical Spine	Scoliosis	Spine X-ray Findings	AVN hips	Acetabular Dysplasia	Foot/Ankle Deformity	Hands/Wrists
1	nl	Yes	Severe scoliosis	No	Bilateral	Equinus	
2	—	Yes	Scoliosis, kyphosis	No	No		
3	nl	Yes	Rounded vertebral bodies	Bilateral	No		AVN scaphoid
4	nl	No	nl	Bilateral	Left		Ganglions
5	nl	—	—	—	Bilateral		CTR
6	nl	No	Anterior protrusions on lateral	No	Bilateral		
7	nl	No	nl	No	Bilateral	Equinovarus	
8	nl	No	nl	No	No		
9	nl	No	nl	No	No		
10	—	—	—	—	—		
11	—	—	—	—	—	Equinovarus	
12	nl	No	nl	Bilateral	Right		
13	nl	No	L1 hypoplasia	No	Bilateral		Madelung's deformity
14	nl	No	L1 hypoplasia	No	Mild		Madelung's deformity
15	nl	No	nl	No	No		Trigger thumb
16	—	No	N/A	—	—		
17	nl	No	nl	No	No		
18	—	—	—	Bilateral	No		

Blanks represent no record of deformity.
AVN indicates avascular necrosis; CTS, carpal tunnel syndrome.

turnover, were found. Dual-energy x-ray absorptiometry scanning revealed significantly abnormal results in the 2 older patients and a normal result in the 11-year-old male (who was still able to stand with assistance). Although none of these patients sustained fragility fractures, nor did any in our patient group, orthopaedists should be aware of this possibility when caring for these patients, and referral to an endocrinologist may be appropriate.

Hip deformities seem to be the most common orthopaedic abnormality found in our group of patients. This includes both acetabular dysplasia and the development of osteonecrosis of the femoral head. Although no interventions have been recommended or performed for our patients with osteonecrosis, 1 patient was treated with proximal femoral varus osteotomies for hip dysplasia. In general, the hip dysplasia seems to be relatively mild in these patients. Given this fact, and the known natural history of this disease, we are reticent to recommend aggressive treatment of hip dysplasia in patients with MPS III.

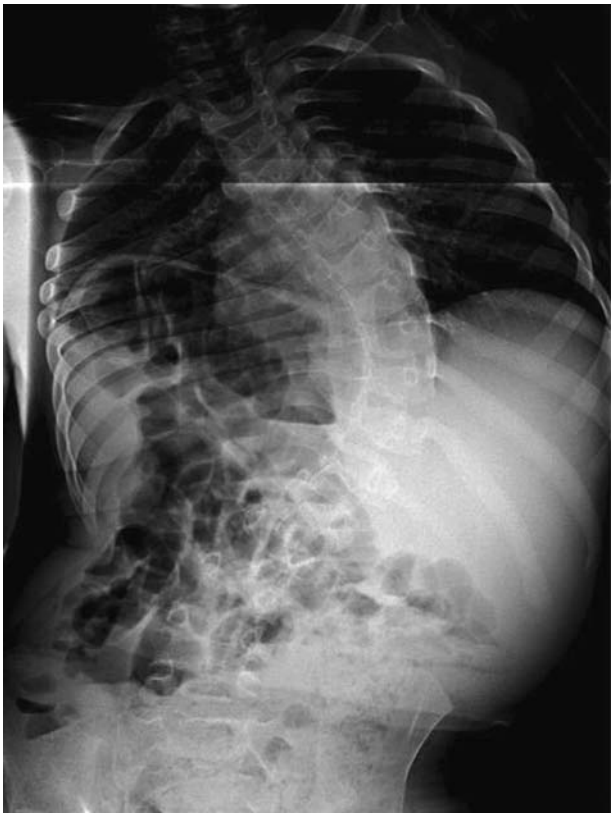

FIGURE 1. Scoliosis in a patient with mucopolysaccharidosis (MPS) type III. Note the wide "oar-shaped" ribs that are pathognomonic for MPS diseases. Although not particularly apparent in this case, vertebral body flattening or anterior hypoplasia can be seen on the lateral views.

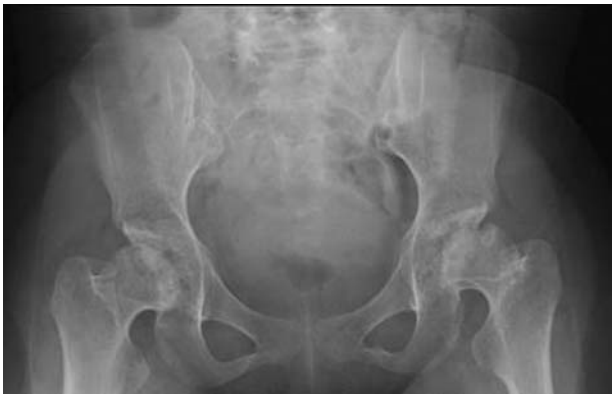

FIGURE 2. Osteonecrosis of the femoral heads is relatively common in mucopolysaccharidosis type III, and can be painful in both ambulatory and nonambulatory patients. This patient also has mild acetabular dysplasia.

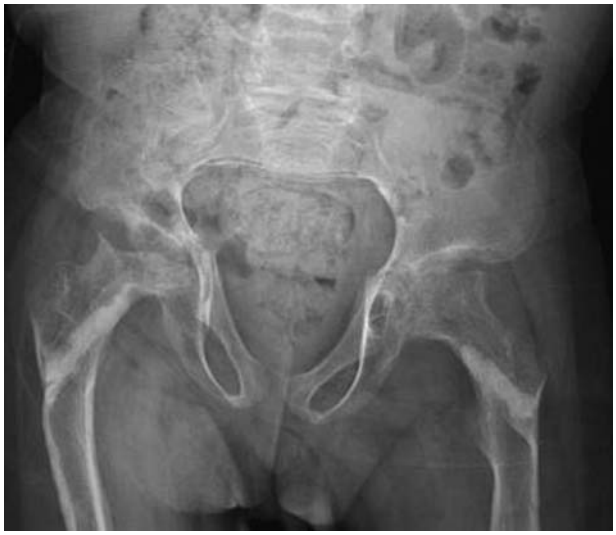

FIGURE 3. Postoperative image of hip dysplasia treated by proximal femoral varus osteotomies. Owing to the relentless osteonecrosis of femoral heads, surgical treatment of hip dysplasia should be approached with caution.

Several of our patients presented for evaluation of hip pain, which seems to be more associated with the presence of osteonecrosis of the femoral head. This epiphyseal dysplasia is typified by a slow but persistent resorption and fragmentation of the femoral head. It does not seem to achieve the healing and remodeling stages seen in Perthes disease. This follows a similar course to that seen in MPS IV (Morquio syndrome) and MPS VI (Maroteaux-Lamy syndrome). Studies in mice with MPS VI indicate that the joint destruction seen in these diseases is inflammatory mediated. The evidence from these studies suggests that glycosaminoglycan storage in MPS induces a complex sequence of molecular changes, leading to inflammation, synovial hyperplasia, and cartilage apoptosis.[13–16] Further animal studies suggest that activation of the toll-like receptor protein 4 pathway in MPS disorders, through glycosaminoglycan accumulation, results in TNF-α activation, which is responsive to systemic treatment with infliximab (Remicade).[16] Large animal and human studies investigating this treatment have not been conducted, but may offer a therapeutic option in the future.

The presence of spinal deformities in MPS III has not been previously described. Spinal abnormalities were found in 6 of 18 patients in this group and are similar to those seen in other forms of MPS. The presence of vertebral body hypoplasia may aid in the diagnosis of MPS III when one has not been previously established, as was true for 1 of our patients. Scoliosis can achieve a significant magnitude in these patients. As with hip deformities, treating clinicians need to consider the overall health of the patient in the uncommon scenario that the scoliosis progression proves to be aggressive. We did not find any cervical spine abnormalities in this patient group, and to our knowledge there have been no cases reported in the literature. As such, routine monitoring of the cervical spine for stenosis and instability, as in other forms of MPS, is not recommended.[17]

There were a number of patients who were treated for equinus and equinovarus deformities and 1 patient was treated for carpal tunnel syndrome. Again, surgical management should be tempered by the overall function of the patient and the expected natural history.

In summary, this study represents the first devoted review of the orthopaedically relevant musculoskeletal outcomes in MPS III (Sanfilippo syndrome). Deformities of the hips, spine, foot and ankle, and upper extremity were identified. These are similar to findings seen in other MPS disorders, but are less prevalent and of milder magnitude. We did not, however, identify any concerns with the cervical spine similar to the other MPS disorders. Although a small minority of patients with MPS III may require surgical treatment, clinicians should be judicious in recommending surgery, given the significant and progressive neurodegenerative nature of this disease.

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