An 8-Year-Old Girl with a History of Stiff and Painful Joints

Julian Raiman, MBBS, MSc, MRCP; and Kristin D’Aco, MD

A 6-year-old, developmentally normal girl with a 1-year history of stiff and painful joints affecting the hands, wrists, knees, elbows, and shoulders was referred to a rheumatologist. Additional medical history at the time of the visit included recurrent otitis media and snoring.

On physical examination, multiple joint contractures in the upper extremities were noted. She received a diagnosis of polyarticular juvenile idiopathic arthritis. Various treatments, including nonsteroidal anti-inflammatory drugs (naproxen), oral and subcutaneous methotrexate, intra-articular steroid injections, and leflunomide, were ineffective.

At 8 years of age, she presented with progressive second and third finger numbness. A nerve conduction study confirmed bilateral carpal tunnel syndrome. Following these tests, a lysosomal storage disorder was suspected and she was referred to a metabolic geneticist. Physical examination demonstrated flexion contractures in distal (Figure 1A, red arrow) and proximal (Figure 1A, blue arrowhead) interphalangeal joints, wrists (Figure 1B), and elbows, and restricted shoulder mobility. The joints of the fingers were described as “thick.” Radiographs of the hands showed mild flexion contractures at the fifth distal interphalangeal (DIP) joints bilaterally, as well as generalized osteopenia (Figure 2); no overt erosions were present.

The patient’s weight was in the 5th percentile, height in the 3rd percentile, and head circumference in the 10th percentile for her age group. Other parameters assessed during the physical exam were within normal limits. There was no coarsening of the patient’s facial features, and she did not present with cardiac murmur, organomegaly, or hernias. The neurological exam was normal with respect to strength and tone, as was the patient’s gait. The patient has two healthy brothers, and her parents are second cousins.

For diagnosis, see page 308

Editor’s note: Each month, this department features a discussion of an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.
Based on the history and physical exam findings, urinary glycosaminoglycan (GAG) analysis and assessment of alpha-L-iduronidase (IDUA) enzyme activity in leukocytes were ordered. Enzyme activity was 1 nmol/h/mg (reference range, 14-41 nmol/h/mg), and urinary GAG analysis detected excess heparan and dermatan sulfate. Echocardiogram showed thickening of the mitral and aortic valves, and brain magnetic resonance imaging demonstrated increased signal in the white matter surrounding dilated perivascular spaces.

The patient’s joint contractures, carpal tunnel syndrome, and ears, nose, and throat symptoms are all consistent with the diagnosis of mucopolysaccharidosis type I (MPS I). The joint contractures and positioning of the fingers in this patient are commonly referred to as “claw-hand” deformity. The absence of coarse facial features and the history of normal development are consistent with the mild end of the phenotypic disease spectrum, also known as attenuated MPS I, or Scheie syndrome. Attenuated MPS I was confirmed by genotyping, which showed that the patient was homozygous for a missense mutation in the IDUA gene: c.1039A>C (p.S347R). Weekly treatment with laronidase (Aldurazyme, Genzyme, a Sanofi company, Cambridge, MA; and BioMarin Pharmaceutical, Novato, CA) enzyme replacement therapy was initiated. Improvements in hand mobility and joint size were noted, as well as less joint discomfort.

DISCUSSION
MPS I is a rare, progressive, life-threatening autosomal recessive condition with a worldwide incidence of approximately 1 per 100,000 live births. It is caused by defects in the gene coding for the enzyme IDUA. Reduced levels of the IDUA enzyme result in impaired lysosomal degradation of the GAGs dermatan sulfate and heparan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body. The resulting accumulation of GAGs leads to progressive cellular and multi-organ dysfunction with variable phenotypes. The most common clinical features of MPS I include facial coarsening, chronic rhinitis, recurrent otitis media, hepatosplenomegaly, corneal clouding, inguinal and umbilical hernias, valvular heart disease, respiratory insufficiency, joint stiffness and contractures, dysostosis multiplex, short stature, developmental delay, and progressive cognitive decline (among the most severely affected patients). Patients typically require multiple surgical interventions to address ear, nose, and throat and airway issues, repair hernias, correct bone malformations, and release peripheral nerve entrapments.

The MPS I disease spectrum encompasses a range of clinical severity, which is categorized into three subjectively defined phenotypes based on the age of onset, the rate of disease progression, and the presence or absence of CNS involvement. The most severely affected patients on the MPS I continuum are categorized as having the Hurler phenotype. These patients experience rapidly progressive disease manifestations in infancy and severe cognitive impairment. With a median age at diagnosis of 0.8 years, the earliest symptoms in patients with Hurler syndrome include coarsening facial features, corneal clouding, inguinal and umbilical hernias, valvular heart disease, respiratory insufficiency, joint stiffness and contractures, dysostosis multiplex, short stature, developmental delay, and progressive cognitive decline (among the most severely affected patients). Patients typically require multiple surgical interventions to address ear, nose, and throat and airway issues, repair hernias, correct bone malformations, and release peripheral nerve entrapments.

The MPS I disease spectrum encompasses a range of clinical severity, which is categorized into three subjectively defined phenotypes based on the age of onset, the rate of disease progression, and the presence or absence of CNS involvement. The most severely affected patients on the MPS I continuum are categorized as having the Hurler phenotype. These patients experience rapidly progressive disease manifestations in infancy and severe cognitive impairment. With a median age at diagnosis of 0.8 years, the earliest symptoms in patients with Hurler syndrome include coarsening facial features, corneal clouding, inguinal and umbilical hernias, valvular heart disease, respiratory insufficiency, joint stiffness and contractures, dysostosis multiplex, short stature, developmental delay, and progressive cognitive decline (among the most severely affected patients). Patients typically require multiple surgical interventions to address ear, nose, and throat and airway issues, repair hernias, correct bone malformations, and release peripheral nerve entrapments.

The MPS I disease spectrum encompasses a range of clinical severity, which is categorized into three subjectively defined phenotypes based on the age of onset, the rate of disease progression, and the presence or absence of CNS involvement. The most severely affected patients on the MPS I continuum are categorized as having the Hurler phenotype. These patients experience rapidly progressive disease manifestations in infancy and severe cognitive impairment. With a median age at diagnosis of 0.8 years, the earliest symptoms in patients with Hurler syndrome include coarsening facial features, corneal clouding, inguinal and umbilical hernias, valvular heart disease, respiratory insufficiency, joint stiffness and contractures, dysostosis multiplex, short stature, developmental delay, and progressive cognitive decline (among the most severely affected patients). Patients typically require multiple surgical interventions to address ear, nose, and throat and airway issues, repair hernias, correct bone malformations, and release peripheral nerve entrapments.

DISCUSSION

MPS I is a rare, progressive, life-threatening autosomal recessive condition with a worldwide incidence of approximately 1 per 100,000 live births. It is caused by defects in the gene coding for the enzyme IDUA. Reduced levels of the IDUA enzyme result in impaired lysosomal degradation of the GAGs dermatan sulfate and heparan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body. The resulting accumulation of GAGs leads to progressive cellular and multi-organ dysfunction with variable phenotypes. The most common clinical features of MPS I include facial coarsening, chronic rhinitis, recurrent otitis media, hepatosplenomegaly, corneal clouding, inguinal and umbilical hernias, valvular heart disease, respiratory insufficiency, joint stiffness and contractures, dysostosis multiplex, short stature, developmental delay, and progressive cognitive decline (among the most severely affected patients). Patients typically require multiple surgical interventions to address ear, nose, and throat and airway issues, repair hernias, correct bone malformations, and release peripheral nerve entrapments.

DISCUSSION

MPS I is a rare, progressive, life-threatening autosomal recessive condition with a worldwide incidence of approximately 1 per 100,000 live births. It is caused by defects in the gene coding for the enzyme IDUA. Reduced levels of the IDUA enzyme result in impaired lysosomal degradation of the GAGs dermatan sulfate and heparan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body. The resulting accumulation of GAGs leads to progressive cellular and multi-organ dysfunction with variable phenotypes. The most common clinical features of MPS I include facial coarsening, chronic rhinitis, recurrent otitis media, hepatosplenomegaly, corneal clouding, inguinal and umbilical hernias, valvular heart disease, respiratory insufficiency, joint stiffness and contractures, dysostosis multiplex, short stature, developmental delay, and progressive cognitive decline (among the most severely affected patients). Patients typically require multiple surgical interventions to address ear, nose, and throat and airway issues, repair hernias, correct bone malformations, and release peripheral nerve entrapments.

DISCUSSION

MPS I is a rare, progressive, life-threatening autosomal recessive condition with a worldwide incidence of approximately 1 per 100,000 live births. It is caused by defects in the gene coding for the enzyme IDUA. Reduced levels of the IDUA enzyme result in impaired lysosomal degradation of the GAGs dermatan sulfate and heparan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body. The resulting accumulation of GAGs leads to progressive cellular and multi-organ dysfunction with variable phenotypes. The most common clinical features of MPS I include facial coarsening, chronic rhinitis, recurrent otitis media, hepatosplenomegaly, corneal clouding, inguinal and umbilical hernias, valvular heart disease, respiratory insufficiency, joint stiffness and contractures, dysostosis multiplex, short stature, developmental delay, and progressive cognitive decline (among the most severely affected patients). Patients typically require multiple surgical interventions to address ear, nose, and throat and airway issues, repair hernias, correct bone malformations, and release peripheral nerve entrapments.

DISCUSSION

MPS I is a rare, progressive, life-threatening autosomal recessive condition with a worldwide incidence of approximately 1 per 100,000 live births. It is caused by defects in the gene coding for the enzyme IDUA. Reduced levels of the IDUA enzyme result in impaired lysosomal degradation of the GAGs dermatan sulfate and heparan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body. The resulting accumulation of GAGs leads to progressive cellular and multi-organ dysfunction with variable phenotypes. The most common clinical features of MPS I include facial coarsening, chronic rhinitis, recurrent otitis media, hepatosplenomegaly, corneal clouding, inguinal and umbilical hernias, valvular heart disease, respiratory insufficiency, joint stiffness and contractures, dysostosis multiplex, short stature, developmental delay, and progressive cognitive decline (among the most severely affected patients). Patients typically require multiple surgical interventions to address ear, nose, and throat and airway issues, repair hernias, correct bone malformations, and release peripheral nerve entrapments.
years, usually from obstructive airway disease, respiratory infection, and cardiac complications. Patients at the other end of the spectrum are categorized as having the Scheie phenotype. These individuals usually have a more attenuated disease course but can experience a similar range of progressively debilitating manifestations. Patients with the Scheie phenotype are usually not diagnosed until adolescence or adulthood because early disease manifestations are subtle or mimic those of other more common disorders. Early symptoms in the Scheie phenotype include cardiac valve abnormalities, corneal clouding, joint contractures, hernias, and carpal tunnel syndrome. Patients with this phenotype retain normal intellect, can attain normal stature, and usually survive into adulthood, although often with significant morbidity. MPS I Hurler-Scheie syndrome is of intermediate severity, with onset in early childhood and mild to moderate cognitive impairment.

Measurement of urinary GAG levels is commonly used as a screening test for MPS I, and although it is relatively sensitive, it is a nonspecific test. In addition, urinary GAG levels may vary with time of collection, and dilute urine can result in false-negative results. Definitive diagnosis of MPS I is made by enzyme assay demonstrating deficient IDUA activity in fibroblasts, leukocytes, serum, or dried blood spots, and can be confirmed by genotyping. Prenatal diagnosis is available for at-risk couples.

Treatment options for patients with MPS I include hematopoietic stem cell transplant for patients with Hurler syndrome, and enzyme replacement therapy with laronidase for patients with Hurler-Scheie and Scheie syndrome. Symptom-based supportive treatment remains an important part of disease management even when an affected individual has received disease-specific therapy. Common surgical interventions include ventriculoperitoneal shunt, corneal transplant, myringotomy, tonsillectomy/adenoidectomy, herniorrhaphy, and cardiac valve replacement. Other supportive therapies consist of special education, hearing aids, and physical and occupational therapy.

CONCLUSION

MPS I should be considered in the differential diagnosis of pediatric patients with carpal tunnel syndrome and/or joint immobility without an inflammatory component.

REFERENCES