THE MUCOPOLYSACCHARIDOSES: A HETEROGENEOUS GROUP OF DISORDERS WITH VARIABLE PEDIATRIC PRESENTATIONS

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The mucopolysaccharidoses (MPSs) are a heterogenous group of lysosomal storage disorders, each caused by deficiency of an enzyme involved in the degradation of glycosaminoglycans (previously called *mucopolysaccharides*). These enzyme deficiencies lead to accumulation of glycosaminoglycans in the lysosomes of most cells (Fig 1), resulting in cell, tissue, and organ dysfunction. During the past decade, our understanding of the molecular basis and the varied clinical manifestations of these disorders has evolved greatly. These disorders are more complex, more heterogenous, and may be more prevalent than was previously assumed.

The various MPS types and subtypes and their biochemical basis (Table I) have been reviewed comprehensively elsewhere[1,2]; here we focus on the signs and symptoms that should alert pediatricians to the possibility of these disorders, for which diagnosis is often delayed. We also address common misconceptions about disease spectrum, nomenclature, and significance of laboratory findings—misconceptions that have arisen because of incomplete and evolving knowledge of these disorders. Finally, we provide an overview of treatment options, focusing on available or soon-to-be-available disease-specific therapies for MPS types I (Hurler, Hurler-Scheie, Scheie), II (Hunter), and VI (Maroteaux-Lamy).

INCIDENCE AND CLINICAL MANIFESTATIONS OF THE MUCOPOLYSACCHARIDOSIS DISORDERS

The overall prevalence of the MPS disorders is difficult to estimate because of the scarcity of population-based studies and epidemiologic data. Most countries, including the United States, have no means of tallying the number of cases diagnosed in a given period. However, a retrospective study of the Australian population from 1980 through 1996 found a combined prevalence of MPS disorders of one per 22,500.[3] The incidence in the United States is unknown. It is hoped that disease registries will aid in collecting data that can be used to assess the actual frequency and document the natural history of these disorders in various populations.

The MPS disorders are inherited in an autosomal-recessive manner, except for MPS II (Hunter syndrome), which is X-linked–recessive and thus primarily affects male patients. A small number of female patients have been diagnosed with MPS II because of autosomal X-chromosomal translocation and nonrandom X-chromosome inactivation.

The MPS disorders have a chronic, progressive course, although the age of the onset of symptoms and severity of clinical disease can vary markedly. Most of the disorders are characterized by multisystem involvement, abnormal facies (Fig 2), organomegaly, and dysostosis multiplex (a specific pattern of radiologic changes caused by defective bone formation; Fig 3).[1] Clinical presentation, severity of symptoms, and central nervous system involvement can vary widely both within and between the seven major types, distinguished by the specific enzyme deficiency, the major clinical features, or both.

HSCT	Hematopoietic stem cell transplantation	MPS	Mucopolysaccharidosis
IDS	Iduronate sulfatase		

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I hereby disclose my following affiliation, financial agreement, or other involvement with the companies whose products are discussed in the article. I have been a principal investigator for the phase I/II and phase III MPS I enzyme replacement clinical trials that are described in this article and that resulted in the approval of enzyme replacement therapy for MPS I. I have no formal consulting arrangement or formal affiliation with either Genzyme Corp or BioMarin Pharmaceutical, the cosponsors of the phase III clinical trial. I do speak at Genzyme Corp-sponsored meetings related to diagnosis, management, and treatment of MPS I. I have been a principal investigator for the phase I/II MPS II enzyme replacement clinical trial (sponsor: Transkaryotic Therapies) mentioned in the article. I am a consultant for Transkaryotic Therapies related to the development of enzyme replacement therapy for MPS II. I have no conflict of interest concerning Genzyme Corp, BioMarin Pharmaceutical, or Transkaryotic Therapies per the University of North Carolina at Chapel Hill guidelines. I do not hold any Transkaryotic Therapies, Genzyme Corp, or BioMarin Pharmaceutical stocks, nor will I receive any income or stocks related to the sale of Aldurazyme.

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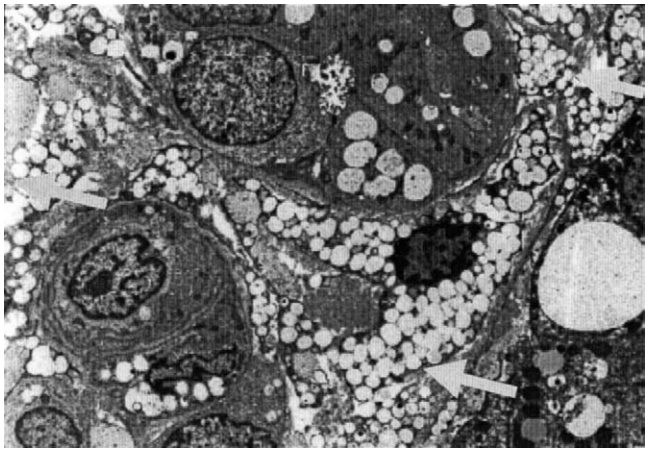

Fig 1. Conjunctival tissue showing substrate storage in MPS I. Conjunctival biopsy showing fibroblasts with multiple distended lysosomes. Printed with permission from Hodder/Arnold Publishers.

Like all lysosomal storage disorders, the MPS disorders are best managed in a multidisciplinary manner, with care coordinated by a physician with experience treating the particular disorder. Supportive therapy can improve quality of life for many patients and their families. Hematopoietic stem cell transplantation (HSCT) using bone marrow or cord blood, although not curative or risk-free, can vastly improve outcome for selected patients, typically those with the severe form of MPS I and MPS VI. Emerging therapies such as enzyme replacement therapy—now approved for patients with MPS I and in clinical trials for two other MPS disorders (MPS II and MPS VI)—have a much lower risk profile and may be helpful to a broad range of patients. Availability of disease-specific therapy heightens the need for early diagnosis so that treatment can be initiated before irreversible disease progression.

NOMENCLATURE

Classification of the MPS disorders is complex and often confusing because the nomenclature has evolved with our understanding of these diseases. Many disorders (or subsets of the disorders with distinct phenotypes) were named for the physician describing the clinical features before the genetic basis of the disorder, its relation to the lysosome, or even the existence of the lysosome was understood. These common or historic names are often used interchangeably with the more specific type designations (which have also changed through the years) that classify the disorders by their biochemical bases. All of this has led to confusion about terminology; for example, many physicians refer to all forms of MPS I as *Hurler syndrome*, when this common name now correctly refers only to severe MPS I. Use of the term *mild* to describe less severe forms of some disorders is also misleading, because even patients with MPS I who have comparatively mild disease (ie, they survive beyond age 10 years) can still have very significant health problems and die in their late teenage years to early 20s. It is more correct to use the term *attenuated* to refer to the less severe MPS forms.

There are seven MPS types: I, II, III, IV, VI, VII, and IX[1,2,4] (Table I). Note that designations V and VIII are no longer used and that only one patient has been described with type IX.[5] Two of the seven types (MPS III and MPS IV) also have subtypes, which indicate a different genetic basis for the same clinical presentation. For example, MPS III, Sanfilippo syndrome, has four subtypes (A–D), each of which has a very similar phenotype and the same storage material, but each subtype is caused by a different enzyme deficiency.

We recommend using the type nomenclature for the MPS disorders because it is more informative and precise than use of the common names.

HETEROGENEITY OF THE MUCOPOLYSACCHARIDOSIS DISORDERS

Each MPS disorder represents a broad continuum of severity and range of manifestations. For example, the severe and attenuated (previously called *mild*) forms of MPS I—named Hurler syndrome and Scheie syndrome, respectively, after their discoverers—were originally thought to be unrelated. It is understandable that no connection was made between these two presentations, considering that Hurler is characterized by onset in infancy or early childhood, severe somatic and neurologic manifestations, and death before age 10 years, whereas Scheie is characterized by normal intelligence and typically normal stature, milder somatic manifestations, and survival until late adulthood. When both syndromes were linked to deficiency of the same enzyme (α-L-iduronidase), it was then thought that there was a Hurler mutation and a Scheie mutation that gave rise to the two phenotypes, and that patients with an intermediate phenotype (referred to as *Hurler-Scheie*) had both mutations (compound heterozygotes). The clinical picture that emerged is much more complex. Hurler syndrome and Scheie syndrome represent two ends of a wide spectrum of clinical severity. To date, 74 MPS I mutations have been detected (http://www.hgmd.org),[6] and most patients fall between the Hurler and Scheie ends of the spectrum. In addition, even among patients with MPS I with the same general disease severity (eg, Hurler-Scheie syndrome), manifestations can vary markedly, with one patient having prominent organomegaly and minor skeletal involvement and another the reverse. Many factors can contribute to this clinical heterogeneity—the nature or type of mutation, the degree of residual enzyme activity, possible environmental factors, and other, unknown genetic factors.

Patients with MPS II can also have atypical features caused by partial or complete deletions of other genes on the X-chromosome adjacent to the gene for iduronate sulfatase (contiguous gene syndrome). The clinical spectrum of disease severity is narrower for the common forms of MPS III (types A and B), with the majority of patients severely involved. Patients with the attenuated or mild forms of MPS III are probably not diagnosed, because the only presenting feature

Table I. Biochemical classification of the mucopolysaccharide disorders

Number*	Eponym	Enzyme deficiency	Glycosaminoglycan stored
MPS I (severe)	Hurler syndrome	α-L-iduronidase	Dermatan sulfate, heparan sulfate
MPS I (attenuated)	Scheie syndrome	α-L-iduronidase	Dermatan sulfate, heparan sulfate
MPS I (attenuated)	Hurler-Scheie syndrome	α-L-iduronidase	Dermatan sulfate, heparan sulfate
MPS II (severe)	Hunter (severe) syndrome	Iduronate sulfatase	Dermatan sulfate, heparan sulfate
MPS II (attenuated)	Hunter (mild) syndrome	Iduronate sulfatase	Dermatan sulfate, heparan sulfate
MPS IIIA	Sanfilippo A syndrome	Heparan N-sulfatase	Heparan sulfate
MPS IIIB	Sanfilippo B syndrome	α-N-acetyl-glucosaminidase	Heparan sulfate
MPS IIIC	Sanfilippo C syndrome	Acetyl CoA:α-glucosaminide acetylytransferase	Heparan sulfate
MPS IIID	Sanfilippo D syndrome	N-acetylglucosamine 6-sulfatase	Heparan sulfate
MPS IVA	Morquio syndrome, type A	Galactose-6-sulfatase	Keratan sulfate, chondroitin 6-sulfate
MPS IVB	Morquio syndrome, type B	β-galactosidase	Keratan sulfate
MPS VI	Maroteaux-Lamy syndrome	N-acetylgalactosamine 4-sulfatase (arylsulfatase B)	Dermatan sulfate
MPS VII	Sly syndrome	β-glucuronidase	Dermatan sulfate, heparan sulfate chondroitin 4-,6-sulfates
MPS IX		Hyaluronidase	Hyaluronan

*Note that MPS type designations V and VII are no longer used.

may be mild mental retardation without any significant physical involvement.

PRESENTING SYMPTOMS

Mucopolysaccharidosis disorders often initially present subtly. Most affected children with an MPS disorder appear normal at birth and only later in infancy or childhood begin to display signs or symptoms. The one exception is that hydrops fetalis is a common presentation of MPS VII.[1]

A study of patients with severe MPS I found that 45% of parents reported that something about their child's appearance was their first clue that their child was not progressing normally and that 25% were unaware that anything was unusual about their child until diagnosis.[7] Table II lists some important red flags that should warrant consideration of an MPS diagnosis. Especially important to follow up are inguinal or umbilical hernias, loss of developmental skills, and any gradual, progressive changes in physical appearance. Note that a constellation of suggestive findings is especially significant, but that absence of a particular finding or characteristic does not necessarily rule out an MPS diagnosis.

All MPS disorders with the exception of MPS III have distinct somatic manifestations. Patients with the severe forms of MPS I, MPS II, and MPS VIII (Sly) also have progressive mental retardation. In contrast, patients with MPS IV (Morquio) and MPS VI have no mental retardation regardless of the severity of their somatic disease. Patients with MPS III have only subtle somatic manifestations but marked central nervous system involvement, resulting in severe mental retardation, hyperactivity, and behavioral problems. Some patients with MPS with severe somatic disease can give the impression of being more neurologically involved than they actually are because of abnormal speech from decreased hearing, an enlarged tongue, and decreased ability to perform manual testing secondary to joint restrictions, poor vision, and respiratory insufficiency.

DIAGNOSIS

Enzyme assays are available for the diagnosis of all of the MPS disorders.[1] Any patient diagnosed with an MPS disorder based on clinical findings does not have a confirmed diagnosis until the suspected enzyme deficiency is documented. All diagnostic testing should be overseen by a clinician who has expertise in lysosomal storage disorders, because the assays are complex and results can be difficult to interpret. Quantitative urinary glycosaminoglycan analysis can be helpful in some cases to determine which enzymes should be tested when the more common MPS disorders have already been ruled out. Note that both female and male patients with multiple sulfatase deficiency have been misdiagnosed with MPS II. All patients with absent iduronate sulfatase activity should have documentation of another normal sulfatase assay before a diagnosis of MPS II is confirmed.

Residual enzyme activity is difficult to quantify accurately when measured in a diagnostic laboratory and is thus not a valid predictor of disease outcome. Patients with MPS I and MPS II with mutations that predict no enzyme production can expect a severe prognosis. However, patients with a residual activity as low as 0.1% to 0.3% when measured with synthetic substrates can have an attenuated clinical course.

When a patient is diagnosed with a MPS disorder, genetic counseling is recommended. Genetic counseling can provide the family with information regarding the genetics, inheritance, and recurrence risks for the specific MPS condition in their family. For all MPS conditions with the exception of MPS II, inheritance is autosomal-recessive, and

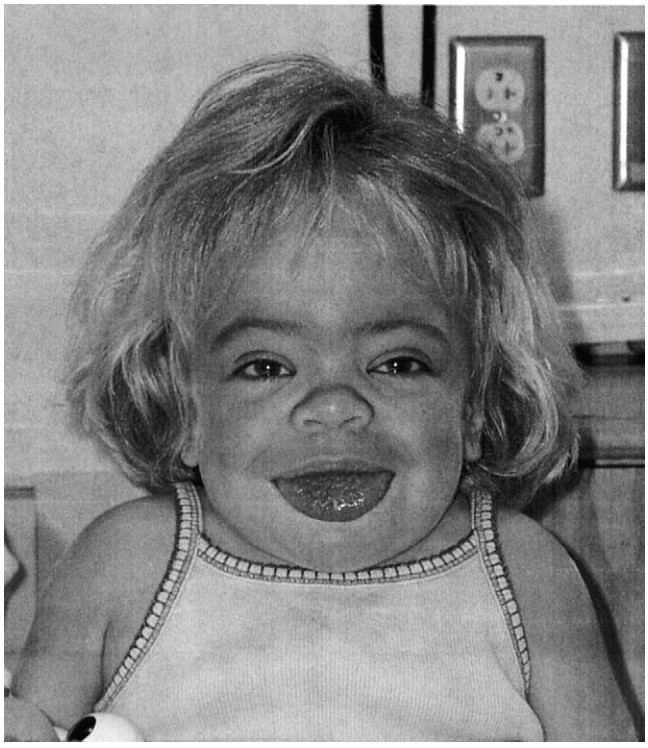

Fig 2. Facial features in MPS I. Five-year-old with severe MPS I (Hurler syndrome) with coarse facial features, macrocephaly, prominent forehead, corneal clouding, and enlarged tongue. Major clinical problems include delayed development, severe obstructive airway disease, hydrocephalus (shunted), valvular heart disease, hearing loss, decreased joint range of motion, and umbilical hernia.

two carrier parents are at 25% risk to have another affected pregnancy.

Mucopolysaccharidosis II is inherited in an X-linked manner and is therefore usually seen in male patients. Male patients may have MPS II as a result of inheriting a mutation in the iduronate sulfatase (IDS) gene from their carrier mother or as the result of a new mutation. If a woman is a carrier of an IDS mutation, four equally likely outcomes are possible for each pregnancy: 25% chance of unaffected male, 25% chance of affected male, 25% chance of unaffected female, and 25% chance of carrier female. Male patients with MPS II who have children will pass the abnormal IDS gene on to all of their daughters and none of their sons.

Siblings of a patient with MPS may be interested in their carrier status to determine if they are at risk for having a child with their sibling's MPS disorder. Accurate estimates of population incidence are not available, and therefore, the carrier frequency in the general population is difficult to determine. Patients with a sibling with an autosomal recessive MPS condition should be counseled that although there is a two in three chance that they are a carrier for that condition, it is unlikely that their partner is also a carrier (assuming that partner does not have a family history of the same MPS disorder), and therefore, their risk of having an affected child is minimal. It is important to note that this risk is considerably less than the general population risk of approximately 3% to 5% of having a child with a physical birth defect or mental retardation.

Mutation analysis is essential for carrier detection and is also recommended for many patients (typically those with MPS I or MPS II), because knowing the nature and type of mutation can sometimes provide information about possible outcome.[1] Carrier detection by enzyme analysis for MPS II is unreliable and has resulted in both false-negative and false-positive results. Prenatal diagnosis can be performed by enzyme assay of tissue obtained by amniocentesis or chorionic villus sampling, although the former is usually easier for most laboratories to perform accurately, because some normal enzyme levels are quite low in chorionic villi. False-negative results have occurred when only chorionic villus sampling has been used for prenatal diagnosis.

TREATMENT

Correction of glycosaminoglycan metabolism in cultured MPS cells has been possible since the early 1970s.[1] Early clinical attempts to replace the missing enzymes in patients with MPS failed probably because inadequate enzyme was given, although only 1% to 2% of residual enzyme activity is needed to correct glycosaminoglycan metabolism.[1] Until the 1980s, only palliative and nonspecific therapies were available for patients with the MPS disorders (eg, speech/behavioral therapy, heart valve replacement, surgery for skeletal abnormalities). This changed with the advent of bone marrow transplantation, which has proven beneficial in select cases, primarily the severe forms of MPS I and MPS VI. Recent clinical trials of enzyme replacement therapy have shown promise in the treatment of MPS I, MPS II, and MPS VI, and enzyme replacement therapy recently became commercially available for MPS I. Other therapies being investigated but not yet in clinical trial include gene therapy and drug therapy with small molecules. Optimal therapy for children with an MPS disorder is likely to involve both disease-specific treatments and symptom-based nonspecific treatments. Early disease-specific treatment before the development of irreversible damage (ie, fibrosis of heart valves) should result in an improved outcome no matter what the type of treatment.

Importance of Multidisciplinary approach to Treatment

Because children with an MPS disorder usually have a broad spectrum of disease manifestations, their overall care is best overseen by a physician (typically a geneticist) with experience in that particular disorder who can refer the patient to specialists as needed and ensure that optimal care is being received on all fronts. Most patients with MPS will require care from a broad range of specialists—cardiologists, neurologists, pulmonologists, otolaryngologists, ophthalmologists,

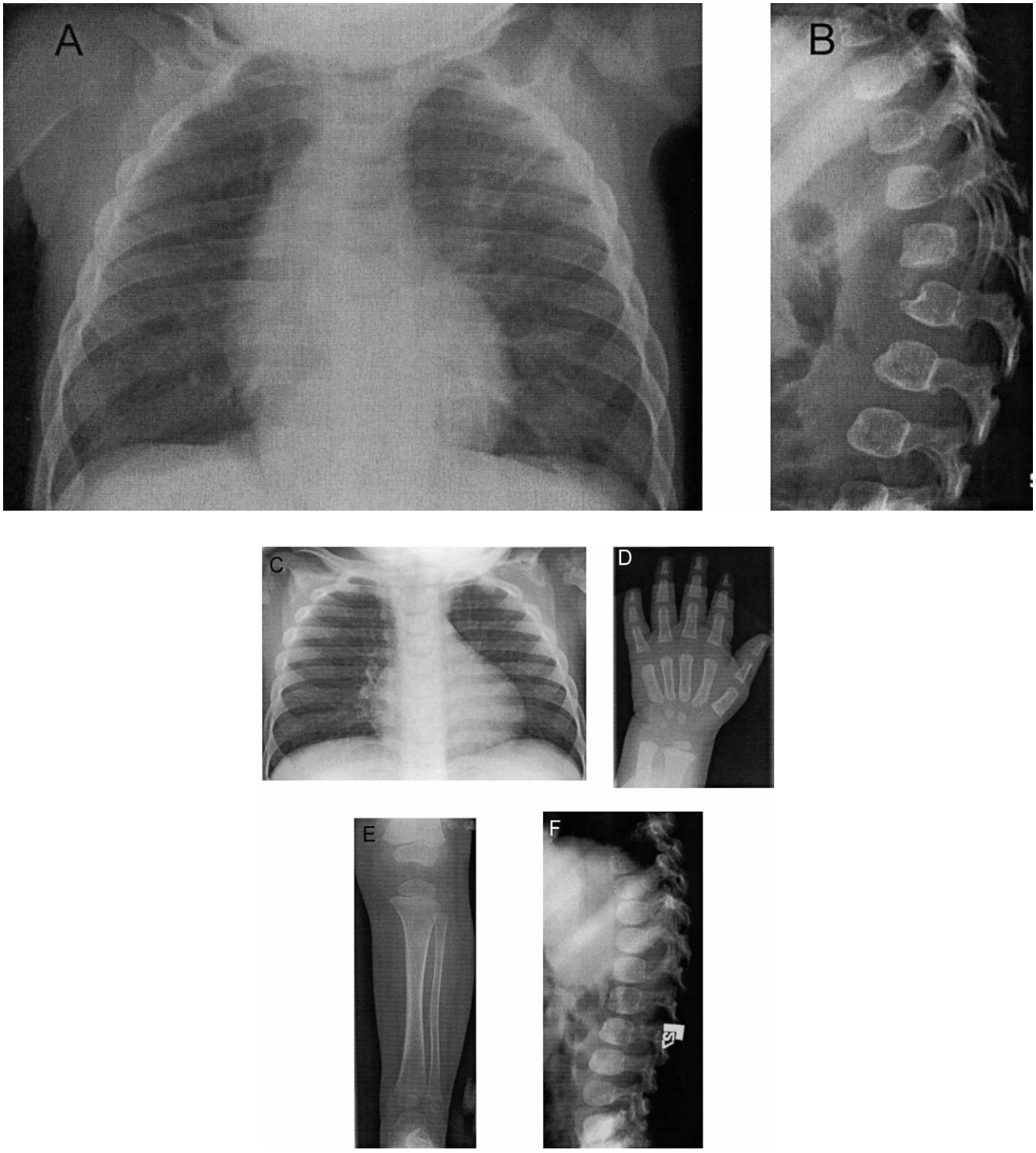

Fig 3. Dysostosis multiplex in severe MPS I and MPS II. **A, B**, Severe MPS I (Hurler syndrome). Note chest with oar-shaped ribs and short thickened clavicles **(A)** and lumbar spine with beaking of the L2 and L3 vertebral bodies and gibbus deformity at L1-L2 **(B)**. C-F, Severe MPS II (Hunter syndrome, severe). Note chest with calvarial thickening, oar-shaped ribs, and normal heart size **(C)**, hand with widening and coarse trabeculations of the metacarpals and short phalanges **(D)**, diaphyseal thickening of lower extremity **(E)**, and lumbar spine with mild beaking of L1, L2, and L3 **(F)**.

orthopedic surgeons, physical therapists, speech therapists, and so forth. All of these specialists should have a basic understanding of the child's disorder and how other disease manifestations may affect treatment decisions or require special consideration. For example, children with MPS I, II, IV, VI, and VII present major anesthetic risks because of limited visibility during intubation caused by redundant supraglottic tissues, an airway smaller than expected for their age,

Table II. Possible presenting features of a MPS disorder in infants and children*

Physical appearance
Macrocephaly
Progressively coarsening of facial features such as prominent forehead, broad nose with flat nasal bridges, macroglossia, and thickened lips
Protruding abdomen due to hepatosplenomegaly
Inguinal or umbilical hernias
Hirsutism
Neurologic/behavioral/developmental
Loss of development skills such as speech and learning
Mild mental deterioration
Behavioral problems
Hyperactivity
Hydrocephalus (communicating type)
Ophthalmologic
Corneal clouding
Photophobia
Ears, nose, and throat
Recurrent otitis media
Chronic rhinitis
Enlarged tonsils and adenoids
Hearing loss
Abnormal teeth (spacing and shape)
Pulmonary
Frequent pneumonias
Reactive airway disease
Noisy breathing
Snoring caused by upper airway obstruction
Cardiac
Murmur caused by valvular disease
Cardiomyopathy
Musculoskeletal
Decreased joint range of motion
Bone deformities (dysostosis multipex)
Decreased hand fine motor skills
Lumber kyphosis
Unusual gait or stance

*Note that these are collective findings; individual patients will have varied presentations, and absence of a particular finding or findings does not necessarily rule out an MPS disorder.

and unstable atlantoaxial joints, and should only undergo general anesthesia in centers staffed by anesthesiologists experienced in these disorders.[1] Death caused by complications of anesthesia still occurs for these disorders.

Psychosocial Aspects

Counseling and psychosocial support are essential resources to offer to patients with MPS and their families, who must live day to day with these devastating, progressive diseases. The anguish parents feel watching a child deteriorate physically or mentally, sometimes with no hope of improvement or of an acceptable quality of life, cannot be underestimated. Caring for a very ill child also severely taxes family resources in all possible ways. Many families find that maintaining contact with other families struggling with similar issues can help them cope with feelings of isolation and despair. Fortunately, several organizations exist that help MPS families connect with one another and also provide up-to-date, comprehensive disease information (Appendix). Booklets on anesthesia and disease specific management of the MPS disorders are available from the National MPS Society.

Disease Management and Nonspecific Therapies

Disease management and nonspecific therapies do not address the underlying cause of disease but can significantly improve lifespan or quality of life for many patients and their caregivers. These include surgical interventions such as ventriculoperitoneal shunting for communicating hydrocephalus, spinal fusion for spinal cord compression or progressive kyphosis, median nerve release for carpal tunnel syndrome, hernia repair, tonsillectomy and adenoidectomy for airway obstruction or eustachian tube dysfunction, corneal transplant for corneal clouding, and cardiac valve replacement for mitral or aortic regurgitation or stenosis. Physical therapy is important for many patients to minimize joint contractures and stiffness and improve muscle strength. Speech therapy and behavioral therapy can also help children and their families cope with diminishing developmental skills. Patients with obstructive sleep apnea may require continuous positive airway pressure or bilevel positive airway pressure, or, as airway disease progresses, a tracheostomy.

Hematopoietic Stem Cell Transplantation

The goal of HSCT in MPS disorders is to reconstitute a patient's hematopoietic system with normal stem cells that produce the missing enzyme. Initially, bone marrow was used as a source of donor cells for HSCT; more recently, cord blood is being used. All cells are believed to produce hydrolytic enzymes for degrading macromolecular compounds in their lysosomes but also release small amounts of these enzymes into the extracellular space. These released lysosomal enzymes may reach nearby cells or other tissues through the systematic circulation. Most cell types are believed to have a receptor-mediated uptake mechanism using the mannose-6-phosphate recognition signal to capture circulating lysosomal enzymes and then deliver the enzyme to the lysosome. Thus, with a successful HSCT, the missing or deficient enzyme is produced endogenously by hematopoietic derived cells, such as circulating macrophages and brain microglial cells, and thus may be taken up by deficient cells. Many factors, most of them not well understood, also contribute to a successful HSCT, such as removal of the tissue storage of glycosaminoglycans by macrophages derived from the new bone marrow.

Hematopoietic stem cell transplantation is at least partially successful in selected patients with the most severe form of MPS I,[8-12] MPS II,[13,14] and MPS VI.[15] More than 200 children with MPS I have received HSCT.[1,16] Early transplantation in MPS I (before 24 months of age and onset of neurologic disease) can prevent central nervous system

involvement, reduce organomegaly, improve cardiac function and linear growth, and improve upper airway obstruction. Although HSCT results in decreased storage in most somatic tissues, eye and skeletal disease in MPS I patients is not significantly improved after transplantation. Multiple orthopedic procedures after successful HSCT in patients with MPS I are typically required with the prolonged life span resulting from transplantation. The use of recombinant enzyme replacement therapy before HSCT in MPS I may improvement engraftment and enhance outcome.[17]

Hematopoietic stem cell transplantation experience in MPS disorders is limited except in MPS I. Although HSCT can improve somatic disease in MPS II and MPS III, it is not currently recommended for those disorders because neurological benefit has not been demonstrated and because the procedure itself is associated with high morbidity and mortality. Morbidity and mortality associated with HSCT have improved, but it is still associated with significant risk (greater than 15%–20% mortality) because of the toxicity of the conditioning regimen, bone marrow ablation, and graft-versus-host disease.

Enzyme Replacement Therapy

Enzyme replacement therapy replaces the missing enzyme exogenously, through regular intravenous infusions. With the advent of genetic engineering techniques, recombinant human enzyme can be generated, obviating the need for enzyme purification from human or animal tissue. The major advantages of enzyme replacement therapy are that it can deliver more enzyme than is produced with HSCT, is associated with significantly lower risk, and is appropriate for a much broader range of patients. Its major disadvantage is that intravenously delivered enzyme cannot cross the blood–brain barrier.

Enzyme replacement therapy is now available for the treatment of three lysosomal storage diseases: Gaucher disease,[18] Fabry disease,[19,20] and MPS I.[21,22] Human macrophage-targeted glucocerebrosidase preparations have been available for treatment of Gaucher disease for more than a decade—first as placentally-derived alglucerase, then as the recombinant human enzyme imiglucerase (Ceredase and Cerezyme, respectively, Genzyme Corp, Cambridge, Mass). Agalsidase alfa (Replagal, Transkaryotic Therapies, Cambridge, Mass) and agalsidase beta (Fabrazyme, Genzyme Corp) were both approved for treatment of Fabry disease in Europe in 2001; in the United States, only agalsidase beta has been approved (April 2003). Laronidase (Aldurazyme, BioMarin Pharmaceutical, Novato, Calif, and Genzyme Corp), recombinant human α-L-iduronidase, was approved for the treatment of MPS I in April 2003 in the United States and in June 2003 in the European Union. In the United States, laronidase is approved for the treatment of the Hurler and Hurler-Scheie forms of MPS 1 and for patients with the Scheie form who have moderate to severe symptoms. In the European Union, laronidase is approved for treatment of the nonneurological manifestation of MPS I. Laronidase has not been evaluated for effects on the central nervous system manifestations of MPS I.

In a phase I/II open-label study, 10 patients with MPS I (eight with the Hurler-Scheie, one with the Hurler, and one with the Scheie form of MPS 1) age 5 to 22 years received weekly infusions of recombinant human α-L-iduronidase (0.58 mg/kg). After 52 weeks of treatment, patients had decreased urinary glycosaminoglycan excretion, reduction in hepatomegaly, improved growth, improved joint range of motion, and improved New York Heart Association scores.[21] A phase III randomized placebo-control study and open-label extension study of 45 patients (37 with the Hurler-Scheie, 7 with the Scheie, and 1 with the Hurler form) confirmed the biochemical changes found in the phase I/II study and demonstrated improved pulmonary function and walking ability.[22]

Two other enzyme replacement therapies for MPS disorders are currently being investigated. Recombinant human iduronate-2-sulfatase (Transkaryotic Therapies, Cambridge, Mass) has been evaluated in 12 patients with MPS II in a double-blind, placebo-controlled, dose-escalation phase I/II trial. After 1 year of treatment, urine glycosaminoglycan excretion and liver and spleen reduction were observed, with improvements in the 6-minute walk test and joint range of motion. Recombinant human arylsulfatase B (Aryplase, BioMarin Pharmaceutical) is currently being evaluated in an open-label phase II trial with 10 patients with MPS VI, after completion of a 24-week phase I/II double-blind trial with six patients. In the phase II study, the MPS VI subjects had improvements in endurance as measured by the 6-minute and 12-minute walk tests and functional improvement in joint pain and stiffness and shoulder joint range of motion. Double-blind, placebo-controlled phase III enzyme replacement clinical trials for MPS II and MPS VI were both started in September 2003.

CONCLUSION

The outlook for children with MPS disorders continues to improve because of progress in our understanding of these diseases and the development of disease-specific treatments. Children with MPS disorders can present in a variety of ways, and pediatricians and pediatric specialists need to be alerted to warning signs and symptoms so that patients can be recognized and provided with up-to-date comprehensive care from clinicians who specialize in these disorders.

REFERENCES

1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. The metabolic and molecular bases of inherited disease. New York: McGraw Hill; 2001. p. 3421-52.

2. Hopwood JJ, Morris CP. The mucopolysaccharidoses: diagnosis, molecular genetics and treatment. Mol Biol Med 1990;7:381-404.

3. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281:249-54.

4. Clarke LA. Clinical diagnosis of lysosomal storage diseases. In: Applegarth DA, Dimmick JE, Hall JG, eds. Organelle diseases. London: Chapman and Hall; 1997. p. 37-71.

5. Natowicz MR, Short MP, Wang Y, Dickersin GR, Gebhardt MC, Rosenthal DI, et al. Clinical and biochemical manifestations of hyaluronidase deficiency. N Engl J Med 1996;335:1029-33.
6. Stenson PD, Ball EV, Mort M, Phillips AD, Shiel JA, Thomas NS, et al. Human Gene Mutation Database (HGMD(R)): 2003 update. Hum Mutat 2003;21:577-81.
7. Colville GA, Bax MA. Early presentation in the mucopolysaccharide disorders. Child Care Health Dev 1996;22:31-6.
8. Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD, et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. Blood 1996;87:4894-902.
9. Guffon N, Souillet G, Maire I, Straczek J, Guibaud P. Follow-up of nine patients with Hurler syndrome after bone marrow transplantation. J Pediatr 1998;133:119-25.
10. Hite SH, Peters C, Krivit W. Correction of odontoid dysplasia following bone-marrow transplantation and engraftment (in Hurler syndrome MPS 1H). Pediatr Radiol 2000;30:464-70.
11. Kachur E, Del Maestro R. Mucopolysaccharidoses and spinal cord compression: case report and review of the literature with implications of bone marrow transplantation. Neurosurgery 2000;47:223-228; discussion 8–9.
12. Peters C, Shapiro EG, Anderson J, Henslee-Downey PJ, Klemperer MR, Cowan MJ, et al. Hurler syndrome, II: outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty-four children. The Storage Disease Collaborative Study Group. Blood 1998;91:2601-8.
13. Hoogerbrugge PM, Brouwer OF, Bordigoni P, Ringden O, Kapaun P, Ortega JJ, et al. Allogeneic bone marrow transplantation for lysosomal storage diseases. The European Group for Bone Marrow Transplantation. Lancet 1995;345:1398-402.
14. Vellodi A, Young E, Cooper A, Lidchi V, Winchester B, Wraith JE. Long-term follow-up following bone marrow transplantation for Hunter disease. J Inherit Metab Dis 1999;22:638-48.
15. Herskhovitz E, Young E, Rainer J, Hall CM, Lidchi V, Chong K, et al. Bone marrow transplantation for Maroteaux-Lamy syndrome (MPS VI): long-term follow-up. J Inherit Metab Dis 1999;22:50-62.
16. Wraith JE. Advances in the treatment of lysosomal storage disease. Dev Med Child Neurol 2001;43:639-46.
17. Krivit W. Stem cell bone marrow transplantation in patients with metabolic storage diseases. Adv Pediatr 2002;49:359-78.
18. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med 2002;113:112-9.
19. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, et al. Safety and efficacy of recombinant human alpha-galactosidase A–replacement therapy in Fabry's disease. N Engl J Med 2001;345:9-16.
20. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001;285:2743-9.
21. Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, Passage M, et al. Enzyme-replacement therapy in mucopolysaccharidosis I. N Engl J Med 2001;344:182-8.
22. Clarke L, Muenzer J, Kolodny EH, Pastores G, Beck M, Wraith JE. RhIDU enzyme replacement therapy for MPS I: 24 week extension study. Am J Hum Genet 2002;71(Suppl):481.

APPENDIX

Organizations Providing Information and Support to Patients With Mucopolysaccharidosis and Families

National MPS Society
45 Packard Drive
Bangor, ME 04401
http://www.mpssociety.org*

The Society for Mucopolysaccharide Disease
46 Woodside Drive
Amersham, Buckinghamshire HP6 6AJ
United Kingdom
http://www.mpssociety.co.uk*

Resources for Healthcare Professionals

Genetics Leadership Collaborative
http://www.geneticleadership.com

Lysosomal Storage Disease Network
http://www.lsdn.com

Lysosomal Disease Center, University of Pittsburgh
http://www.pitt.edu/AFShome/g/e/geneorb/public/html/ctr-lyso.html

*These Web sites also provide links to other national and international organizations.