



MEDICAL CARE
FOR CHILDREN & ADULTS WITH
DEVELOPMENTAL
DISABILITIES

SECOND EDITION

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prehensive public health program that literally touches nearly every newborn. Fortunately, parents have many readily available on-line resources (see <http://www.savebabies.com> or <http://www.genes-r-us.utshcsa.edu>). Filter paper card NBS uses various technologies that have saved thousands of children from death and disability. With ongoing evaluation and input from a spectrum of health care professionals and families, NBS will continue as a public health program that benefits the vast majority of infants by protecting them from the consequences of an increasing number of devastating genetic and metabolic disorders.

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7.2 MUCOPOLY-SACCHARIDOSES

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Mr. and Mrs. Klein were devastated to learn that their two daughters, Hillary and Anya, had Hurler syndrome. Hillary had been a typical, healthy baby born full term after an uncomplicated pregnancy when Mrs. Klein (G1P0) was 29 years old. Hillary's skill attainment was normal, and she could walk, climb, and follow simple commands. Mrs. Klein became concerned, however, when Hillary's expressive language was limited to several single words. By 20 months old, Hillary had a history of unusual facial features, chronic congestion, and recurrent otitis media that required placement of bilateral myringotomy tubes.

A physical examination performed by a specialist revealed that Hillary had mild hirsutism; macrocephaly; unusual facial features that included a prominent forehead, flattened nasal bridge, epicanthal folds, thickened lips, and an enlarged tongue; contracted fingers; a gibbus deformity (lumbar kyphosis); a small umbilical hernia; and hepatosplenomegaly. A skeletal X-ray survey noted dysostosis multiplex—a characteristic pattern of skeletal deformities, including a large skull with a deep and elongated sella, oar-shaped ribs, deformed and hook-shaped lower thoracic and lumbar vertebrae, pelvic dysplasia, and shortened tubular bones. Hillary's urine mucopolysaccharide profile was abnormal and noted dermatan sulfate and heparan sulfate. Her α -L-iduronidase activity was absent in leukocytes, confirming the diagnosis of mucopolysaccharidosis I (MPS I). The specialist informed Mr. and Mrs. Klein that Hillary's clinical features were consistent with the most severe form of MPS I, Hurler syndrome. Enzyme testing later confirmed that 6-month-old Anya also was affected.

Hillary underwent bone marrow transplantation from an unrelated donor and seemed to tolerate the procedure well. After a second transplant at 33 months of age, however, she contracted pneumonia and experienced acute renal failure. She passed away at 33 months of age. Mr. and Mrs. Klein were overwhelmed but tried to focus on Anya's treatment. At 11 months old, Anya underwent a successful transplant. By 19 months of age, she demonstrated good growth and development and minimal physical stigmata of Hurler syndrome.

The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by the deficiency of enzymes that catalyze the stepwise degradation of glycosaminoglycans (previously called *mucopolysaccharides*). Glycosaminoglycans form the polysaccharide chains of proteoglycans, which are extracellular matrix macromolecules that are abundant in connective tissue and are

important determinants of the viscoelastic properties of joints and other structures subjected to mechanical forces. The major glycosaminoglycans are chondroitin 6-sulfate, keratan sulfate, heparan sulfate, dermatan sulfate, and hyaluronate (Stryer, 1981).

Depending on the enzyme deficiency, the catabolism of one or more of the glycosaminoglycans is impaired. The lysosomal accumulation of glycosaminoglycan molecules results in cellular, and ultimately organ, dysfunction. Partially or nondegraded glycosaminoglycans are excreted in excess amounts in urine, which is the basis of screening tests. The clinical phenotype is dependent largely on the type and amount of storage material. For example, heparan sulfate is vital to neuronal cell mem-

brane function, and its accumulation in the brain leads to severe neurological complications such as those seen in MPS III (Sanfilippo syndrome) and the severe forms of MPS I (Hurler syndrome) and MPS II (Hunter syndrome). Dermatan sulfate predominates in bone and soft tissues, which accounts for the somatic features seen in MPS I, II, and IV and its relative absence in MPS III. Keratan sulfate, which is even more bone-specific, accounts for the more predominant skeletal features seen in MPS IV.

Ten distinct enzyme deficiencies cause six distinct MPS disorders and their subtypes. Table 7.2-1 outlines the various disorders and their biochemical abnormalities (Beck, 2000).

Table 7.2-1. 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)	Hurler-Scheie syndrome	α -L-iduronidase	Dermatan sulfate, heparan sulfate
MPS I (attenuated)	Scheie syndrome	α -L-iduronidase	Dermatan sulfate, heparan sulfate
MPS II (severe)	Hunter (severe) syndrome	Iduronate-2-sulfatase	Dermatan sulfate, heparan sulfate
MPS II (attenuated)	Hunter (mild) syndrome	Iduronate-2-sulfatase	Dermatan sulfate, heparan sulfate
MPS IIIA	Sanfilippo A syndrome	Heparan-N-sulfatase	Heparan sulfate
MPS IIIB	Sanfilippo B syndrome	α -N-Acetylglucosaminidase	Heparan sulfate
MPS IIIC	Sanfilippo C syndrome	Acetyl-CoA: α -glucosaminide acetyltransferase	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: MPS type designations V and VII are no longer used.

From Beck, M. (2000). Mucopolysaccharidoses and oligosaccharidoses. In J. Fernandes, J.M. Saudubray, & G. Van den Berghe (Eds.), *Inborn metabolic diseases: Diagnosis and treatment* (p. 419; Tables 36.1 and 36.2). New York: Springer; reprinted by permission. With kind permission of Springer Science and Business Media.

CLINICAL PRESENTATION

MPS I is caused by a deficiency of the lysosomal enzyme α -L-iduronidase and is the prototype of all MPS disorders. The spectrum of clinical phenotypes encompasses severe (Hurler disease), intermediate (Hurler-Scheie syndrome), and mild forms (Scheie disease), although it should be appreciated that the disease is a continuum and that "mild" is relative only with respect to the "severe" form, not the general population. *Severe* and *attenuated* are more recently introduced terms used to distinguish individuals with and without progressive cognitive impairment.

Although most babies with Hurler syndrome appear normal at birth, their first year of life is complicated by frequent ear, nose, and throat infections. Macrocephaly, macrosomia, hernias, and noisy breathing are often early features that go unnoticed. Children with severe MPS I subsequently develop unusual facial features (see Figure 7.2-1), thick skin, corneal clouding, hearing loss, hepatosplenomegaly, valvular heart disease, upper airway obstruction, skeletal deformities, joint stiffness, and secondary short stature. Skeletal survey reveals dysostosis multiplex (Figure 7.2-2). Children typically die within the first decade of life due to cardiopulmonary disease and/or neurologic decline.

Individuals with the milder variant (Scheie syndrome) are typically diagnosed in childhood to adulthood, have near-normal height and intelligence, and may have a normal life span. Somatic problems include stiff and painful joints, corneal opacities, carpal tunnel syndrome, and mild skeletal changes. Joint symptoms may be mistaken for arthritis. Chronic respiratory illnesses and mitral and aortic regurgitation due to valvular thickening affect most individuals with Scheie disease. Other individuals with the intermediate phenotype



Figure 7.2-1. The clinical spectrum of MPS I. Microcephaly and unusual facial features in a girl with a more severe form (left photo) and lack of distinctive facial features in an attenuated patient (right photo). (Right photo courtesy of Professor F.A. Wijburg.)



Figure 7.2-2. Multiple bony abnormalities in a 10-month-old boy with severe MPS I (Hurler syndrome). (a) skull x-ray showing a thickened calvarium and a J-shaped sella tursica; (b) chest x-ray showing oar-shaped ribs and short, thickened clavicles; (c) pelvic x-ray showing shallow acetabulum and small capital femoral epiphyses; (d) upper limb x-ray showing widening and abnormal contours of the long bones; (e) hand x-ray showing short and broad metacarpal and phalangeal bones; (f) spine x-ray showing thoracolumbar gibbus deformity with anteroinferior beaking of vertebrae at the thoracolumbar junction.

(Hurler-Scheie syndrome) develop somatic symptoms during childhood that can become debilitating and lead to death in the second to third decades but have little to no cognitive impairment.

Hunter syndrome, or MPS II, is the only X-linked MPS, and thus, almost exclusively affects boys. This dis-

order is caused by a deficiency of iduronate-2-sulfatase, which also leads to the accumulation of heparan sulfate and dermatan sulfate. MPS II can have severe or mild presentations. The severe form of MPS II is similar to MPS I, except for the lack of corneal clouding and slower progression of multisystem problems. The mild form of the disorder is associated with little to no cognitive impairment, a slow somatic course, and a prolonged life span (typically 40s or 50s, with the oldest survivor age 87; Neufeld & Muenzer, 2001).

Sanfilippo syndrome, or MPS III, has four subtypes caused by deficiencies of four different enzymes that all result in the impaired degradation and subsequent accumulation of heparan sulfate. All four subtypes of Sanfilippo syndrome result in severe central nervous system deterioration with minimal somatic problems, which makes this phenotype unique among the MPS disorders. Most individuals with this syndrome appear normal until 3–4 years of age, at which time developmental regression occurs, including loss of speech and gait abnormalities. As the disease progresses, hyperactivity and aggressive behavior usually occur.

Although bony changes are minimal and height growth is typically normal, characteristic somatic signs include coarse, often blond hair as well as hirsutism. Unusual facial features and prominent hepatosplenomegaly are not typical. Individuals also can have seizures and hearing loss. Progressive neurological deterioration typically results in death from aspiration pneumonia during the first or second decade of life.

Two different enzyme defects result in Morquio syndrome, or MPS IV, and an accumulation of keratan sulfate. The disorder is characterized by short-trunked dwarfism, spondyloepiphyseal dysplasia on x-ray, fine corneal deposits, and normal intellect. Additional features include hepatomegaly, valvular heart disease, small teeth with thin enamel and frequent caries, unusual facial features, and hearing loss. The long-term prognosis is dependent on the development of skeletal-related complications, including atlanto-axial subluxation, cervical myelopathy with resulting paralysis, and restricted chest wall movement. The movie, *Simon Birch*, adapted John Irving's *A Prayer for Owen Meany*, recounts the life of a boy with Morquio syndrome.

Maroteaux-Lamy syndrome, or MPS VI, is caused by a deficiency of arylsulfatase B and accumulation of dermatan sulfate. This MPS disorder also has a clinical spectrum and similar somatic features as seen in MPS I but without cognitive impairment. The physical and visual complications, however, may affect development and result in psychomotor delays. In addition, the most severe form of MPS VI is associated with in-

creased morbidity and mortality from cardiac and skeletal complications.

Sly syndrome, or MPS VII, results from a deficiency of β -glucuronidase and has an extremely variable phenotype ranging from hydrops fetalis to a Hurler-like presentation that includes dysostosis multiplex and hepatosplenomegaly and a later onset form (after age 4) with normal intelligence, mild skeletal changes, and minimal corneal clouding.

Hyaluronidase deficiency (MPS IX) is extremely rare, having been described in a single person with mild short stature, periarticular soft tissue masses, and hyaluronate accumulation.

DIAGNOSTIC TESTS

Typically, individuals with various forms of MPS disorders come to medical attention because of secondary complications arising from developmental delay, hepatosplenomegaly, and skeletal abnormalities. Table 7.2-2 summarizes most of the common presenting features. Many times, these features are so prominent that the diagnosis is obvious; however, differentiating between severe and milder subtypes, or between various MPS disorders with similar somatic but different neurological complications, is difficult. Therefore, definitive diagnosis requires confirmation by enzymatic assay in serum, leukocytes, and/or fibroblasts (Muenzer, 2004). In addition, the use of deoxyribonucleic acid (DNA) mutational analysis, particularly for individuals with MPS I and II, can provide information about possible outcome.

The first step in the biochemical diagnosis of a given MPS usually involves the measurement of urinary glycosaminoglycans. Because spot studies may produce false negatives and false positives, the use of a quantitative method such as the spectrophotometric assay using the dye dimethylene blue or one- or two-dimensional electrophoresis for the detection of glycosaminoglycans is recommended. Additional diagnostic adjuncts can include skeletal survey for dysostosis multiplex or other skeletal abnormalities; blood smears for the detection of abnormal cytoplasmic inclusions in lymphocytes; and histologic analysis of skin, liver, and bone marrow biopsies for the detection of enlarged lysosomes filled with abnormal storage material. Although readily available enzymatic assays negate the need for bone marrow biopsy in most cases, unusual clinical presentations may result in this procedure in some instances.

The differential diagnosis for a given MPS disorder includes other MPS types; oligosaccharidoses, in-

Table 7.2-2. Common presenting features of MPS disorders in infants and children

Physical appearance
Macrocephaly
Unusual facial features (prominent forehead, broad nose with flat nasal bridges, macroglossia, and thickened lips)
Protruding abdomen due to hepatosplenomegaly
Inguinal or umbilical hernias
Hirsutism
Neurologic, behavioral, and developmental features
Loss of development skills such as speech and learning
Mild mental deterioration
Behavioral problems
Hyperactivity (MPS III)
Hydrocephalus (communicating)
Ophthalmologic features
Corneal clouding (MPS I, IV, VI, and VII)
Photophobia
Ears, nose, and throat features
Recurrent otitis media
Chronic rhinitis
Enlarged tonsils and adenoids
Hearing loss
Abnormal teeth (spacing and shape)
Pulmonary features
Frequent pneumonias
Reactive airway disease
Noisy breathing and snoring
Obstructive sleep apnea
Cardiac features
Murmur caused by valvular disease (mitral, aortic)
Cardiomyopathy
Musculoskeletal features
Decreased joint range of motion
Bony abnormalities (dysostosis multiplex)
Decreased hand fine motor skills
Gibbus (lumbar kyphosis)
Stooped gait or stance

Note: These findings are collective. Individuals will have varied presentations, and absence of a particular finding or findings does not necessarily rule out an mucopolysaccharidosis disorder. Adapted from *Journal of Pediatrics*, 144(5 Suppl.), Muenzer, J., The mucopolysaccharidoses: A heterogeneous group of disorders with variable pediatric presentations, S32, Copyright 2004, with permission from Elsevier.

cluding Sialidosis; mucopolidoses (ML), in particular ML II or I-cell disease; the early infantile form of GM1 gangliosidosis; and genetic syndromes with unusual facial features (e.g., Coffin-Lowry, Fryns, and Costello syndromes). If an investigation for MPS disorders fails to diagnose an individual with a suspected MPS disorder, the addition of urinary oligosaccharides and disease-specific enzyme studies for other diagnostic possibilities, including ML II, are indicated.

GENETICS

When an individual is diagnosed with an MPS disorder, genetic counseling is recommended to inform couples of their recurrence risk and the availability of prenatal diagnosis as well as to offer testing to brothers and sisters. With the exception of MPS II, all MPS disorders are inherited in an autosomal recessive manner, meaning that a couple with a previously affected child has a 1 in 4, or 25%, recurrence risk for each subsequent pregnancy.

MPS II is X-linked and with rare exception (i.e., X-chromosome abnormalities) all affected individuals are boys. Both spontaneous new mutations in the iduronate-2-sulfatase gene causing this disorder and inheritance of a mutation from an asymptomatic carrier mother can result in MPS II. A woman found to be a carrier is faced with three possible future pregnancy outcomes: 25% chance of an affected son, 50% chance of an unaffected son or daughter, and 25% chance of a carrier daughter. Fathers with MPS II will pass on their altered iduronate-2-sulfatase gene to all of their daughters but none of their sons.

Couples who have had a child with an MPS disorder may be interested in prenatal diagnosis for subsequent pregnancies and should be informed of its availability. Enzymatic testing can be completed on amniocytes or tissue obtained by chorionic villus sampling; however, amniocytes are preferred by most testing laboratories. In addition, there have been some cases of false negative reports using chorionic villus sampling. Preimplantation genetic diagnosis of 8–16 cell stage blastomeres is theoretically possible if the mutation(s) are known.

At-risk siblings, particularly younger ones, should be tested to determine if they are affected. With recent advancements in treatment modalities, early diagnosis and treatment of an individual with an MPS disorder may improve functional status and slow disease progression. Older brothers and sisters may be interested in knowing their own carrier status because of concerns for having a child with an MPS disorder. Fortunately, DNA testing is now available to determine carrier status for all forms of MPS.

For autosomal recessive MPS disorders, healthy brothers and sisters should be counseled that they face a $\frac{2}{3}$ risk of being a carrier. Because the incidence of individual MPS disorders (< 1 in 100,000) and their carrier frequencies (< 1 in 150) in the general population are low—much lower than the common genetic disorders such as cystic fibrosis (1 in 2,500 incidence and 1 in 25 carrier frequency)—the risk of a carrier having a

child with an MPS disorder via a spouse who has no family history of MPS is very low (approximately 0.1%). Sisters of individuals with MPS II face the same recurrence risk as their mothers if they are found to carry the affected gene.

TREATMENT

Three types of treatment options are available for individuals with MPS: symptom-based or palliative care, hematopoietic stem cell transplantation (HSCT), and enzyme replacement therapy (ERT). Only HSCT and ERT address the underlying pathophysiology. The choice of therapeutic approach is dependent on the type of MPS, the neurological and medical status of the individual, and the availability of specific treatment options (e.g., ERT is available for MPS I and VI). Regardless of the treatment course taken, all individuals with an MPS disorder and their families should be offered counseling and psychosocial support to assist them in coping with the devastating, multifaceted effects of chronic illness. Such services can be provided by any number of groups, including local social work resources or national organizations such as the National MPS Society.

Palliative Care

A system-based approach to the complications seen with a given MPS disorder typically requires the coordination of care by a physician familiar with the widespread problems seen with these disorders, including the high risk of intubation difficulties and complications due to an enlarged tongue, redundant pharyngeal tissue, small airway, and unstable atlanto-axial joints. Ideally, a geneticist or metabolic specialist fills that role, but limitation of access to these specialists in many communities may dictate that a pediatrician, internist, or other specialist such as a developmental pediatrician assume that responsibility.

Most individuals with an MPS disorder will require care from many health care providers, including cardiologists, neurologists, otolaryngologists, pulmonologists, orthopedists, and physical and speech therapists. Ongoing treatment may require corrective surgeries for cardiac or orthopedic complications; the use of hearing aids and wheelchairs; institution of continuous positive airway pressure (CPAP) for obstructive sleep apnea; pain management; and various physical, occupational, and speech therapies. Managing physicians may use the MPS I Registry guidelines (see Table 7.2-3) developed by an International Board of Advisors to monitor individuals with MPS I (Genzyme Corp.,

2005). These guidelines may be individualized for other MPS disorders and are updated periodically on the MPS I Registry web site.

Hematopoietic Stem Cell Transplantation

HSCT provides individuals with an MPS disorder with normal donor stem cells that produce the missing or deficient enzyme and subsequently improves the secondary complications caused by the underlying disease. The high morbidity (e.g., graft-versus-host disease, infections) and mortality (greater than 15%–20%) associated with this procedure limits its use to severely affected individuals early in their disease course. Several studies have reviewed the outcomes of more than 200 children with MPS I who underwent HSCT (Neufeld & Muenzer, 2001; Wraith, 2001). Transplants performed before 24 months of age in children with developmental quotients greater than 70 were associated with better outcomes, including preservation of central nervous system function; reduced hepatosplenomegaly; and improved cardiac function, linear growth, and upper airway obstruction. Ophthalmologic and skeletal complications, however, were not significantly improved. Despite HSCT, many individuals with an MPS disorder still require orthopedic procedures to maintain quality of life.

Initial case reports have suggested that the use of ERT in individuals with MPS I prior to HSCT may improve their clinical status and ability to tolerate the transplant (Grewal et al., 2005). The use of HSCT for other MPS disorders, including most individuals with MPS II and all with MPS III, is not recommended because the procedure has not been associated with an appreciable improvement in neurological outcome. Some individuals with MPS VI and VII have received transplants.

Historically, bone marrow has been the source of donor cells, but increasingly umbilical cord blood is being used and appears to be more promising. Cord blood is more readily available than bone marrow, and it potentially has a higher rate of engraftment and lower rate of graft-versus-host disease (Staba et al., 2004).

Enzyme Replacement Therapy

Aldurazyme (laronidase or recombinant human α -L-iduronidase; BioMarin-Genzyme LLC) ERT was approved for the treatment of MPS I in the United States and European Union in 2003 and in several additional countries since. Aldurazyme (0.58 mg/kg or 100 Units/kg) provides individuals with an exogenous source of missing enzyme that is delivered as a weekly intravenous infusion over 4 hours. The Phase 3 clinical study was a

Table 7.2-3. Minimum schedule of assessments for MPS I

	Initial assessment	Every 6 months	Every 12 months	Every other year
General				
Demographics	X			
Patient diagnosis	X			
Medical history	X	X		
Physical exam	X	X		
General appearance	X	X		
MPS I disease clinical assessments				
Neurologic/central nervous system				
• Neurocognitive testing, including DQ-IQ	X		X	
• MRI of brain	X			X
• MRI of spine	X			X
• Nerve conduction studies (carpel tunnel syndrome)	X			X
Ophthalmologic				
• Visual acuity	X		X	
• Retinal exam	X		X	
• Corneal exam	X		X	
Auditory				
• Audiometry	X		X	
Cardiac				
• Echocardiogram	X			X
• Electrocardiogram	X			X
Respiratory				
• Forced vital capacity/forced expiratory volume	X	X		
• Sleep study	X		X	
Gastrointestinal				
• Spleen volume	X			X
• Liver volume	X			X
Musculoskeletal				
• Skeletal survey by x-ray	X			X
Vitals and laboratory tests				
Height/weight	X	X		
Head circumference	X	X		
Blood pressure	X	X		
Enzyme activity level	X			
Urinary glycosaminoglycan level	X	X		
Urinalysis	X	X		
MPS health assessment				
MPS Health Assessment Questionnaire	X	X		

Key: DQ = developmental quotient; IQ = intelligence quotient; MPS = mucopolysaccharidosis; MRI = magnetic resonance imaging.

From Genzyme Corp. (2005). *Minimum schedule of assessments for monitoring patients with MPS I*. Retrieved February 28, 2005, from <http://MPSI.Registry.com>; reprinted by permission.

double-blind, placebo-controlled study that demonstrated improvements in respiratory function (forced vital capacity) and mobility (6-minute walk test and joint range of motion) as well as reductions in urinary glycosaminoglycan excretion and hepatomegaly in patients treated for 26 weeks (Wraith et al., 2004). Sleep

apnea and shoulder flexion improved in the most severely affected.

Although the effects of Aldurazyme on the central nervous system have not been evaluated, the most common reported adverse side effects were infusion reactions, including flushing, fever, headache, and rash. The

most serious reaction was anaphylaxis in one individual. Although most individuals have developed IgG antibodies to the recombinant enzyme, their significance is unknown.

Enzyme replacement therapies also have been developed for MPS II and VI. Somatic changes and functional improvements similar to that following enzyme replacement therapy in MPS I have been reported in initial clinical trials (Staba et al., 2004, Harmatz et al., 2004). Double-blind, placebo-controlled Phase 3 clinical studies have recently been completed for both enzymes. Recombinant human iduronate-2-sulfatase for the treatment of MPS II is undergoing regulatory review. Naglazyme (galsulfase, recombinant human arylsulfatase B) has been shown to improve walking and stair-climbing capacity in individuals with MPS VI. Naglazyme was approved by the FDA for the treatment of individuals with MPS VI in 2005.

PROGNOSIS

All of the MPS disorders are chronic, progressive diseases, and most individuals die prematurely from associated complications involving cardiopulmonary disease. The life span of an individual with an MPS disorder depends on the phenotype, advancement of the disease process at the time of diagnosis, and available treatment modalities. Despite significant improvements in the care and treatment of individuals with an MPS disorder, morbidity and mortality remain high. For example, individuals with Hurler syndrome typically die by 10 years of age with a mean age of death of 5 years. Individuals with Hurler-Scheie syndrome typically die by 25 years of age (mean 15 years), and those with Scheie syndrome typically die by mid-adulthood.

CONCLUSION

MPS disorders are caused by specific deficiencies of lysosomal enzymes that catalyze the stepwise degradation of glycosaminoglycans. All MPS disorders share a chronic and progressive course, multisystem involvement, and result in significant disability and often premature death. Intellectual disabilities are seen in the severe forms of MPS I (Hurler syndrome) and MPS II (Hunter syndrome) and in all cases of MPS III (Sanfilippo syndrome). Normal intellect can be seen in the

other types. Excess amounts of partially degraded glycosaminoglycan fragments are detected in the urine of individuals with the various forms of MPS. Definitive diagnosis of a specific disorder requires enzyme assays in serum, leukocytes, or fibroblasts. This group of disorders is inherited in an autosomal recessive fashion, with the exception of MPS type II (Hunter syndrome), which is X-linked. Prenatal diagnosis is available.

HSCT may improve the clinical course in some individuals with severe MPS I disease, but the procedure has high morbidity and mortality that limits its use to individuals early in the course of their illness. New breakthroughs in the use of ERT for MPS I, II, and VI, and the use of cord blood for HSCT offer new hope for individuals with an MPS disorder and their families.

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