Mucopolysaccharidoses Fact Sheet

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What are the mucopolysaccharidoses?

The mucopolysaccharidoses are a group of inherited metabolic diseases caused by the absence or malfunctioning of certain enzymes the body needs to break down molecules called glycosaminoglycans—long chains of sugars (carbohydrates) in each of our cells. These cells help build bone, cartilage, tendons, corneas, skin, and connective tissue. Glycosaminoglycans (formerly called mucopolysaccharides) are also found in the fluid that lubricates our joints.

People with a mucopolysaccharidosis disorder either do not produce enough of one of the 11 enzymes required to break down these sugar chains into proteins and simpler molecules or they produce enzymes that do not work properly. Over time, these glycosaminoglycans collect in the cells, blood, brain and spinal cord, and connective tissues. The result is permanent, progressive cellular damage that affects the individual's appearance, physical abilities, organ and system functioning, and, in most cases, mental development. Symptoms may be similar or vary among the different types of the disorder.

The mucopolysaccharidoses are classified within a larger group of disorders called lysosomal storage diseases. These are conditions in which large numbers of molecules that normally break down or degrade into smaller pieces in intracellular compartments called lysosomes accumulate in harmful amounts in the body's cells and tissues, particularly in the lysosomes. The main function of lysosomes is to digest nonfunctional cell and other materials (including bacteria and cellular debris).

Another lysosomal storage disease often confused with the mucopolysaccharidoses is *mucolipidosis*. In this disorder, excessive amounts of fatty materials known as lipids (another principal component of living cells) are stored, in addition to smaller carbohydrates called sugars. Individuals with mucolipidosis may share some of the clinical features associated with the mucopolysaccharidoses (certain facial features, bony structure abnormalities, and damage to the brain).

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Who is at risk?

Estimates indicate that approximately one in every 25,000 babies born in the United States will have some form of the mucopolysaccharidoses. These are autosomal recessive disorders, meaning that only individuals inheriting the defective gene from both parents are affected. When both parents have one copy of the defective gene, each pregnancy carries with it a one in four chance that the child will be affected. The

parents and siblings of an affected child may have no sign of the disorder. Unaffected siblings and select relatives of a child with one of the mucopolysaccharidoses may carry one copy of the defective gene and could pass it on to their own children. (The one exception is MPS II, or Hunter syndrome, which is an X-linked recessive disorder. In MPS ll, the mother alone passes along the defective gene to a son.)

In general, the following factors may increase the chance of having or passing on a genetic disease:

- A family history of a genetic disease
- Parents who are closely related or part of a distinct ethnic or geographically clustered community
- Parents who do not show disease symptoms but carry a disease gene.

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What are the signs and symptoms?

The mucopolysaccharidoses share many clinical features but have varying degrees of severity. These features can or may not be apparent at birth but progress as the storage of glycosaminoglycans affects bone, skeletal structure, connective tissues, and organs. The age of presentation varies widely.

Neurological complications may include damage to neurons (specialized nerve cells that send and receive signals throughout the body). Pain and impaired motor function (ability to start and control muscle movement) may result from compressed nerves or nerve roots in the spinal cord or in the peripheral nervous system. The peripheral nervous system connects the brain and spinal cord to sensory organs such as the eyes and to other organs, muscles, and tissues throughout the body. Affected individuals may have normal intellect or may have profound intellectual disability, may experience developmental delay, or may have severe behavioral problems. Many individuals have problems with hyperactivity, depression, speech, and hearing impairment. Hydrocephalus, an excessive accumulation of cerebrospinal fluid in the brain that can cause increased pressure inside the head, is common in some of the mucopolysaccharidoses. The eye's cornea often becomes cloudy from intracellular storage, and degeneration of the retina and glaucoma also may affect the person's vision.

Physical symptoms generally include coarse facial features (including a flat nasal bridge, thick lips, and enlarged mouth and tongue), short stature with disproportionately short trunk (dwarfism), abnormal bone size and/or shape (dysplasia) and other skeletal irregularities, thickened skin, enlarged organs such as liver or spleen, hernias, incontinence, and excessive body hair. Short and often claw-like hands, progressive joint stiffness, and carpal tunnel syndrome can restrict hand mobility and function. Recurring respiratory infections are common, as are obstructive airway disease and obstructive sleep apnea. Many affected individuals also have heart disease, often involving enlarged or diseased heart valves. People with MPS also have a significantly shortened life span.

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What are the different types of the mucopolysaccharidoses?

Seven distinct clinical types and numerous subtypes of the mucopolysaccharidoses have been identified. Although each mucopolysaccharidosis (MPS) differs clinically, most individuals experience a period of normal development followed by a decline in physical and/or mental function.

MPS I has historically been divided into three broad groups based on severity of symptoms—**Hurler, Hurler-Scheie**, and **Scheie** (in decreasing order of severity). (Scheie syndrome was previously known as MPS V before being included in MPS I.) MPS I may be viewed as a continuous spectrum of disease, with the most severely affected individuals on one end, the less severely affected (attenuated) on the other end, and a wide range of different severities in between. All individuals with MPS I have an absence of, or insufficient levels of, the enzyme alpha-L-iduronidase, which is needed to break down glyclosaminoglycans.

Children with MPS l often show no symptoms at birth but they develop complications after the first year of life. Neurological symptoms may include hydrocephalus (the excess build-up of cerebrospinal fluid in the brain), an enlarged head, and clouded corneas as the child ages. Other common neurological complications may include impaired vision and vision loss, carpal tunnel syndrome or other nerve compression, and restricted joint movement.

- Children with less severe forms of MPS l may have normal intelligence or mild to moderate mental impairment or learning difficulties. Some children may have psychiatric problems. Respiratory problems, sleep apnea, and heart disease may develop in adolescence. Individuals with the least severe form of MPS can live into adulthood, while other individuals in this spectrum may live into the late teens or early twenties.
- In the most severe form of MPS I (Hurler syndrome), developmental delay is evident by the end of the first year. Children usually stop developing between ages 2 and 4. This is followed by progressive mental decline and loss of physical skills. Language may be limited due to hearing loss. Physical symptoms include a slowing in growth before the end of the first year, short stature, multiple skeletal abnormalities, hernias, distinct facial features, and enlarged organs. Feeding may be difficult for some children. Children with severe MPS I often die before age 10 due to obstructive airway disease, respiratory infections, or cardiac complications.

MPS II (also called **Hunter syndrome**) is caused by lack of the enzyme iduronate sulfatase (which breaks down the glycosaminoglycans heparin sulfate and dermatan sulfate inside cells). Although it was once divided into two groups based on the severity of symptoms, MPS II is also considered a continuous spectrum of disease. MPS II is the only mucopolysaccharidosis disorder in which the mother alone can pass the defective gene to a son (called X-linked recessive). The disease is almost exclusively found in young males, although cases of affected females have been reported.

- Children with the more severe form of MPS II share many of the neurological and physical features associated with severe MPS I but with milder symptoms. Onset of the disease is usually between ages 2 and 4. Developmental decline is usually noticed between the ages of 18 and 36 months, followed by progressive loss of skills. Other neurological symptoms may include increased intracranial pressure, joint stiffness, retinal degeneration, and progressive hearing loss. Whitish skin lesions may be found on the upper arms, back, and upper legs. Death from upper airway disease or cardiovascular failure usually occurs by age 15.
- Children with a less severe form of MPS II are often diagnosed in the second decade of life. Intellect and social development are not affected. Physical characteristics in these children are less obvious and progress at a much slower rate, and skeletal problems may be less severe. Individuals with less severe MPS II may live into their 50s or beyond, although respiratory and cardiac complications can contribute to premature death.

MPS III (also called **Sanfilippo syndrome**) is marked by severe neurological symptoms that include progressive dementia, aggressive behavior, hyperactivity, seizures, some deafness and vision loss, and an inability to sleep for more than a few hours at a time. MPS III affects children differently and progresses faster in some children than in others. Early mental and motor skill development may be somewhat delayed. Affected children show a marked decline in learning between ages 2 and 6, followed by eventual loss of language skills and loss of some or all hearing. These children tend to lose learned words first followed by loss of motor function. Some children may never learn to speak. As the disease progresses, children become increasingly unsteady on their feet and most are unable to walk by age 10.

Life expectancy in MPS III is extremely varied. Most individuals with MPS III live into their teenage years, and some live into their 20s or 30s.

There are four distinct types of MPS III, each caused by alteration of a different enzyme needed to completely break down the heparan sulfate sugar chain. Few clinical differences exist between these four types but symptoms appear most severe and seem to progress more quickly in children with type A.

- MPS IIIA is caused by the missing or altered enzyme heparan *N*-sulfatase
- MPS IIIB is caused by the missing or deficient enzyme alpha-*N*-acetylglucosaminidase
- MPS IIIC results from the missing or altered enzyme acetyl-CoA:alpha-glucosaminide acetyltransferase
- MPS IIID is caused by the missing or deficient enzyme *N*-acetylglucosamine-6-sulfate.

MPS IV (also called **Morquio syndrome**) has two subtypes that result from the missing or deficient enzymes *N*-acetylgalactosamine 6-sulfatase (Type A) or beta-galactosidase (Type B) needed to break down the keratan sulfate sugar chain. Clinical features are similar in both types but appear milder in MPS IVB. Onset is between ages 1 and 3. Neurological complications include spinal nerve and nerve root compression resulting from extreme, progressive skeletal changes, as well as hearing loss and clouded corneas. Intelligence is normal unless hydrocephalus develops and is not treated.

Physical growth slows and often stops around age 8. Among the many skeletal abnormalities seen in individuals with Morquio syndrome, the bones that stabilize the connection between the head and neck can be malformed (odontoid hypoplasia), and a surgical procedure called spinal cervical bone fusion can be lifesaving. Other skeletal changes include a protruded sternum, a spine that is curved side to side and back to front, and knock-knee deformity (where the knees angle in and touch each other). Restricted breathing, joint stiffness, and heart disease are also common. Children with the more severe form of MPS IV may not live beyond their 20s or 30s.

MPS VI (also called **Maroteaux-Lamy syndrome**) is caused by the deficient enzyme *N*-acetylgalactosamine 4-sulfatase. MPS VI has a variable range of severe symptoms. While children usually have normal intellectual development, they share many of the physical symptoms found in severe MPS I. In addition to many of the neurological complications seen in other MPS disorders, individuals with MPS VI have a thickening of the dura (the membrane that surrounds and protects the brain and spinal cord) and may become deaf. Eye problems include clouding of the cornea, glaucoma (a group of disorders that damage the optic nerve), swelling of the optic nerve or disc, and a degeneration of the optic nerve.

Growth is normal at first but stops suddenly around age 8. Skeletal changes are progressive, and this limits movement. Nearly all children have some form of heart disease, usually involving valve dysfunction.

MPS VII (also called **Sly syndrome)** is one of the least common forms of the mucopolysaccharidoses. The disorder is caused by deficiency of the enzyme beta-glucuronidase. In its rarest form, MPS VII causes children to be born with *hydrops fetalis*, in which extreme amounts of fluid are retained in the body. Survival in these cases is usually a few months or less. Most children with MPS VII are less severely affected. Neurological symptoms may include mild to moderate intellectual disability by age 3, hydrocephalus, nerve entrapment, some loss of vision, joint stiffness, and restricted movements. In addition to skeletal problems, some individuals may have repeated bouts of pneumonia during their first years of life. Most children with MPS VII live into the teenage or young adult years.

MPS IX disorder results from hyaluronidase deficiency. It is extremely rare. Joint movement and intelligence are not affected. Symptoms include nodular soft-tissue masses located around joints, with episodes of painful swelling of the tissue masses and pain that ends spontaneously within 3 days. Other traits include mild facial changes, short stature, multiple soft-tissue masses, and some bone erosion seen on pelvic radiography.

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How are the mucopolysaccharidoses diagnosed?

Clinical examination and tests to detect excess excretion of mucopolysaccharides in the urine are the first steps in the diagnosis of an MPS disease. Enzyme assays (testing a variety of cells or blood in culture for enzyme deficiency) are needed to provide definitive diagnosis. Prenatal diagnosis using amniocentesis and chorionic villus sampling can verify whether a fetus is affected with the disorder. Genetic counseling can help parents with a family history of MPS determine if they are carrying the mutated gene that causes the disorders.

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How are the mucopolysaccharidoses treated?

Currently there is no cure for these disorders. Medical care is directed at treating systemic conditions and improving the person's quality of life. Changes to the diet will not prevent disease progression.

Surgery can help drain excessive cerebrospinal fluid from the brain and free nerves and nerve roots compressed by skeletal and other abnormalities. Corneal transplants may improve vision among individuals with significant corneal clouding. Removing the tonsils and adenoids may improve breathing among individuals with obstructive airway disorders and sleep apnea. Some people may require surgical insertion of an endotracheal tube to aid breathing.

Enzyme replacement therapies are currently in use for MPS I, MPS II, MPS IVA, MPS VI, and MPS VII, and are being tested in other MPS disorders. Enzyme replacement therapy involves an intravenous solution containing an enzyme that is deficient or missing from the body. It does not cure the neurological manifestations of the disease but has proven useful in reducing non-neurological symptoms and pain.

Bone marrow transplantation (BMT) and umbilical cord blood transplantation (UCBT) have had limited success in treating the mucopolysaccharidoses. Abnormal physical characteristics, except for those affecting the skeleton and eyes, may be improved, but

neurologic outcomes have varied. BMT and UCBT are high-risk procedures and are usually performed only after family members receive extensive evaluation and counseling.

Physical therapy and daily exercise may delay joint problems and improve movement.

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What research is being done?

The mission of the National Institute of Neurological Disorders and Stroke (**NINDS**) is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease. The NINDS is a component of the National Institutes of Health, the leading supporter of biomedical research in the world.

Much of what we know about the biochemistry of the mucopolysaccharidoses was discovered at **NIH** by Dr. Elizabeth Neufeld.

NINDS, along with other **NIH** institutes, supports the Lysosomal Disease Network, a network of centers that addresses some of the major challenges in the diagnosis, management, and therapy of diseases, including the mucopolysaccharidoses. Centers are conducting longitudinal studies of the natural history and/or treatment of these disorders. Additional studies will emphasize the quantitative analysis of the central nervous system structure and function, as well as develop biomarkers (signs that can indicate the diagnosis or progression of a disease) for these disorders.

Research funded by **NINDS** has shown that viral-delivered gene therapy in animal models of the mucopolysaccharidoses can stop the buildup of storage materials in brain cells and improve learning and memory. No gene therapy for MPS disorders has been approved for clinical use at this time but several studies are actively recruiting patients (see **www.clinicaltrials.gov**and search using the terms "mucopolysaccharidosis" and "gene therapy). Researchers are planning additional studies to understand how gene therapy prompts recovery of mental function in these animal models. It may be years before such treatment is available to humans.

Scientists are working to identify the genes associated with the mucopolysaccharidoses and plan to test new therapies in animal models and humans. Animal models are also being used to investigate therapies that replace the missing or insufficient enzymes needed to break down the sugar chains. Studies are investigating enzyme replacement therapy to reverse or halt neurologic decline in the mucopolysaccharidoses.

Scientists know that Hurler disease is caused by a nonsense mutation (a point in a mutation of DNA that results in an incomplete and usually malfunctioning protein). NINDS-funded scientists are testing two drugs in an animal model to see if the drugs can suppress the nonsense mutations and restore enough functional protein to reduce disease progression.

NINDS, along with other **NIH** Institutes and Centers, is conducting a long-term study of MPS disorders to gain information that will more accurately inform individuals of potential neurobehavioral outcomes as well as develop sensitive measures of disease progression and treatment. Other researchers hope to use a telephone-based surveillance system to collect information about children diagnosed with a lysosomal storage disease and more accurately follow and understand changes in development and behavior.

Scientists also hope to identify biomarkers (signs that help diagnose a disease or monitor its progression) for the mucopolysaccharidoses.

More information about research on the mucopolysaccharidoses supported by **NINDS** and other **NIH** Institutes and Centers can be found using NIH RePORTER (**www.projectreporter.nih.gov**), a searchable database of current and past research projects supported by **NIH** and other federal agencies. RePORTER also includes links to publications and resources from these projects. Enter the term "mucopolysaccharidosis" to start your search.

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Where can I get more information?

For information on the mucopolysaccharidoses and other neurological disorders or research programs funded by the NINDS, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
800-352-9424

More information about the mucopolysaccharidoses is available from the following organizations:

National MPS Society, Inc.
PO Box 14686
Durham, NC 27709-4686
919-806-0101
877-677-1001

Hide and Seek Foundation for Lysosomal Disease Research/SOAR
6475 East Pacific Coast Highway, Suite 466
Long Beach, CA 90803
844-762-7672

Hunter's Hope Foundation
21 Princeton Plaza, Suite 12
P.O. Box 643
Orchard Park, NY 14127
716-667-1200

National Organization for Rare Disorders (NORD)
55 Kenosia Avenue
Danbury, CT 06810
203-744-0100

National Tay-Sachs and Allied Diseases Association
2001 Beacon Street
Suite 204
Boston, MA 02135
617-277-4463
800-906-8723

ClinicalTrials.gov
A database of clinical studies around the world.

Genetic and Rare Diseases Information Center
National Center for Advancing Translational Sciences/**NIH**

U.S. National Library of Medicine
National Institutes of Health
8600 Rockville Pike
Bethesda, MD 20894
301-594-5983
888-346-3656

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See a list of all NINDS disorders

Publicaciones en Español

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