



Hurler, Hurler-Scheie, and Scheie Syndromes



A Guide to Understanding

MPS I

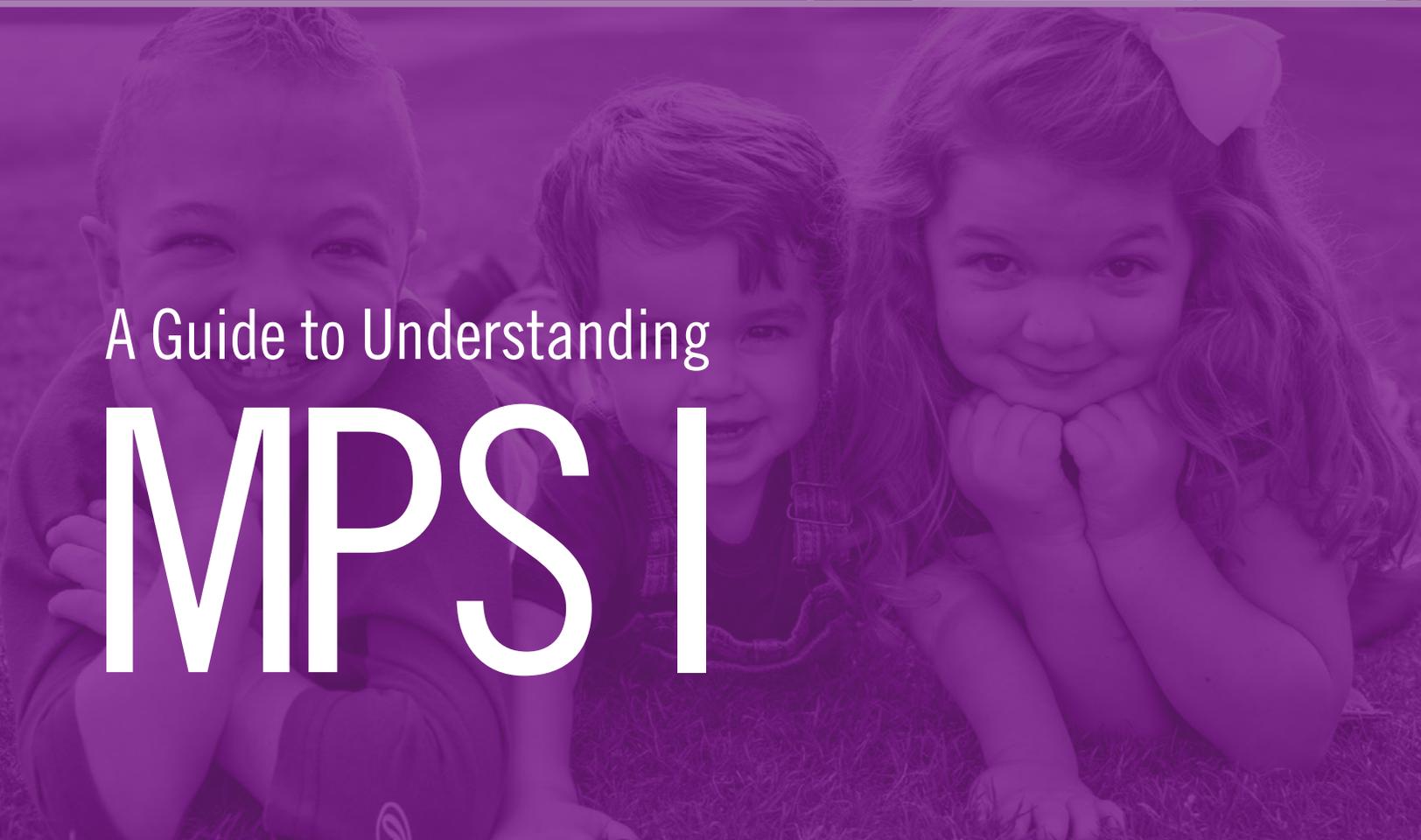


Table of Contents

What is MPS I?	2
How is MPS I diagnosed?	3
Specific treatment of MPS I	5
Are there different forms of MPS I?	8
How common is MPS I?	8
How is MPS I inherited?	9
Why does disease severity vary so much?	12
How long do individuals with MPS I live?	13
Signs and symptoms of MPS I	14
Living with MPS I	43
General treatment of MPS I	47
Research for the future	54
Benefits of the National MPS Society	56
Glossary	57

The National MPS Society exists to find cures for MPS and related diseases. We provide hope and support for affected individuals and their families through research, advocacy, and awareness of these diseases.

Pictured on cover: (top) Myles, (bottom) Zachary, Luke, Amelia
Pictured on right: (top to bottom) Charlie Grace, Owen, Teagan



What is MPS I?

Mucopolysaccharidosis I (MPS I; pronounced “mew·ko·pol·ee·sak·ah·ri·doh·sis one”) is a rare genetic disorder that affects the entire body. It is also known as Hurler syndrome, named after Dr. Gertrude Hurler, a general practitioner, who in 1919 first described a boy and girl with severe symptoms of the condition. In 1962, Dr. Harold Scheie, an ophthalmologist, described individuals who displayed attenuated (less severe) symptoms and primarily were affected by corneal clouding. This apparently new condition was named Scheie syndrome (also temporarily known as MPS V) and was thought to be a different disease from Hurler syndrome. In the 1970s, there were several reports of individuals whose symptoms of intermediate severity did not fit clearly in either syndrome, and consequently, were categorized as Hurler-Scheie syndrome.

MPS I belongs to an inherited group of metabolic diseases called mucopolysaccharidoses (MPS), a subgroup of lysosomal storage disorders (LSDs). MPS is a degenerative disorder in which at least one long-chain sugar carbohydrate called a glycosaminoglycan (GAG; pronounced “gly·cose·a·mee·no·gly·can” and formerly called mucopolysaccharide) accumulates in the lysosome (an organelle within cells) and causes increasing problems over time. There are seven distinct clinical types of MPS, some of which have several subtypes.

If you are a parent of a newly diagnosed child, or someone who has been diagnosed with MPS I yourself, it is important to remember that there is a wide spectrum of severity in how MPS I shows up and progresses:

- It can be an attenuated (less severe) form that usually manifests in adolescence and progresses slowly, which is called Scheie syndrome and is less common; OR
- It can be an intermediate form that usually manifests in late childhood, has some features of both the attenuated and severe forms, and progresses at an intermediate pace, which is called Hurler-Scheie syndrome; OR
- It can be a severe form that manifests shortly after birth and progresses rapidly, which is called Hurler syndrome and is more common.

MPS I has a wide spectrum of clinical severity. It is more appropriate to view MPS I as a continuous spectrum of disease, from the most severely affected individuals (Hurler syndrome) to those with intermediate severity (Hurler-Scheie syndrome), to the less severely affected (attenuated) individuals (Scheie syndrome).

Even children from the same family may be affected somewhat differently. A range of possible problems is described in this booklet; however, this does not mean that you or your child will experience all of the symptoms described. Some complications arise early in childhood, while others present much later or may never occur. As yet, there is no cure for individuals affected by MPS I, but there are FDA-approved treatments and other ways to manage the challenges they have, to ensure their best quality of life.

The word “mucopolysaccharide” can be broken down into its parts: “Muco” refers to the thick, jelly-like consistency of the molecules; “poly” means many; and “saccharide” is a general term for a sugar molecule (think of saccharin).

In healthy individuals, GAGs are used in the building of bones, cartilage, skin, tendons, and many other tissues in the body. For instance, the slippery synovial fluid that lubricates your joints contains GAGs as does the rubbery cartilage in your joints. All tissues have some of this substance as a normal part of their structure. As more GAGs are produced, older GAGs are broken down. This is the normal cycle of events that maintains a healthy balance in the body. However, when this cycle does not function properly and GAGs are not broken down, they accumulate within the cells. This malfunction results in progressive, often permanent, cellular damage that affects the individual's appearance, physical abilities, proper functioning of organs and systems, and, in most cases, cognitive development.

MPS I is caused by accumulation of two particular GAGs called dermatan sulfate (DS) and heparan sulfate (HS). DS is found in the cornea and sclera of the eye, which helps to maintain corneal transparency and the shape of the eye, respectively. DS is also found in high quantities in blood vessel walls, heart valves, and the umbilical cord. HS is everywhere and is found on cell surfaces and in the extracellular matrix. HS is also one of the most complex GAGs in the body. When these GAGs are not degraded, they remain stored inside the cells in the body. While the GAGs are not intrinsically toxic, their accumulation in great amounts can lead to many physical problems. Babies may show little sign of the disease, but as more and more GAGs accumulate, symptoms start to appear as a result of progressive damage.

How is MPS I diagnosed?

Doctors may consider testing for MPS I when signs and symptoms of the disease are present and are not explained by other causes. All diagnostic tests should be overseen by a doctor with expertise in LSDs, as the tests are complicated, and results may be difficult to interpret.

To diagnose MPS I, the doctor will typically first do a urine test to look for GAG levels that are higher than normal. The results are compared to GAG levels that are known to be normal for age-matched individuals without MPS I. Most, but not all, individuals with MPS I have GAG levels in their urine that are higher than those of individuals without MPS.

A urine test is only one of the first steps in diagnosing MPS I. A clear diagnosis requires a test to measure levels of enzyme activity in the blood or skin cells. In healthy individuals, the tests show white blood cells, serum, and skin cells that contain normal levels of enzyme activity. In individuals with MPS I, the enzyme activity levels are much lower or absent.

Early diagnosis of MPS I is critical. An early diagnosis and treatment can potentially prevent some of the permanent damage caused by the disease. Supportive care from physicians and your family network will help you and your loved one moving forward.

A clear diagnosis of MPS I requires tests conducted by experts showing enzyme activity much lower than normal or absent.

Genetic testing

DS and HS are both degraded by the same enzyme, alpha-L-iduronidase. The gene that encodes this enzyme is called *IDUA*. When this gene contains mutations (genetic changes), little or no enzyme is made.

DNA tests can identify the specific changes in the *IDUA* gene that are responsible for making the missing enzyme. For example, while we know that every individual with MPS I has a deficiency of the alpha-L-iduronidase enzyme, there are many different DNA mutations in the gene that can cause the deficiency. There are two major types of gene mutations. Some mutations (missense mutations) encode for an enzyme that is just slightly modified, while other mutations (nonsense mutations) are so severe that no enzyme is produced at all. While the implications of each of the many possible mutations are not understood at this time, individuals who have mutations in which no enzyme is produced are very likely to have the severe form of MPS I.

There are a handful of “common” (found in multiple unrelated families) mutations that cause MPS I, mostly associated with the most severe form of the disease (Hurler syndrome). Some laboratories offer specific testing for these types of mutations. However, for many individuals with MPS I, at least one of their two genetic changes are not one of the “common” mutations and may be specific to their family or has not been identified before. In these cases, it is difficult to predict the severity of the disease.



OCEAN

New DNA technologies have been developed to include multi-gene panels that allow the sequencing of just the MPS disease-causing genes. Some of these panels are currently being offered free of charge. Please contact the National MPS Society for more details.

An MPS I Registry was created in 2003. It is maintained to accumulate essential data that will hopefully make the prediction of disease severity more accurate in the future.

Individuals with MPS I should receive DNA testing prior to discussing treatment options.

Individuals with MPS I should have DNA testing through analysis of urine or blood after the initial diagnosis. In many cases, severity can be determined by mutational analysis.

Specific treatment of MPS I

Overview

The goals of treating MPS I are to improve quality of life, slow down the progression of the disease, and prevent permanent tissue and organ damage. Currently, there is no cure for MPS I; however, early intervention may

help prevent irreversible damage. Treatment options for MPS I include those aimed at disease and symptom management.



TITUS

Enzyme replacement therapy (ERT)

ERT for MPS I was approved by the FDA in 2003. ERT is the development of a synthetic, or manufactured enzyme to emulate the missing enzyme. Aldurazyme[®] is a drug that is a manufactured version of the body's natural alpha-L-iduronidase enzyme. Aldurazyme improves lung function, increases endurance, reduces the size of the liver, and decreases the GAG levels in certain tissues and the urine. When taken all together, these benefits tend to increase the lifespan of the individual. It does not cross the blood-brain barrier at normal doses and thus, does not prevent neurocognitive decline that occurs in individuals with severe MPS I. As a result, ERT is generally used by individuals with the attenuated form of MPS I.

Treatments of Aldurazyme are given weekly through intravenous (IV) infusions. Intrathecal (injected into the spinal canal) administration of ERT is currently being studied to treat the brains of individuals with MPS I.

For parents to fully understand the risks, benefits, and limitations of ERT, it is important to talk with physicians familiar with MPS I ERT and families undergoing this treatment. The National MPS Society can put you in touch with physicians and families so you can become better informed before deciding to use ERT.

Aldurazyme is a registered trademark of BioMarin/Genzyme.

ERT can improve many symptoms of MPS I that do not involve the brain and central nervous system.

Hematopoietic Stem Cell Transplant (HSCT)



LUKE

Like ERT, the goal of HSCT is to restore activity of the deficient enzyme. HSCT has become the treatment of choice for many individuals with Hurler syndrome (it is used less frequently for Hurler-Scheie and is not recommended for Scheie syndrome). The first HSCT transplant for MPS I was performed in 1980. Many MPS I patients have undergone this therapy with success, and it is now considered a standard of care. HSCT should occur as soon as possible after diagnosis, before the age of 2, if possible.

Stem cells (cells that are capable of differentiating into a wide variety of specific cell types) are harvested from the bone marrow, peripheral blood, or umbilical cord blood of a healthy donor. They are typed in advance to avoid rejection by the recipient. The stem cells are infused into the bloodstream of the recipient, where they migrate into the bone marrow and multiply into new, healthy, enzyme-producing blood cells. These healthy cells migrate back to many parts of the body, where they produce properly functioning enzymes. Some of these new cells will migrate into the brain to produce the missing enzyme, thereby preventing further neurological and cognitive damage.

When successful, this treatment only needs to be performed one time. It will provide a continuous source of healthy enzyme as the body begins creating the enzyme on its own in many places. There may be improvements in joint stiffness, vision, sleep apnea, heart disease, coarsened facial features, upper airway obstruction, respiratory function, hearing loss, and enlarged liver and spleen. Hydrocephalus may be stabilized or prevented.

Because IV ERT does not cross the blood–brain barrier, HSCT has become the treatment of choice for the severe form of MPS I. It has been shown to help delay declines in cognitive and psychomotor functions when performed early enough, before there is permanent damage.

HSCT is not able to significantly correct bone or eye problems that frequently require future therapies and surgeries. It is also not effective with cardiac valve abnormalities, and it cannot reverse preexisting cognitive and intellectual decline.

Before deciding on an appropriate treatment, it is important to verify the diagnosis of MPS I with genetic analysis as the severity of the disease can sometimes be determined once the specific DNA mutations have been confirmed.

Donor stem cells must be carefully chosen to match the recipient as closely as possible to minimize rejection. Before a transplant, the individual needs a conditioning protocol. Typical protocols include chemotherapy and other medications to prepare the body to accept the transplanted stem cells and to avoid or minimize graft-versus-host disease (GVHD). This process eliminates

the individual's immune system that will be "rebuilt" over time as the new donor cells reproduce, and repopulate the individual. After a transplant procedure the child will need to repeat all vaccinations received prior to the procedure.

The disadvantages of HSCT include the risk of mortality, the problem of finding a suitable donor, GVHD, and the necessity of a very specialized medical facility. In 2005, the European group for Blood and Marrow Transplantation developed transplantation guidelines for HSCT in MPS that have led to more successful outcomes. The procedure has been improved over time so that experienced centers now report up to 90% survival rates, which were previously much lower.

Transplants require very specialized medical centers and extended hospitalizations. They also require frequent follow-ups and regular evaluations. Transplants should be performed at Centers of Excellence familiar with the unique needs of individuals with MPS.

Although treatment protocols vary among medical centers, ERT is now being used in some protocols to help stabilize an individual's condition before the transplant and to prepare the individual for HSCT. Some centers also use ERT after the procedure to minimize disease progression while the new cells are being established and producing sufficient enzyme.

As HSCT cannot reverse preexisting cognitive effects, it is generally recommended that HSCT be performed as early as possible. MPS I is included on the recommended uniform screening panel (RUSP) in the US and is currently included in newborn screening programs in many states, some European countries, and Taiwan. Because of this, individuals can now be treated within the first few months of life, which is expected to minimize most of the limitations seen in patients treated at later disease stages.

HSCT is the treatment of choice for severe MPS I. It is recommended for Hurler syndrome, but not for Scheie syndrome. It is important to obtain the correct diagnosis, to work with physicians who treat MPS I, and to have transplants performed at Centers of Excellence familiar with the unique needs of individuals with MPS.

For individuals to fully understand the risks, benefits, and limitations of HSCT, it is important to talk with transplant physicians and families who have had the procedure. The National MPS Society can put you in touch with physicians and families so you can become better informed before reaching a treatment decision.

For more information see the HSCT Fact Sheet <https://mpssociety.org/learn/education/fact-sheets/hsct/>.

Are there different forms of MPS I?

As stated above, although there are different severities of the disease resulting in different names, there is only one form of MPS I caused by a deficiency in the enzyme called alpha-L-iduronidase. Enzymes are special types of proteins that help build and break down complex molecules inside a cell. Alpha-L-iduronidase is responsible for the breakdown of both DS and HS.

MPS I has a wide spectrum of clinical severity. It is more appropriate to view MPS I as a continuous spectrum of disease from the most severely affected individuals (Hurler syndrome) to those with intermediate severity (Hurler-Scheie syndrome) to the less severely affected (attenuated) individuals (Scheie syndrome).

It is appropriate to view MPS I as a continuous spectrum of disease with a variety of symptoms. The disease is extremely varied in its effects.

How common is MPS I?

MPS I is a rare mucopolysaccharide disease. Reliable incidence figures are not available for the United States. Studies on babies born in British Columbia, Canada, Australia, Netherlands, and the United Kingdom estimate 1 in 100,000 live births for severe MPS I (Hurler syndrome), 1 in 115,000 live births for intermediate MPS I (Hurler-Scheie syndrome), and 1 in

500,000 live births for mild (attenuated) MPS I (Scheie syndrome). Although MPS I itself is rare, the cumulative incidence of all MPS diseases is 1 in 25,000 births and is part of the larger family of Lysosomal Storage Disorders (LSDs), collectively occurring in about 1 in every 5,000 to 7,000 births.



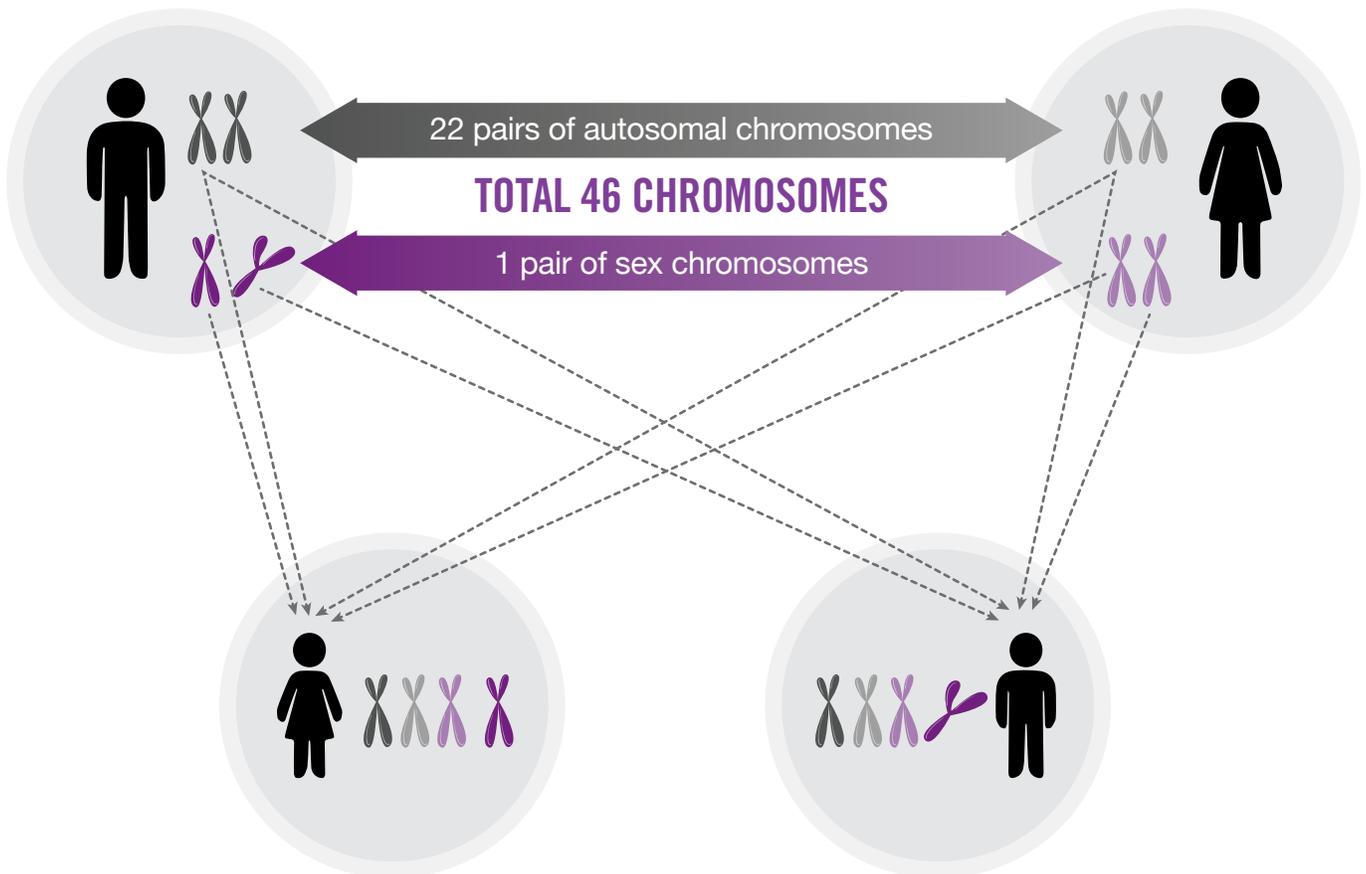
KENNEDY

How is MPS I inherited?

To understand inheritance of MPS I, it is important to grasp some basic concepts about genetics and inheritance (**Figure 1**). All humans have 2 complete sets of chromosomes—1 set of 23 from each parent for a total of 46 chromosomes. Each chromosome is a string of many genes. Twenty-two of the 23 chromosomes are matched and are termed “autosomal.” These 22 chromosomes contain genes that are needed for all individuals regardless of gender. The remaining pair are the sex chromosomes (XX for female and XY for male; the Y chromosome comes from the father). Each of the matched

autosomal chromosomes contain the same genes; i.e., chromosome 1 from the father has the same set of genes as does chromosome 1 from the mother, chromosome 2 from the father has the same set of genes as does chromosome 2 from the mother, and so on. Thus, every individual has two copies of each gene, 1 copy from each parent, located on the autosomal chromosomes. Consequently, every individual, other than those with certain chromosomal abnormalities, has 22 matched sets of autosomal chromosomes and 1 mismatched set of sex chromosomes totaling 46 chromosomes.

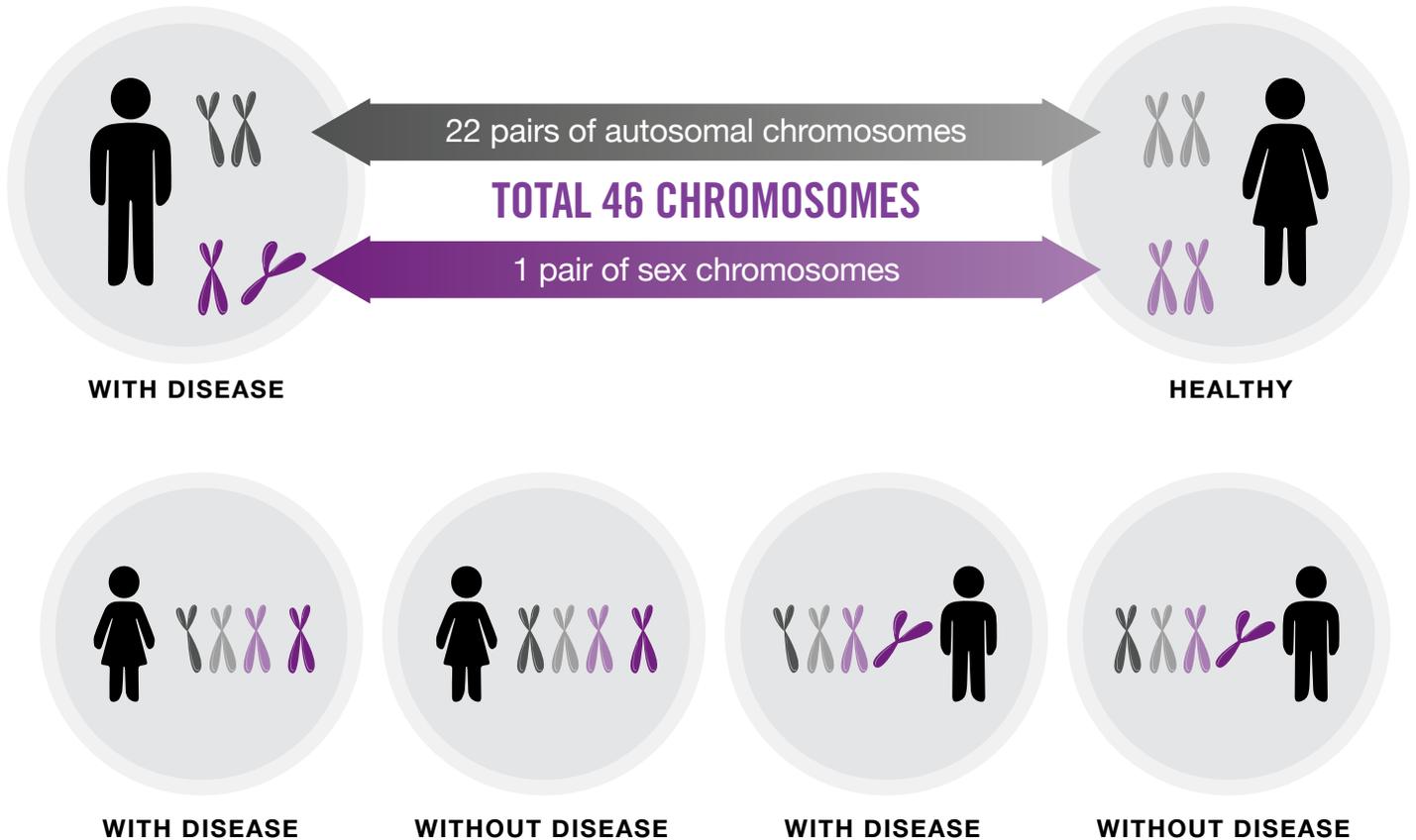
Figure 1. Normal inheritance.



Most people consider a genetic disease to be one that gets passed down from father or mother to child, in other words, at least one parent clearly has the disorder and so does the child. When only one parent

is affected and so is the child, the disease is considered “dominant” (**Figure 2**) because the inappropriately functioning gene from the parent who has the disease dominates over the healthy gene of the other parent.

Figure 2. Autosomal dominant inheritance with one parent affected.

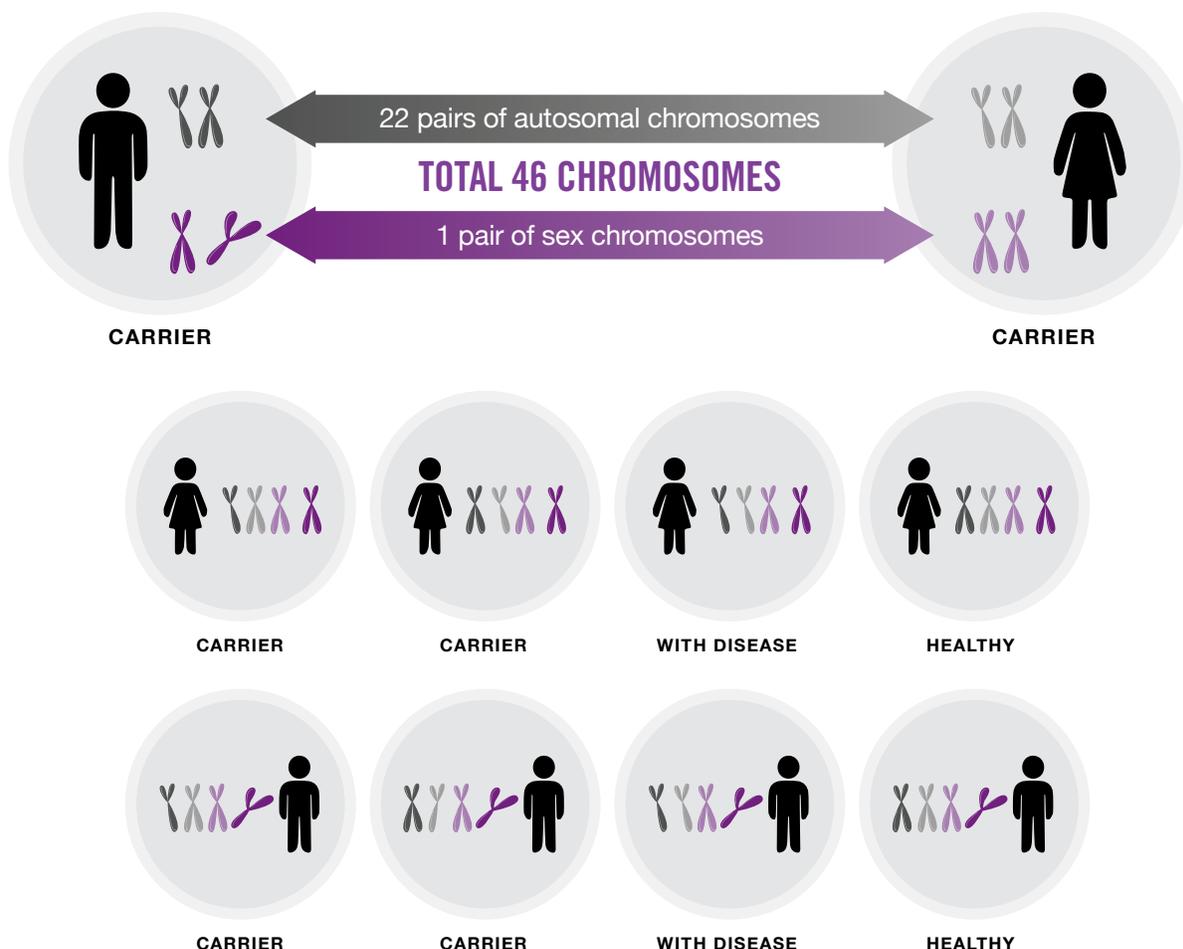


However, there are some genetic disorders that appear to show up suddenly without any strong indication that either parent has the disease. These genetic diseases are termed “recessive” or “hidden” because they show up only when genes inherited from both parents are not functioning correctly. MPS I is this type of disease. People with these recessive genes appear normal because they have one normally functioning gene from one of their parents that “hides” or overcomes the improperly functioning gene inherited from the other parent. Such individuals are termed “carriers” because

although they themselves do not exhibit the disease, they carry the defective gene that can be passed on to their children (**Figure 3**).

Genetic testing can trace the defective gene back up the family tree for several generations, even if none of the ancestors showed signs of the disease. Depending on whether the affected gene is on 1 of the 22 autosomal chromosomes or on the sex chromosomes, the disease is described as autosomal, X-linked, or Y-linked.

Figure 3. Autosomal recessive inheritance with both parents as carriers.



Females have 2 X chromosomes, 1 each inherited from the father and the mother. Corresponding genes on both X chromosomes need to be mutated for the female to exhibit a recessive disorder. Males have 1 X chromosome inherited from the mother and 1 Y chromosome inherited from the father. Mutations in genes on either chromosome will result in the disease becoming manifest, even in the case of rare disorders, since there is no corresponding healthy counterpart to overcome the defective gene.

- 50% chance of inheriting 1 normal gene and 1 diseased gene and be a carrier without evident disease, just like the parents;
- 25% chance of inheriting the defective gene from both the mother and the father and thus having the disease;
- 25% chance of inheriting the normal gene from both parents and thus being healthy and also not being a carrier.

Any child born of carrier parents (those couples in which both have a recessive gene on an autosomal chromosome) has a:

Any child of parents who are carriers of MPS I will have a one-in-four (25%) chance of having MPS I.

Therefore, any child has a 75% chance of inheriting at least one normal gene and will not manifest disease.

Furthermore, there is a 67% chance that unaffected brothers and sisters of individuals with the disease will be carriers of the defective gene. This is why individuals who are related to each other should not conceive children. The probability of related parents having similar recessive gene mutations increases dramatically.

Some genes code for enzymes. Since there are two copies of each gene, one inherited from the father and the other from the mother, each enzyme is produced from two genes. A defective gene produces a defective enzyme, i.e., an enzyme that does not have full function or may even be completely inactive. If one of

the two genes is defective (as is the case for carriers), the functional enzyme produced by the good gene helps the body compensate for the defective enzyme produced by the defective gene. This prevents the carrier from having symptoms of the disease. Only when genes inherited from both the father and the mother are defective and producing very little or inactive enzyme does the individual exhibit symptoms.

MPS I is an autosomal recessive genetic disease. That means that the gene that causes this disease is on 1 of the 22 autosomal chromosomes, specifically chromosome 4, and that it shows up only when both copies of the gene, each inherited from the father and mother, are not functioning properly (**Figure 3**).

MPS I is a genetic recessive disease caused by deficiency in a specific enzyme.

All families of individuals with MPS I should seek further information from their geneticist or genetic counselor if they have questions about genetics and MPS I or any questions related to inheritance.

Why does disease severity vary so much?

Any change in a gene is called a mutation. Many mutations do not have any effect on the gene function; in other words, the fundamental gene structure does not change. These are called “silent” mutations. However, other mutations trigger changes in the gene structure that cause them to behave abnormally; i.e., a defective gene could result in either an excess or a deficiency in the gene production. When the defective gene codes for an enzyme, this could mean too much or too little enzyme activity. In the case of MPS I, the gene coding for alpha-L-iduronidase is defective, resulting in highly reduced or completely absent enzyme activity.

The gene coding for alpha-L-iduronidase, *IDUA*, has been studied extensively, and many mutations that cause enzyme deficiency have been identified. Some common mutations result in absolutely no enzyme being produced. If both copies of the defective gene inherited by an individual are of this kind, evidence suggests that this individual’s symptoms will likely be at the severe end of the spectrum (Hurler syndrome; less than 0.13% of normal enzyme activity). Other mutations result in approximately 7% enzyme activity (or less) and correspond to the more attenuated (mild) end of the spectrum (Scheie syndrome). Mutations that

result in intermediate enzyme activity levels correspond to intermediate severity of disease (Hurler-Scheie syndrome). The lower the enzyme activity, the more severe the disease. There are yet other mutations that do not correlate with disease severity, some of which are not common at all and may only occur in a single known family. Further, data suggests there are other factors, which are not yet fully understood, involved in determining disease severity. Thus, DNA tests or mutational analysis are not always sufficient to predict disease severity.

As MPS I is a condition that gets worse with time, all untreated individuals will experience progression of symptoms no matter where they are on the spectrum of disease severity when first diagnosed. However, it is important to understand that although symptoms worsen and become more pronounced with time, individuals' symptoms do not progress to such a degree that they move from one syndrome to the next, i.e., individuals with attenuated disease (Scheie syndrome) at diagnosis will never experience symptoms as harsh as those with severe disease (Hurler syndrome), as they get older.

MPS I is a complex disease with widely varying severity. Hurler syndrome is the most severe, rapidly progressing form and manifests shortly after birth. Hurler-Scheie syndrome is an intermediate form that usually manifests in late childhood, progresses at an intermediate pace, and can have features of both Hurler and Scheie syndromes. Scheie syndrome is an attenuated form that progresses slowly and usually manifests in adolescence.

How long do individuals with MPS I live?

The lifespan of an individual with MPS I depends on many factors including, but not limited to, severity of the disease, specific symptoms, treatment received, when the treatment was started, and how long the treatment continued. Without treatment, individuals with attenuated disease (Scheie syndrome) may have a reasonably normal lifespan; individuals with intermediate disease (Hurler-Scheie syndrome) usually do not live beyond their teens or early adulthood; and individuals

with severe disease (Hurler syndrome) rarely live past 10 years of age with many dying at a much younger age. However, treatments, such as ERT and HSCT, can significantly extend these time frames with many individuals now living into their 20s and 30s. There is always hope for better outcomes for individuals with MPS I with ever-improving newer treatments, surgical procedures, and technology.

The lifespan of individuals with MPS I can vary widely depending on severity of disease and treatment received.

Signs and symptoms of MPS I

With tips for care and management

MPS I affects the entire body, including multiple organ systems, and is associated with a wide range of symptoms. Signs and symptoms of MPS I are summarized in the table below with detailed

descriptions following. Please note that not all individuals with MPS I will exhibit all symptoms or to the same degree. The symptoms and their severity can vary widely among individuals.

Table 1. List of symptoms exhibited by individuals with MPS I by organ system.

General symptoms	Physical appearance
<ul style="list-style-type: none"> • Reduced endurance • Fatigue 	<ul style="list-style-type: none"> • Coarse facial features (such as flat face, depressed nasal bridge, bulging forehead, enlarged mouth, thick lips) • Short neck • Large head (macrocephaly) • Longer than normal head from front to back (scaphocephaly) • Ridge across forehead • Severely short stature • Excessive hair (hirsutism) • Bent-over gait
Heart and blood vessels	
<ul style="list-style-type: none"> • Heart valve disease, especially aortic/mitral valves • Abnormal heart muscle (cardiomyopathy) • Irregular heartbeat (arrhythmia) • Thickened valves due to storage buildup 	
Gastrointestinal system (abdomen and intestines)	
<ul style="list-style-type: none"> • Enlarged liver and spleen (hepatosplenomegaly) • Enlarged abdominal organs • Umbilical and inguinal hernias • Protruding belly • Diarrhea and constipation 	Musculoskeletal system (bones and joints)
Respiratory system (lungs and breathing)	<ul style="list-style-type: none"> • Malformed neck (odontoid dysplasia) • Joint stiffness • Joint deformities and contractures • Skeletal abnormalities (dysostosis multiplex) • Carpal tunnel syndrome • Claw hands • Widened, oar-shaped ribs • Reduced flexibility of ribs–breastbone (sternum) junction • Abnormal chest shape; smaller thorax • Deformed feet • Abnormal hip formation (hip dysplasia) • Bone deformities in the spine (scoliosis, gibbus, kyphosis), or knees (knock-knees or genu valgum) • Delay in motor function
Endocrine system	
<ul style="list-style-type: none"> • Precocious puberty 	

Mouth and teeth	Eyes
<ul style="list-style-type: none"> • Enlarged mouth, thick lips • Small jaw • Enlarged tongue (macroglossia) • Abnormal teeth (widely spaced and very thin enamel) 	<ul style="list-style-type: none"> • Vision problems, such as corneal clouding • Retinal degeneration • Glaucoma
Ear, nose, and throat	Brain and nerves
<ul style="list-style-type: none"> • Frequent ear infections (otitis media) • Hearing loss • Chronic nasal discharge • Frequent upper respiratory tract infections (e.g., tonsillitis) • Enlarged adenoids and tonsils • Enlarged vocal cords (deep, hoarse voice) • Difficulty swallowing 	<ul style="list-style-type: none"> • Developmental delays (may be limited or absent in individuals with intermediate and attenuated disease) • Delay in motor function • Fluid in the brain (hydrocephalus) • Compression of the cervical spinal cord • Carpal tunnel syndrome • Short-term memory loss

Although not all individuals will experience all symptoms, there are some that are more prevalent in individuals with severe disease (Hurler syndrome) than in those with attenuated disease (Scheie syndrome) as listed in Table 2.

Table 2. Symptoms, severity, and time of presentation in severe or attenuated MPS I.*

Symptom	Severe disease (Hurler syndrome)		Attenuated disease (Scheie syndrome)	
	Severity	When noticed	Severity	When noticed
Coarse facial features	+++	Pre-diagnosis [†]	–	Not applicable
Fluid in the brain (hydrocephalus)	+++	Pre-diagnosis	–	Not applicable
Hernia (inguinal or umbilical)	+++	Pre-diagnosis [†]	+	Pre-diagnosis [†]
Enlarged liver and spleen	+++	Pre-diagnosis	+	Pre-diagnosis
Stiffened joints	+++	Pre-diagnosis	++	Pre-diagnosis [†]
Skeletal (bone) abnormalities	+++	Pre-diagnosis [†]	++	Post-diagnosis
Recurrent upper airway infections	+++	Pre-diagnosis	+	Pre-diagnosis
Corneal clouding	+++	Pre-diagnosis	++	Pre-diagnosis [†]
Abnormally shaped teeth [‡]	+++	Pre-diagnosis	–	Not applicable
Carpal tunnel syndrome	+++	Post-diagnosis	++	Post-diagnosis
Heart (valve) disease	+++	Post-diagnosis	++	Post-diagnosis
Spinal cord compression	+++	Post-diagnosis	+	Post-diagnosis
Hearing loss	+++	Post-diagnosis	+	Post-diagnosis
Delayed mental development	+++	Post-diagnosis	–	Not applicable
Lung disease/sleep apnea	+++	Post-diagnosis	+	Post-diagnosis

*Note that this is intended as a general guideline for when symptoms may appear and may not apply to everyone, since symptoms appear at different times for different people and diagnosis may occur earlier or later in the course of the disease.

[†]Symptoms that often prompt parents or caregivers to seek medical attention, leading to a diagnosis of MPS I.

[‡]If a child is old enough to have teeth.

MPS I affects many areas of the body. Because its signs and symptoms are so variable, it can affect each individual very differently.

Growth

Individuals with MPS I are usually shorter than normal, dependent upon the severity of the disorder.



ALLISON

Physical appearance

Facial features of individuals with MPS I are usually altered to some extent, depending on the severity of the disease. Those with severe MPS I have several facial features in common. They are often described as having “coarse facial features,” which is not intended to be insensitive, but rather help with quick and accurate diagnosis. These include a large head, a flat face, a broad nose with a flat bridge, upturned nostrils, shallow eye sockets with slightly protruding eyes, and a large

Severe disease (Hurler syndrome)

Individuals with severe disease can be quite large at birth and grow faster than the average child at first. However, growth slows down between 6 months and 18 months of age and often stops around 3 years of age. The individual may not grow taller than 4 feet.

Intermediate disease (Hurler-Scheie syndrome)

The growth of individuals with intermediate disease is highly variable, but most are shorter than 95% of individuals their age without MPS I (below 5th percentile for height).

Attenuated disease (Scheie syndrome)

Individuals with attenuated disease usually grow to normal height, reaching 5 feet or more. Growth hormone therapy has been successfully used in some individuals with attenuated MPS I. Parents interested in considering growth hormone therapy should discuss this with their physicians well ahead of their child reaching puberty.

tongue, which sometimes sticks out. The head tends to be longer than normal from front to back, with a bulging forehead (scaphocephalic) due to how the bones of the skull join after birth to generate its shape. When all babies are born, their skulls are soft, with the individual bones separated by a thin tissue. In the front (anterior) above the forehead and in the back (posterior) near the hair whorl are soft spots (fontanelles) which close and fuse during the first few years. In individuals with severe

MPS I, the bones along the top of the head fuse together much sooner than normal forcing the skull to expand downward, resulting in the long shape of the head and the prominent forehead. Often, there is a ridge across the forehead where the skull has closed prematurely.



JACOB

Individuals with severe MPS I typically have coarser hair, which is more abundant (hirsutism) than those without this disease. They may have protruding bellies and also may stand and walk bent over due to joint stiffness and bone deformities (contractures) at the hips, shoulders, elbows, and knees.

Individuals with attenuated disease vary considerably in appearance and may even appear to be unaffected. In general, adults may have a stocky build with a short, stiff neck and a trunk that is shorter than average.

Individuals with intermediate disease also vary considerably in appearance and may have some features in common with those with either the severe or the attenuated form of the disease.

The physical appearance of individuals with MPS I can vary considerably, from distinctive features among those with severe disease to no apparent difference from average among those with attenuated disease.

Mouth and teeth

Individuals with severe MPS I may have a small jaw, enlarged mouth, thick lips, and enlarged tongue.

The gum ridges are broad, with teeth that are widely spaced and poorly developed with a fragile outer layer (enamel). It is important that the teeth are well cared for, as tooth decay can be a cause of pain. Teeth should be cleaned regularly. If the water in your area has not been treated with fluoride, individuals with MPS I should speak with their dental and medical providers to determine a plan for fluoride administration. Cleaning inside the mouth with a small sponge on a stick soaked in mouthwash will help keep the mouth fresh and help avoid bad breath. However, even with the best dental care, an infection (abscess) around a tooth can develop due to its abnormal formation. Irritability, crying, and restlessness can sometimes be the only signs of an infected tooth in a young child.

If an individual with MPS I has a heart problem, it is advised that antibiotics be given before and sometimes after any dental treatment. This is because certain bacteria in the mouth may get into the bloodstream and cause an infection in the abnormal heart valve, potentially damaging it further. Depending on the antibiotic used, side effects could differ. Some common side effects of antibiotics include diarrhea, nausea, and vomiting. Antibiotics may also cause skin rashes and allergic reactions.

If teeth need to be removed under anesthesia, the procedure should be done in the hospital under the care of both an experienced anesthetist and a dentist, but never in the dentist's office. Dentists should be informed of the diagnosis of MPS I and provided contact information for other medical providers working with the individual.

Teeth should be cleaned regularly, and if the water in your area has not been treated with fluoride, individuals with MPS I should discuss supplemental fluoride with their dentist. Cleaning inside the mouth with a small sponge on a stick soaked in mouthwash will help keep the mouth fresh and avoid bad breath.

Dental surgery under anesthesia, including simple extractions, must be done only in a hospital setting with an experienced anesthetist and dentist or oral surgeon. Additional precautions must be taken for those with heart conditions. It is advised that antibiotics be given before and sometimes after any dental treatment.

Skin

Individuals with MPS I tend to have thickened and tough skin, making it difficult to draw blood or place IV catheters. Severely affected individuals may have extra hair on their face and back (hirsutism).

If the hands or feet are blue or cold from time to time, there may be a problem with blood circulation. Please consult a cardiologist (heart specialist) to check whether there is a problem with the heart or the aorta (the large blood vessel that transports blood from the heart to the rest of the body). Poor blood circulation can cause cold hands and/or feet and the skin to appear blue.

Children with MPS I may also have “Mongolian spots” (the medical term for birthmarks such as a Mongolian spot is “congenital dermal melanocytosis”). Importantly, the skin in these areas is not cold to touch. The reasons for occurrence of Mongolian spots in individuals with MPS I are not yet clearly understood.

This sign should not be confused with temporary blueness of the hands or feet due to poor blood circulation, which is usually accompanied by cold skin as discussed above.

Note: Mongolian spots often occur at birth or appear during the first weeks of life. These are bluish-colored spots that appear on the skin, often in the lower back area, and are not the result of an injury. Mongolian spots occur because of clusters of unusually high levels of pigment-producing cells in the skin. They cannot be prevented, and it is not known why some babies have them and others do not, although they are more common in infants with darker skin, e.g., those of Asian, Hispanic, Native American, African, and East Indian descent. Mongolian spots, in and of themselves, are not painful, do not pose any health risks, and do not require any medical treatment. Most babies who have them will outgrow them and do not have any health effects from them.

Individuals with MPS I tend to have thickened and tough skin, extra hair, periodic cold and blue hands and feet, and Mongolian spots.

Eyes

Symptoms related to eyes, including corneal clouding, loss of depth perception, glaucoma, and retinal degeneration (including night blindness), are common across the disease spectrum in individuals with MPS I. It is often difficult to determine which combination of problems is responsible for the decrease in eyesight experienced by individuals with MPS I. An eye specialist (ophthalmologist) can perform special tests to help determine whether the problem with vision in an individual with MPS I is due to how light gets in the eye (i.e., related to the cornea) or how the eye responds to light (i.e., related to the retina or optic nerve).

Corneal clouding

The circular window at the front of the eye (cornea) can become cloudy due to storage of GAGs. Corneal clouding is common among individuals with MPS I. If corneal clouding is severe, it may reduce sight, especially in dim light. Some individuals cannot tolerate bright light, as the clouding causes uneven refraction of light. Wearing caps with visors or sunglasses can help. Surgical correction may be required for those with severe corneal clouding.

Corneal transplant surgery is often used to treat corneal clouding in patients with MPS I. In this procedure, the surgeon removes the damaged tissue and replaces it with healthy tissue from a human donor. Depending on the extent of the damage, the surgeon will perform a traditional penetrating keratoplasty (PK) transplant or a newer deep anterior lamellar keratoplasty (DALK) procedure.

A PK transplant replaces the full thickness of the cornea. However, in many individuals with MPS I, the GAG damage is limited to the exterior of the cornea

and the DALK procedure is then preferred as it is less invasive and lessens the risk of graft rejection.

Although corneal transplants can improve vision for many individuals with MPS I, there are several risks involved with this procedure. These include, but are not limited to, infection, rejection of the transplanted cornea, and allergic reaction to medication, e.g., local anesthetic for the procedure. It may take a year or longer for vision to return to normal when an individual may experience complications.

In older individuals with MPS I, corneal transplants may be problematic as the cornea can become stiff and difficult to manipulate during surgery. Corneal transplants should be done by an ophthalmologist familiar with MPS.

Loss of depth perception

Loss of depth perception is a symptom common among individuals with MPS, including MPS I. The cause for this is unclear and may be due to greater nerve damage in one eye caused by accumulation of GAGs. It is important that individuals with loss of depth perception be seen by an eye doctor (ophthalmologist) to determine the cause and treatment.

Glaucoma

Storage of GAGs in the eyes can also increase pressure in the eye (glaucoma), resulting in problems with vision. These should be checked by an eye doctor (ophthalmologist) and corrective action taken to prevent further loss of vision. Individuals with increased eye pressure need to be tested immediately for increased intracranial pressure and hydrocephalus, which will require urgent attention.

Retinal degeneration

Storage of GAGs in the retina can cause changes in the retina, leading to night blindness and the loss of peripheral vision (ability to see things out of the corner of the eyes). Night blindness may hamper a person's ability to go through dark areas or lead to waking up at

night and being afraid. Adequate, but not too bright, night lighting in the bedroom or hall can help alleviate the last issue. It is important to consult an ophthalmologist to take corrective action.

Problems with eyesight are common among individuals with MPS I across all severities of the disease. It is important to consult an eye doctor (ophthalmologist) to determine the cause for vision loss and take corrective action.

Ears



SYDNEE

Some degree of deafness is common in MPS I. Problems may occur at various points in the normal hearing process, potentially leading to hearing loss. Deafness in individuals with MPS I may be conductive deafness, sensorineural deafness, or both (mixed deafness) and could be made worse by frequent ear infections. It is important that individuals with MPS I have their hearing monitored regularly so that problems can be treated early to maximize their ability to learn and communicate.

With normal hearing, sound waves cause the eardrum (a thin membrane between the outer and middle ear) to vibrate. Three small bones in the middle ear amplify these vibrations. The middle ear needs to be at the same pressure as the outside air in order to work properly. The Eustachian tube, which reaches from the middle ear to the back of the throat, is used to regulate the pressure in the middle ear. The vibrations of the middle ear bones are picked up by the inner ear. Tiny hair cells in the inner ear sense these vibrations and send a message through the auditory nerve to the brain, which then interprets them as sound.

Conductive deafness

Conductive deafness occurs when something prevents the eardrum or middle ear bones from vibrating properly. Correct functioning of the middle ear depends on the pressure behind the eardrum being the same as that in the outer ear canal and the atmosphere. This pressure is equalized by the Eustachian tube, which runs to the middle ear from the back of the throat. If the tube is blocked, the pressure behind the eardrum will drop and the drum will be drawn in. If this negative pressure persists, fluid from the lining of the middle ear will build up and in time become thick like glue (middle ear effusion). This can prevent the eardrum or middle ear bones from vibrating properly, resulting in conductive deafness because of a blocked Eustachian tube. This is an important factor contributing to hearing loss in individuals with MPS I.



HOLLY

If it is possible for the child to have a light general anesthetic, a small incision through the eardrum can be made (myringotomy) to remove the fluid by suction. A small ventilation tube may then be inserted to keep the hole open and allow air to enter from the outer ear canal until the Eustachian tube starts to work properly again. The tubes placed in the eardrum may quickly

fall out. If this happens, the surgeon may decide to use tympanostomy tubes (T tubes, see “Use of T tubes,” page 23), which usually stay in place much longer. It is expected that, once a ventilation tube is in place, fluid should drain out and hearing should improve.

Sensorineural (nerve) deafness

In most cases, nerve deafness is caused by damage to the tiny hair cells in the inner ear. Unlike conductive deafness, sensorineural deafness cannot be managed by inserting ear tubes. The hair cells are small, delicate, and difficult to repair. For this reason, sensorineural deafness is often not reversible. Nerve or sensorineural deafness can be managed by the fitting of a hearing aid or aids in most individuals. In general, it is felt that hearing aids are underutilized in MPS diseases. Many hearing aids now come equipped with Bluetooth and other features to support smooth integration into listening environments, such as at school, in public places, and at home. Hearing aids require fitting by an audiologist.

Mixed deafness

When individuals experience both conductive and nerve deafness, it is referred to as mixed deafness. Managing mixed deafness involves treating both types of deafness as described above.

What is otitis media (OM)?

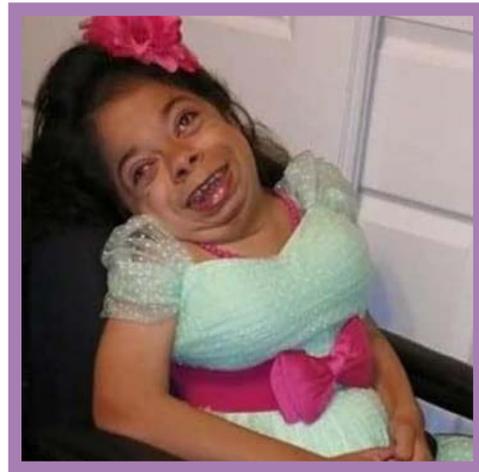
OM is the medical term for an infection of the middle ear. It is common for healthy children to have OM usually caused by blockage of the Eustachian tubes due to large adenoids or problems with drainage of fluid from the middle ear. In children with MPS I, this is complicated by the buildup of GAGs in the middle ear, nose, mouth, and throat and the infections become more stubborn resulting in exacerbating the problems. There are two types of OM, acute and OM with effusion

(OME). Individuals with MPS I may not present with typical symptoms of ear infection. With pain thresholds often higher than in the general population, drainage from the ear (with or without an odor present) may be the first sign. If any drainage is observed, seek medical care.

Acute OM: This occurs when fluid is present in the middle ear, along with signs or symptoms of ear infection such as bulging eardrum often with pain, ear tugging, fever, irritability, decreased appetite, vomiting, and diarrhea. Complications, although rare, can include broken eardrum (tympanic membrane perforation), inflammation in the area surrounding the middle and inner ear (acute mastoiditis), or a mass of cells and cholesterol in the middle ear (cholesteatoma). Very rarely, serious, potentially life-threatening inflammation of the membranes covering the brain (meningitis) and inflammation of the area between the skull bone and the membranes covering the brain (epidural abscess) can occur. Language development can also be affected by repeated ear infections.

OME: OME is diagnosed when there is fluid in the middle ear without signs or symptoms of middle ear infection. OME can lead to conductive deafness, difficulty with learning speech and language (hearing problems interfere with speech and language development), thickening or scarring of the eardrum, and a mass of cells and cholesterol in the middle ear (cholesteatoma).

For some individuals with MPS I, a number of middle ear infections may occur before MPS I is diagnosed. The individual may not have any symptoms, but hearing can be affected. Any individual who has fluid in the middle ears for at least 3 months should have a hearing test. A careful examination of the ear may be difficult for a child with MPS I but is essential for proper diagnosis. Ear, nose, and throat (ENT) specialists, also called otolaryngologists, can help diagnose



REILENE

MPS I by identifying children with recurrent infections and abnormalities seen under examination. Once a diagnosis of MPS I has been made, the ENT specialist can be very helpful with many of the issues regarding managing the symptoms associated with the ears, nose, and throat.

Medication: Children with MPS I tend to have many ear infections that can be very difficult to treat. If your child has ear infections that are hard to get rid of, it may be necessary for the doctor to do a “culture” of the fluid in the middle ear. The doctor will take a sample of this fluid and test it to see which bacteria, viruses, or fungi are living in the fluid. Identifying the bacteria, virus, or fungus that may be causing the infection allows the doctor to prescribe the appropriate medication. For example, if the infection is fungal, frequent antibiotic use will only worsen the situation.

Antibiotics are the usual treatment for OM. There is a wide array of antibiotics available for treatment. Some require refrigeration or frequent dosing. Antibiotic injections can be considered for a child who has difficulty taking medications by mouth. Some common side effects of antibiotics include diarrhea, nausea, and vomiting. They may also cause skin rashes and allergic reactions. Occasionally, older children may



EVELYN

have infections caused by other bacteria such as *Pseudomonas aeruginosa* or *Staphylococcus aureus* that can be more difficult to treat.

If the child has T tubes, ear drops may be used to treat the infection. Steroid drugs that reduce inflammation (corticosteroids) may also be helpful. Always continue taking the full course of antibiotics as prescribed, even if the infection appears to clear quickly.

Use of ear tubes: In most cases of repeated ear infections, inserting tubes into a hole in the eardrum (tympanostomy) is recommended to allow the fluid to drain. Tympanostomy tube insertion is a 10- to 15-minute procedure usually performed under general anesthesia. The tubes help the child by keeping the middle ear ventilated. There are several different types of ear tubes. Individuals with MPS I may require multiple sets of T tubes, as they may become dislodged over time. Though less commonly used, metal grommet tubes may be a consideration for placement.

Ear tubes may become blocked or infected. They may also damage or scar the eardrum. It is important to consult with an ENT specialist experienced with MPS I to determine which tube is best. Please note that this should always be done at a properly equipped hospital

and only after consultation with the anesthesiologist, because of anesthesia concerns for children with MPS I (described in a separate section in this resource). After the procedure, a culture should be made from the drained fluid to identify the offending organism.

Surgery: Removal of the adenoids (tissues at the back of the nasal cavity) and tonsils might also be recommended for children with MPS I who have recurrent acute OM. If the child is to have general anesthesia for the placement of ear tubes, removal of the adenoids and tonsils should also be considered at the same time. This avoids the risk by reducing the number of procedures requiring anesthesia. It is important to note that the adenoid tissue may “grow back” and individuals with MPS I can require more than one surgery to remove this.

Prevention: Children can receive a vaccine for *Streptococcus pneumoniae*, which is one of the more common bacteria that cause ear problems. This might help reduce the number of future bacterial infections. Vaccines may cause a mild fever or pain, redness, or swelling at the site of injection. More serious side effects include allergic reactions (these are rare). Some children may benefit from eliminating common food allergens from the diet. These can include soy, citrus, peanuts, wheat, fish, eggs, corn, and tomatoes. Some parents report positive results from supplementation with cod liver oil or other fish oils. Check with your doctor about adding a multivitamin to the child's diet. Exposure to secondhand cigarette smoke is recognized as a risk factor for OM, and every effort should be made to keep children away from smoke exposure.

Ear infections seem to be a persistent problem in children with MPS I, and anything that can help relieve the symptoms may be warranted. Each child may respond differently to various treatments, so every option should be tried, if needed. Speak to your

doctor before trying a new treatment, including herbal or alternative treatments. Frequent ear infections, hearing loss, an enlarged tongue, decreased mental capacity, and blocked airways may lead to speech and language problems in individuals with MPS I. As a result, a speech therapist may help those with MPS I

with their speech. Hearing aids and using other forms of communication such as sign language, augmentative communication devices, and the Picture Exchange Communication System may also be useful for people with hearing loss.

It is important that individuals with MPS I have their hearing monitored regularly.

It is important to consult with an ENT specialist experienced with MPS I to determine how best to treat ear infections and deafness.

Treatment for OM may include medication, ear tubes, or surgery. Surgery should only be performed in a hospital under appropriate anesthesia and under the care of specialists with expertise in treating MPS I or at least MPS in general.

Prevention of ear infections in individuals with MPS I may be an option. Please consult your doctor about vaccinations.

Nose and throat

Nose and throat problems are more common among individuals with more severe MPS I than among individuals with attenuated disease, who are likely to have fewer and less severe symptoms.

Runny nose

Typically, the bridge of the nose among severely affected individuals is flattened and the passage behind the nose may be smaller than among individuals not affected by MPS I. This is due to the bones in the mid-face not having grown well and the mucosal lining in the nose being thicker. GAG buildup in the soft tissues of the nose and throat, combined with abnormal bones, can cause the airway to become easily blocked.

Individuals with severe MPS I often have a long-term (chronic) discharge of thick mucus from the nose (rhinorrhea) and chronic ear and sinus infections.

Throat

The adenoids (tissues at the back of the nasal cavity) and tonsils often become enlarged and can partly block the airway. In addition, the neck is usually short, and together both contribute to problems in breathing. The windpipe (trachea) becomes narrowed by stored GAGs and may be floppy, or softer than in individuals without MPS I, due to abnormal cartilage rings in the trachea. Nodules, bumps, or folds of excess tissue can further block the airway.

Nose and throat problems are worse in individuals with more severe MPS I. Please consult an ENT specialist (otolaryngologist) to determine the best course of action for nose and throat issues that arise.

A speech therapist may be able to help individuals with MPS I with their communication.

Respiratory system

Individuals with MPS I tend to have short necks and unusually narrow airway passages, which make airway blockage (obstruction) a common experience. In addition, the tonsils and adenoids (tissues at the back of the nasal cavity) can become enlarged and block the airway, thereby making breathing difficulties worse. Individuals with more severe disease often have an abnormally shaped chest and a small thorax (the part of the body between the neck and the abdomen, surrounded by the ribs and breastbone, containing the heart and lungs). The junction between the ribs and the breastbone (sternum) is not flexible making the chest rigid and incapable of moving freely. The diaphragm

(muscle at the base of the chest) is pushed upward by the enlarged liver and spleen (hepatosplenomegaly). All of these structural abnormalities reduce the space available for the lungs, allowing them to take in only small amounts of air and preventing intake of a large volume of air, as would be normal for someone with a healthy respiratory system. This reduced air intake prevents individuals with MPS I from breathing in adequate amounts of oxygen and can lead to difficulty breathing while awake or asleep. When individuals cannot fully exhale (breathe out), the lungs do not fully clear out, and there is an increased risk of infection (pneumonia).

Individuals with MPS I tend to have structural abnormalities of the chest resulting in breathing problems, including infections. Please consult your doctor for appropriate treatment.

Individuals with MPS I tend to have short necks and unusually narrow airway passages, which make airway obstruction a common experience.

Sleep apnea

Obstructive sleep apnea, defined as temporary breathing interruptions (usually 10–30 seconds) while asleep, is a common airway problem for individuals with MPS I. It occurs when the airway in the neck becomes blocked as muscles in the airway relax. The risk of the airway becoming blocked is increased in individuals with MPS I due to some of the structural issues stated earlier and enlarged tonsils and adenoids.

Many individuals with MPS I breathe very noisily, even when there is no infection. When sleeping, they often are restless and snore. This noisy breathing, which stops and starts, can sound very alarming to parents or bed partners who may fear that the person is dying. If the breathing is noisy during sleep, the individual's oxygen level may be low, which can cause heart problems. Although many individuals with MPS I may

breathe like this for years, a sleep specialist should be consulted for an evaluation through a sleep study, especially if a parent or bed partner notices significant choking or episodes of interrupted breathing.

Individuals with MPS I may be admitted to the hospital overnight for a sleep study in which monitors are placed on the skin and connected to a computer to measure the levels of oxygen in the blood, breathing effort, brain waves during sleep, and other indicators of the body's function. From this study, sleep experts can assess the severity of breathing blockage, the difficulty in inhaling (moving air into the lungs) during sleep, and the effect on the body as a whole.

Sleep apnea can be treated in some patients by removing the tonsils and adenoids (which may regrow) or opening up the airway during sleep with a continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) machine, or a tracheostomy (a hole into the airway made in the front of the neck), which is only needed in very severe cases of sleep apnea with heart failure.

Untreated sleep apnea can have a dramatic effect on the individual's waking hours, such as excessive sleepiness and irritability. Successful treatment may greatly improve an individual's quality of life.

Sleep apnea is common among individuals with MPS I. Sleep apnea can be treated by removing the tonsils and adenoids, or airway pressure machines (CPAP/BiPAP), or a tracheostomy (in the most severe cases).

Infections

Colds are caused by viral infections and do not require antibiotic treatment. However, many individuals with MPS I experience secondary bacterial infections in addition to colds. These bacterial infections usually occur in the sinuses or middle ear (discussed earlier). In individuals with MPS I, storage of GAGs in the throat and nasal passages causes the sinuses to have abnormal shapes and become blocked, thereby increasing the risk of sinus infections. Furthermore, poor drainage of the sinuses and middle ear make treating infections difficult. Bacterial infections of the sinuses should be treated with antibiotics under the care of a physician knowledgeable about MPS.

There are many different antibiotics available, and each one has its own spectrum of side effects. Some common side effects of antibiotics include diarrhea, nausea, and vomiting. They may also cause skin rashes and allergic reactions. Since the sinuses do not drain



JETT

properly, overcoming infections can be difficult. It is common to have infections seem to go away while the individual is taking antibiotics and then come back after the antibiotic course is over. Many individuals with MPS I may become allergic to antibiotics or may develop resistant infections. Your doctor can prescribe other antibiotics to help manage this problem. While overusing antibiotics is never advised, most people with MPS I will often require multiple treatments for most infections. Drugs may affect people with MPS I differently, so it is essential to consult your doctor before using over-the-counter (OTC) medications. Drugs for

controlling mucus production may not help. Drugs such as antihistamines (allergy medications) may dry out the mucus, making it thicker and harder to dislodge. Decongestants usually contain stimulants that can raise blood pressure and narrow blood vessels, both undesirable for people with MPS I. Cough suppressants

or drugs that have sedatives may cause more problems with sleep apnea by decreasing muscle tone and breathing rates. Individuals with MPS I and caregivers will need a doctor with whom they can develop a good working relationship to manage the frequent infections.

Bacterial infections of the respiratory system are common among individuals with MPS I. Bacterial infections can be treated with antibiotics, but often recur when treatment is stopped. Multiple rounds of treatments may be needed.

Please consult a physician knowledgeable in treating MPS to treat infections. Please be aware that OTC medications can cause more harm than good or work differently in the body of an individual with MPS I.

Secretions

Individuals with MPS I often have collections of mucus (secretions) in the lungs. Chest postural drainage is a technique that can help with clearing such secretions. It involves placing the affected person in different positions to help mucus drain from the lungs. It may be used in combination with tapping the chest or back with a cupped hand (chest percussion), which helps loosen the mucus. A respiratory therapist will be able to teach the technique to you, your family, and someone at school for children with MPS I. Possible side effects of chest postural drainage include injury to the ribs, lungs, or diaphragm; bleeding in the lungs; vomiting and aspiration (inhaling mucus, saliva, or vomit into the breathing tubes), difficulty getting enough oxygen during treatment; and fainting (certain positions for chest postural drainage can cause the blood to rush from the head, causing the individual to lose consciousness).

There are also some mechanical devices that can help with clearing secretions. Inflatable vests (“shaky vests”) deliver high-frequency oscillations to the chest. The vibrations help to loosen and potentially thin the mucus



HANNAH AND MAGGIE

in the lungs. The individual puts on the vest, connects it to the vest machine, and breaths normally as the chest is massaged. After 5 minutes they stop the machine and attempt to cough. This procedure is repeated for about 30 minutes or as directed by the doctor. There are also cough assist machines that are basically a mask and mouthpiece connected to a machine. The cough assist device slowly blows air into the lungs through the mouthpiece and then quickly pulls the air out along with any mucus, simulating a cough. A nebulizer can also be used alone or in conjunction with these devices to deliver saline or prescribed medications into the lungs to help thin secretions.

Chest postural drainage, a technique to drain mucus from the lungs, may be required for some individuals with MPS I and must be done with training from a respiratory therapist or pulmonologist. Please be aware of the side effects of this technique and take the appropriate care. Cough assist vests and machines may help certain individuals.

Heart

Heart disease is a major cause of death in individuals with MPS I. Heart disease is common in those with severe and attenuated forms of the disease. Heart disease can be categorized into effects on (a) the heart muscle, (b) heart rhythm, (c) heart blood vessels, and (d) heart valves.

Effects on the heart muscle

Severely affected individuals, even children, may have an abnormal heart muscle (cardiomyopathy) and/or scarred and stiff heart (endocardial fibroelastosis or

fibrosis) due to the storage of GAGs. Of the many types of cardiomyopathy, the one most common among individuals with MPS I, is an abnormal thickening of the heart muscle (hypertrophic cardiomyopathy). As the condition worsens, the heart may become enlarged (cardiomegaly), which causes the heart to pump more weakly (dilated cardiomyopathy). As noted above, individuals with MPS I often have abnormal lungs. This adds to the strain placed on the heart as it pumps blood through the affected lungs.

Individuals with MPS I often have abnormal heart muscles, which make them susceptible to heart disease. Please consult with a heart specialist (cardiologist) knowledgeable in MPS diseases for appropriate treatment and care.

Effects on heart rhythm

Cardiomyopathy in individuals with MPS I can increase the risk of irregular heartbeat patterns (arrhythmias), which can lead to sudden death.

Effects on the blood vessels of the heart

GAG storage in the heart blood vessels (coronary arteries) of individuals with MPS I can damage these vessels, similar to that seen among older people and can lead to death. Sometimes, the coronary arteries of individuals with Hurler syndrome may become narrowed and cause episodes of chest pain (angina). The narrowed blood vessels can also lead



BENJI

to poor circulation in the arms and legs. Signs of poor circulation in these areas include cold hands and feet. If you or the person you are caring for has MPS I and notice these symptoms, please consult your doctor and/or cardiologist. If your young child has MPS I and you notice that he/she is distressed, crying, pale, sweating, and keeping still, please consult your doctor as soon as possible. The doctor may refer your child for

an electrocardiogram. This is a noninvasive procedure in which a number of electric leads are attached to the chest and body. The test is painless and can identify problems with the heart muscle and heart function, but like many tests, it cannot detect all possible problems. Many individuals with MPS I also have high blood pressure (hypertension), which is related to narrowing of blood vessels caused by GAG storage.

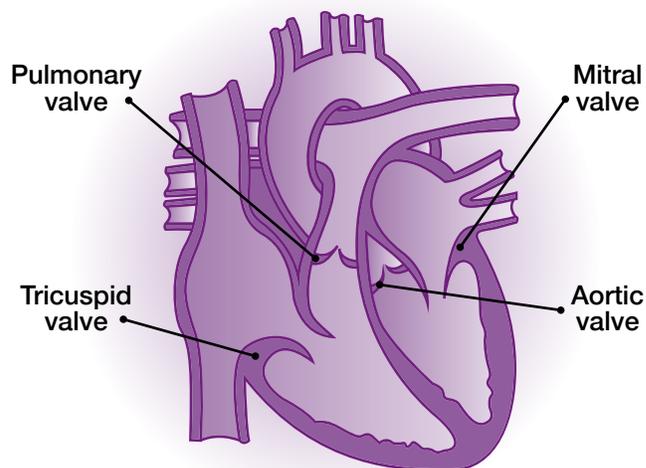
Individuals with MPS I often have abnormal blood vessels, especially those in the heart, which make them susceptible to chest pain (angina), poor circulation, and high blood pressure. Please consult with a heart specialist (cardiologist) knowledgeable in MPS diseases for appropriate treatment and care.

Effects on the heart valves

Many individuals with MPS I across the disease spectrum may experience problems, including thickening or stiffening of the heart valves due to GAG storage. There are four valves in the heart: the tricuspid, the mitral, the pulmonary, and the aortic.

The tricuspid valve is on the right side of the heart between the right atrium (also known as “auricle,” a collecting chamber for blood flowing back from the body) and the right ventricle (a muscular pumping chamber that pumps blood to the lungs). The valve prevents blood from flowing backwards into the right atrium when the right ventricle of the heart contracts.

The mitral valve is on the left side of the heart between the left atrium (a collecting chamber for blood flowing back from the lungs) and the left ventricle (a muscular pumping chamber that pumps blood to the rest of the body). The valve prevents blood from flowing backward into the left atrium when the left ventricle of the heart contracts.



The pulmonary valve sits between the right ventricle and the pulmonary artery (the vessel that transports blood from the heart to the lungs). The valve prevents blood from flowing backward into the heart between its contractions.

The aortic valve sits between the left ventricle and the aorta (the vessel that transports blood from the heart to the rest of the body). The valve prevents blood from flowing backward into the heart between its contractions.

The doctor may hear heart murmurs (sounds caused by turbulence in blood flow in the heart) if the valves become damaged by stored GAGs. The heart valves are designed to close tightly to prevent blood from flowing back in the wrong direction. Individuals with MPS I with defective valves due to damage by GAG accumulation may experience regurgitation (blood shooting backward) and/or stenosis (stiffening of the valve).

Regurgitation: This occurs when the weakened valve cannot shut firmly enough and a small amount of blood may shoot backward, causing turbulence and a murmur, e.g., when the mitral valve does not shut firmly causing blood from the left ventricle to flow back into the left atrium (mitral valve regurgitation), or when the aortic valve does not shut firmly causing blood from the aorta to flow back into the left ventricle (aortic valve regurgitation).

Stenosis: Stenosis refers to a stiffened heart valve. The valve may not be able to open completely thereby narrowing the opening through which the blood is pumped. When the problem becomes severe, the damaged heart valves may need to be replaced surgically.

Heart valve replacement is common for individuals with MPS I. There are two types of valves used for valve replacements – tissue or mechanical. Mechanical valves are made of strong materials that can last for a patient's lifetime; however, in order to prevent blood clots from forming, patients usually receive blood-thinning medication for the rest of their lives.

Tissue valves are created from animal tissue and can last from 10 to 20 years in individuals without MPS. They do not usually require the need for blood thinners. However, GAGs can still build up on the replacement tissue possibly limiting their effectiveness or resulting in them needing to be replaced. Most published cases used mechanical valves. However, newer technology allows some tissue valves to be replaced without reopening the chest, which may affect these choices in the future. Please consult with a heart specialist (cardiologist) knowledgeable in MPS diseases for appropriate treatment and care.

Individuals with MPS I often have abnormal heart valves, which make them susceptible to reverse blood flow (regurgitation) and/or stenosis (stiffened heart valves) that may require surgical intervention. Please consult with a heart specialist (cardiologist) knowledgeable in MPS diseases for appropriate treatment and care.

Since heart problems occur so frequently among individuals with MPS I, all those affected should have a test known as an echocardiogram regularly (or as often as recommended by the doctor) to catch signs of problems as early as possible. The test is painless and similar to the ultrasound screening of babies in the womb. It can identify problems with the heart muscle, heart function, and heart valves but, like many tests, it cannot detect all possible problems.

Because of the unusual special problems that can occur in these disorders, you should choose a cardiologist with some knowledge of MPS I. If this is not possible, you should inform the doctor about the heart problems experienced by individuals with MPS I. Medications are available to help manage the heart problems that occur as a result of MPS I.

Heart problems are common among individuals with MPS I. It is recommended that individuals with MPS I get regular tests of heart function. Please consult with a heart specialist (cardiologist) knowledgeable in MPS diseases for appropriate treatment and care.

Gastrointestinal system

Liver and spleen

In more severely affected individuals, both the liver and spleen are enlarged (hepatosplenomegaly) due to accumulation of GAGs. The liver may also be enlarged in individuals with attenuated disease. The enlargement of these organs does not usually lead to problems, but it can interfere with eating and breathing and cause hernias.



WESLEY

Although enlargement of the liver and spleen itself may not be problematic, it can interfere with eating and breathing and cause hernias.

Abdomen and hernias

In most individuals with MPS I, the abdomen bulges out due to posture, weakness of the connective tissue and muscles, and the enlarged liver and spleen. Frequently, part of the abdominal contents will push out behind a weak spot in the wall of the abdomen. This is called a hernia. The hernia can come from behind the navel (umbilical hernia) or in the groin (inguinal hernia). Inguinal (groin) hernias should be repaired surgically, but they may recur. Umbilical (navel) hernias are not usually treated unless they cause entrapment of the intestine

(intestine gets caught in the abdominal opening, which cuts off its blood supply) or are very large and are causing problems. Individuals with attenuated MPS I are less likely to have hernias because they are less likely to have an enlarged liver and spleen. If a hernia becomes red or purple, painful, hard, or you are unable to push it back into place gently with your fingers, it is considered a medical emergency and may require immediate treatment.

Inguinal (groin) hernias should be repaired surgically but may recur. Umbilical hernias are usually not treated unless they cause other, more serious problems.

Bowel problems

It is unclear why many individuals with MPS I periodically experience loose stools and diarrhea. Sometimes, the problem is caused by severe constipation and leakage of loose stools from behind the solid mass of feces. More often, however, it “comes straight through.” GAG buildup has been found in nerve cells of the intestine, which may cause a problem with the autonomic nervous system, the system that controls those bodily functions usually beyond voluntary control, resulting in abnormal bowel movements and diarrhea.

An examination by a physician, supplemented by an X-ray if necessary, may establish the cause of diarrhea. In children with MPS I, the problem may disappear as they get older. However, it can be made worse by antibiotics prescribed for other problems. If the diarrhea appears to be affected by the diet, it may help to eliminate those foods causing it.

If the diarrhea appears to be caused by antibiotics, eating plain live-culture yogurt may help, especially during episodes. This provides a source of lactobacillus (“friendly” bacteria in the bowel) to help prevent the growth of harmful organisms within the bowel wall, which can cause the diarrhea or make it worse. A diet low in roughage (fiber) may also be helpful. Please consult your doctor before starting live-culture yogurt or a diet low in roughage.

Constipation may become a problem as children with MPS I get older and less active and the muscles weaken. If an increase in roughage in the diet does not help or is not possible, the doctor may prescribe laxatives or a disposable enema. Depending on the type of laxative used, side effects may include bloating, gas, abdominal cramps, or diarrhea. Side effects of enemas include rectal irritation or damage.



BENNETT

Most individuals with MPS I experience bowel problems. Please consult a doctor knowledgeable in MPS diseases to determine the cause and receive the optimum treatment.

Dietary considerations

There is no scientific evidence that any particular diet is helpful for people with MPS I. Symptoms such as diarrhea tend to come and go naturally. However, some parents find that a change in their child's diet can ease problems such as excessive mucus, diarrhea, or hyperactivity. Reducing intake of milk, dairy products, and sugar, as well as avoiding foods with too many additives and coloring, have helped some individuals. Please consult your doctor or a dietician if you plan major dietary changes to make sure that

the proposed diet does not leave out any essential items. If the individual's problems are eased, foods can be reintroduced one at a time to test whether any particular item seems to increase symptoms. It is important to note that there is no diet that can prevent the storage of GAGs as these are naturally synthesized by the body as part of its normal functioning. So, reducing sugar intake or other dietary components cannot reduce GAG storage.

Although there is no evidence of specific diets being generally helpful for individuals with MPS I, eliminating certain foods may improve symptoms for some individuals. Diets cannot prevent storage of GAGs. Please consult your doctor and/or dietician knowledgeable in MPS diseases to determine optimum nutrition.

Musculoskeletal system (bones and joints)

People with MPS I tend to have significant problems with bone formation and growth. This leads to multiple abnormally shaped bones (called dysostosis multiplex) as well as neurological problems if nerves are squeezed by bone. Dysostosis multiplex occurs when bones do not form correctly at cartilage growth centers near the ends of the bones throughout the body.

Spine

The bones of the spine (vertebrae) normally line up from the neck to the buttocks. Individuals with more severe MPS I often have poorly formed vertebrae that may not stably interact with each other. One or two of the vertebrae in the middle of the back are sometimes slightly smaller than the rest and set back in line from the rest. This backward slippage of the vertebrae can cause an angular curve, called kyphosis (forward bend) or gibbus (bump in the lower back), to develop. Kyphosis occurs in about 90% of children with severe

MPS I. Gibbus (also called thoracolumbar kyphosis) develops from poor bone growth in the upper front part of the vertebrae. This causes a wedging of the vertebrae (bones are smaller in the front than in the back). In the past, spine surgery for gibbus was not performed on children with MPS I for fear that it would reduce the child's quality of life, especially when life expectancy was short. Now, with treatments like ERT and stem cell transplants being available, children with gibbus are considered for surgery to prevent it from getting worse.

Some individuals with MPS I may also have scoliosis (curving from side to side) of the spine, which can be treated with surgery, although this is less common. When not treated, scoliosis can progress to the point that individuals have difficulty expanding their chest wall for breathing. Occasionally, individuals may have both kyphosis and scoliosis ("kyphoscoliosis"), making surgical procedures more likely and more complicated. Bracing may slow the progression of both spinal

kyphosis and scoliosis, delaying – but not preventing – surgery. Bracing can be uncomfortable for individuals,

and young children rarely tolerate it. Consequently, bracing is usually not recommended for children.

90% of children with severe MPS I will have a forward bending of the spine (kyphosis). Individuals with MPS I may also have sideward bending of the spine (scoliosis). Bracing may slow progression of both kyphosis and scoliosis, but surgery may be needed eventually.

Conditions determining a need for surgery vary depending on the needs of the individual, especially children, and the desires of the family. Current experience suggests that, if possible, delaying spinal surgery until later ages allows the best growth of the spine and further development of already thin and brittle bone.

Surgery for scoliosis usually involves an incision from the back, while surgery for kyphosis almost always requires incisions from the front (through the flank or ribcage) and back. The procedure is called an instrumentation and fusion. The “fusion” is actually the placement of bone from the pelvis or ribs over the spine on the rear or between vertebrae on the front. The “instrumentation,” or metal hardware, is typically made of stainless steel or titanium, and provides temporary support to the spine until the fusion heals. Once placed, it is not usually removed unless there is a complication, such as an infection, caused by its presence.



SCOLIOSIS

Most individuals will require a combination of a cast and/or brace from 3 months to a year following surgery. When successful, the extra bone heals to form a strut or support between the vertebrae, which prevents the spine from curving further. Unsuccessful fusions (one where the bone strut does not form) can be painful and may require repeat surgery.

Spinal surgery comes with a number of risks, including the risks associated with anesthesia, infection, bleeding, blood clots, damage to the spinal cord, or death. In order to minimize spinal cord damage, many surgeons use intraoperative neurophysiological monitoring during the procedure. Various measurements of nerve activity must be monitored to be sure the brain and spinal cord remain functional.

Neck

In more severely affected individuals, the bones that stabilize the connection between head and neck are often malformed (odontoid dysplasia), making the neck unstable. This puts individuals with MPS I at risk for spinal cord compression (a condition where fluid



MYLES, KYPHOSIS

or tissues such as bones are pressing on the spinal cord). This can be treated by surgery to connect the bones to each other (fusion surgery), preventing them from slipping further. Some individuals with severe MPS I appear to have occasional pain in the back of the neck. Parents of children with MPS I should be cautious about how the area of the spine around the neck is handled. It is recommended that children with

MPS I should avoid “high-risk” activities such as contact sports and gymnastics. In addition, these children must be treated with caution when undergoing positioning for anesthesia. If there is severe pain or pain associated with weakness or tremors in the lower legs, the person should have studies of the neck to evaluate for slippage of the neck vertebrae.

The bones that stabilize the head and neck may be malformed (odontoid dysplasia), which can be treated by fusion surgery to prevent further damage. Children with MPS I should avoid high-risk activities such as contact sports and gymnastics.

Joints

Joint stiffness is common in individuals with MPS I, and the maximum range of movement of all joints may become limited. Later in the individual’s life, joint stiffness may cause pain, which may be relieved by warmth and pain medications. The limited movement

in the shoulders and arms may make dressing difficult. Anti-inflammatory drugs, such as ibuprofen, can help with joint pain, but their use should be monitored closely to make sure that irritation and ulcers in the stomach do not occur.

Joint stiffness and pain are common among individuals with MPS I making simple tasks, such as getting dressed, very difficult. Pain can be treated with anti-inflammatory drugs, but their use should be carefully monitored.

Hands

The shape of the hands of individuals with MPS I is very noticeable and has been used as the symbol of MPS societies. The hands are short and broad with stubby fingers. Over time, the fingers stiffen and gradually

become curved, due to limited joint movement caused by GAG buildup. The tips of the fingers can become permanently bent over, giving rise to the characteristic “claw hand.”

Hips

Like the spine, the hip joint suffers from altered bone formation. The hip is a ball-and-socket joint situated at either side of the pelvis. The “ball” is the head of the thigh bone (femur) and the “socket” is the cupped part of the pelvis (the acetabulum) that surrounds the ball. In abnormal formation of the hip (hip dysplasia), there is a shallow acetabulum, the head of the femur

is underdeveloped, and the top of the thigh bone at the neck of the femur is straightened (a condition called coxa valga). This combination of bone defects results in hip instability and sometimes dislocation. Hip dysplasia is found to some degree in nearly all children with severe MPS I, and can also be found in children with attenuated MPS I. Most children with hip dysplasia

eventually require corrective hip surgery. Surgery on the hips is done more easily at a younger age, around age 5 to 7, for the best results. Successful surgery (i.e., surgery that is able to correct the hip dysplasia) becomes much more difficult at older ages. If the hips have already dislocated, the surgery becomes technically very difficult, and the results are much less predictable. Hip surgery for dysplasia is a combination of precise bone cuts (osteotomies), which allow the surgeon to reposition the bones and optimize the working of the hip. Cuts are made in the pelvis and sometimes the femur. The surgery on the bones may be performed in conjunction with tightening the soft tissues around the hip. Without hip surgery, there is progressive pain and stiffness and eventually dislocation of the hips,



NIKKOLAS

resulting in a greatly decreased ability to walk. Thus far, the results of hip surgery in some individuals with MPS I have been promising. Hip surgery carries a number of risks, including the risks associated with anesthesia, infection, bleeding, or blood clots.

Hip dysplasia is common among individuals with MPS I and can be corrected with surgery, which is best done at an early age.

Legs and feet

The feet of individuals with MPS I are broad and may be stiff with the toes curled under, similar to the fingers of the hands. In younger children, parents should check the skin around the toes and feet as it is a common area for blisters and skin infections. Wearing appropriately fitted (usually widely sized) shoes and engaging in routine cleaning and skin care around the toes can help to prevent and treat irritations. Many individuals with MPS I stand and walk with their knees and hips flexed. This, combined with a tight Achilles tendon, may cause them to walk on their toes. Some children with MPS I have genu valgum or “knock-knees” (a condition in which the knees are bent in so much they touch each other when walking) severe

enough to require surgery. During this surgery, staples are placed in the bone on the inner side of the knee through a relatively small incision. These staples prevent bone growth on the inner side of the knee, allowing the outer side to catch up. As a result, the knees straighten over time, and usually the staples are removed with a second surgery. Occasionally, the staples can dislodge, requiring them to be removed and, if necessary, new ones are inserted to replace them. For children too small for staples to be used, bone cuts (osteotomies) in the large bones around the knee may be required. Although osteotomies are more invasive and painful, experience has shown that the children heal well.

Many individuals with MPS I stand and walk with their knees and hips flexed. Knock-knees in children can be treated with corrective surgery to allow knees to straighten over time.

Physical and occupational therapy

The joint stiffness and bone malformations caused by MPS I can make it hard to walk, dress, wash hair, tie shoes, and do other activities. Physical therapy may help relieve symptoms and improve the person's ability to function. Occupational therapy teaches affected individuals how to adapt to their unique daily environment. Range-of-motion exercises (passive stretching and bending of the arms and legs) may offer some benefits in preserving joint function. Exercises that cause pain should be avoided. Once joints become

significantly stiff, it may not be possible to increase the range of motion (flexibility) in the joints. However, it may still be possible to limit further losses of flexibility. It makes sense for individuals to be as active as possible to maintain joint function and improve their general health. The doctor or physical therapist may be able to suggest ways of achieving this through a combination of daily activities and passive range-of-motion exercises.

The many problems with bones and joints make it difficult for individuals with MPS I to perform daily activities and work. Physical therapy should be considered to help alleviate physical symptoms, improve joint motion, and the individual's ability to function. Occupational therapy can help individuals adapt to school, home, and the work environment.

Brain and central nervous system

GAG storage in the nerve cells (neurons) in the brain can adversely affect brain function, the extent of which depends on the severity of disease. Thus, there is a spectrum of effects with those with severe MPS I exhibiting many, including developmental delays, whereas individuals with attenuated disease may experience only a few, if any. The problems with various organ systems discussed above that are experienced by individuals with MPS I can also contribute to poor brain function, including low oxygen levels, lack of sleep (sleep deprivation) due to sleep apnea, increased fluid pressure in and around the brain (hydrocephalus), and effects on the eyes and ears that affect the ability of the individual to see and hear normally.

Cognitive function

It is important to remember that MPS I is a spectrum of disease conditions and that problems with mental function (cognition) vary with disease severity. Some individuals

may exhibit milder learning disabilities, while others may have more severe cognitive (mental) function. Early access to treatment for MPS I may lead to some stability in cognitive function.

Those with severe MPS I (Hurler syndrome) experience a slowing of mental development by 1 to 3 years of age, followed by a progressive loss of skills (i.e., the child's mental development and skills gradually become less advanced over time) for the rest of their lives. This is further exacerbated by other medical problems that can reduce their learning and performance abilities, including chronic ear infections, poor vision, poor hearing, communicating hydrocephalus (sometimes called "water on the brain"), and sleep apnea (the temporary stoppage of breathing while sleeping). Treating these medical problems can improve the function of severely affected individuals. Also, there is great variation in the severity of the condition, with some children being able to learn



HENRIQUE

only a few words, while others may learn to read a little. Usually, they enjoy nursery rhymes and simple puzzles. It is important to help those with severe MPS I learn as much as possible before the disorder progresses. Even when the child starts to lose the skills he/she has learned, there may still be some prior learned abilities left. Children will continue to understand and to find enjoyment in life even if they lose the ability to speak. Thorough medical checkups should be performed for individuals whose development is significantly affected to ensure that damage to cognitive abilities is minimized. With early treatment, much of the cognitive function may be maintained.

Individuals who are moderately affected (Hurler-Scheie syndrome) may have moderate learning difficulties, but some can have normal cognitive function. Like those with more severe disease (Hurler syndrome), these individuals also can experience the effects of the other medical problems that hinder their learning and communication. There are some reports of mental health concerns and memory loss in individuals with Hurler-Scheie syndrome.

Those with attenuated MPS I (Scheie syndrome) usually have normal cognitive function, although there have been some reports of mental health issues in this group. It is reported that one of Dr. Scheie's patients tested at near-genius level. Memory loss is a symptom reported by some adults with attenuated MPS I as they age.

The effects of MPS I on the brain and nervous system may cause problems with learning and self-care for some individuals. Individuals with MPS I may need special learning programs and caregivers to help them with their daily activities.

Individuals with MPS I can exhibit a spectrum of cognitive dysfunction from mild, almost normal mental health among those with attenuated disease to significant loss of learning and mental skills among those with severe disease. Individuals with MPS I may need special learning programs and caregivers to help them with their daily activities.

Hydrocephalus

MPS I can cause hydrocephalus, a condition where fluid accumulates in the brain, causing a pressure buildup that can lead to brain damage. Hydrocephalus was once known as “water on the brain.” The “water” is actually cerebrospinal fluid (CSF), a clear fluid surrounding the brain and spinal cord. The CSF protects the brain and spinal cord from injury by providing a liquid cushion and is continually being

produced, circulated, and absorbed. Communicating hydrocephalus (also known as “non-obstructive hydrocephalus”) is caused when the CSF is not absorbed properly. This causes the CSF to build up, leading to an abnormal enlargement of the spaces in the brain called ventricles. This causes potentially harmful pressure on the tissues of the brain.

Hydrocephalus is more common in individuals with severe neurological (brain and nerve) symptoms. Early detection and treatment of hydrocephalus is believed to improve quality of life. However, neurosurgeons are often unfamiliar with the unique aspects of diagnosing communicating hydrocephalus in MPS I, creating a frustrating situation for parents and caregivers.

Effects of hydrocephalus: In infants, the most obvious sign of hydrocephalus is often a rapid increase in head circumference or an unusually large head size. In older children and adults, typical symptoms may include a headache followed by vomiting, nausea, blurred or double vision, downward deviation of the eyes (called “sunsetting”), problems with balance, poor coordination, abnormal walking patterns, urinary incontinence (difficulty holding urine), slowing or loss of development, lethargy, drowsiness, irritability, memory loss, or other changes in personality or thinking. If hydrocephalus develops slowly, these typical signs and symptoms may not be seen.

Diagnosing hydrocephalus: Hydrocephalus is diagnosed through clinical neurological evaluation (where the doctor checks the individual’s brain and nerve function); by using imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI); and through techniques to measure pressure, such as lumbar puncture (spinal tap).



CHARLIE RAE

It is recommended that individuals with MPS I have a “baseline” head scan (CT or MRI) at the time of diagnosis with regular follow-up scans (as frequently as the doctor recommends). Measuring intracranial pressure (pressure inside the brain) allows the doctor to diagnose hydrocephalus. Intracranial pressure is measured in millimeters of mercury (mm Hg), and once the pressure is over 180 to 200 mm Hg, it is considered to be high. Once the fluid buildup is too severe, the doctor may recommend a shunt (see below). Medications to reduce pressure may be attempted prior to surgical placement of a shunt. With these medications, electrolyte levels should be monitored.

An alternate method of measuring intracranial pressure is by CSF opening pressure, also called opening pressure at lumbar puncture. A high measure can be an indication of increased intracranial pressure. A normal measurement is often considered less than 25 to 28 cm H₂O (sometimes also written as 250–280 mm H₂O); however, there are some doctors who report up to 29 cm H₂O as normal in certain children.

Lumbar puncture is often necessary for the diagnosis of hydrocephalus, as CT and MRI often do not demonstrate ventricular enlargement for individuals with MPS. Additionally, if elevated pressure on the optic nerve (papilledema), is noticed during eye examinations, assessment should quickly be made for signs of increased intracranial pressure to prevent blindness. Blindness has been reported in cases of delayed diagnosis.

Use of shunts: Hydrocephalus is most often treated with the surgical placement of a shunt. A shunt is a flexible plastic tube (cannula) that diverts the flow of CSF from the brain to another area of the body where it can be absorbed as part of the circulatory process. If a shunt is placed, specialists recommend a high-pressure shunt to prevent rapid decompression (reduction of fluid in the ventricles of the brain). Shunts must be inserted surgically. Before surgery, doctors should check for signs of blockage in the form of spinal cord compression, which is described below.

Spinal cord compression

Usually, the length of the spinal cord is surrounded by a system of tissue, ligaments, and bones that are intended to protect it from damage when there is movement. In individuals with MPS I, GAG accumulation over time causes these tissues and ligaments to gradually become thicker and start pressing against the spinal cord. This results in a condition called spinal cord compression, particularly in the neck (cervical) region of the spinal column. This condition can be quite common in older individuals with MPS I. As a result of this compression, individuals may experience a range of symptoms including neck pain, weakness or numbness in the limbs, poor balance, and dizziness. The compression may also obstruct

the proper flow of the CSF around the brain and spinal column, which can contribute to hydrocephalus (described earlier). Doctors usually can detect spinal cord compression with X-ray or MRI evaluation. The main method used to relieve this condition is a surgical procedure called a laminectomy. In this procedure, the joints that surround the spinal cord may be trimmed and/or some of the cervical vertebrae (bones surrounding the spinal cord) are removed or adjusted to make more room for the spinal column and ease the compression. Surgery should only be undertaken with an anesthesiologist and surgical team knowledgeable in the complexities associated with MPS I.

Individuals with MPS I, especially those with severe disease, can have hydrocephalus (water on the brain). Hydrocephalus is diagnosed through a clinical neurological evaluation and, when severe, is treated with a shunt. Individuals should be tested for spinal cord compression via X-ray or MRI, prior to surgical implantation of a shunt.

Carpal tunnel syndrome

Individuals with MPS I sometimes experience pain and loss of feeling in the fingertips as a result of carpal tunnel syndrome. The wrist, or carpus, consists of eight small bones known as the carpals, which are joined by bands called ligaments. A nerve called the median nerve passes through the space between the carpal bones and the ligaments in the wrists. Thickening of the ligament called the “transverse carpal ligament” causes pressure on the median nerve, and this can cause permanent nerve damage. The nerve damage will cause the muscle at the base of the thumb to waste away and will make it hard for the individual with MPS I to use his/her thumb for grasping objects. Although an individual with MPS I may not experience pain, carpal tunnel syndrome may be severe.

If an individual with MPS I has pain in his/her hands, particularly at night, he/she may wish to have an electrical test called a nerve conduction or electromyography study performed. This test will show whether carpal tunnel syndrome is the cause. If there is any weakness at all in the hand or there are problems grasping objects, a test by the neurologist may be needed. Be persistent, as many doctors may not believe that carpal tunnel syndrome is present without the usual symptoms.

Carpal tunnel syndrome is often not diagnosed early enough in young children with MPS I. Some families may notice children running their hands under water of extreme temperatures (especially hot water) or biting

their hands. If parents notice that the skin on their child's hands doesn't prune or wrinkle in warm water, this can also be a sign of carpal tunnel syndrome.

Most individuals affected by MPS I do not have the classic symptoms of carpal tunnel syndrome, even with severe nerve entrapment and damage. In some cases, surgery, called "carpal tunnel release," may be used to cut the transverse carpal ligament and relieve the pressure on the median nerve. As with any surgical procedure for an individual with MPS I, it is important

to meet with the anesthesiologist prior to the surgery. As excess GAGs are a continual problem for individuals with MPS I, it is possible that GAGs might build up again after surgery.

Individuals with MPS I may also experience tarsal tunnel syndrome, which is essentially the equivalent disorder in the ankles. In severe cases, surgery called "tarsal tunnel release" may be considered.

Individuals with MPS I, especially those with severe disease, can have carpal tunnel syndrome even without the classic symptoms. Be persistent with the doctor to ensure that it is diagnosed properly. If the syndrome is present, surgery to relieve the pressure on the median nerve may be needed.

At what age are people usually diagnosed with MPS I?

This varies among individuals depending on the severity of the disease. In general, individuals with severe MPS I (Hurler syndrome) tend to have early diagnoses at an average of 9 months of age, while individuals with other forms of MPS I tend to have diagnoses later at an average of 9 years of age. Individuals with intermediate disease (Hurler-Scheie syndrome) receive diagnoses at an average of 6.5 years of age, and individuals with attenuated disease (Scheie syndrome) receive diagnoses at an average of 13.5 years of age.

Recently, there has been an increase in diagnosis in adults 30 years and older due to the availability of DNA testing.

Early diagnosis of MPS I is critical. The earlier that MPS I is diagnosed, the sooner potential treatment options can be explored and supportive care may be started. This can help you or your loved one potentially prevent some of the permanent damage that may be caused by the disease.

Early diagnosis of MPS I is critical and allows earlier intervention.

Newborn screening

Newborn screening is the testing of newborn babies to see whether they have specific genetic disorders. The goal is to help with early diagnosis and treatment. Each state makes its own decisions about which health conditions should be included in their newborn

screening programs. MPS I is now included on the RUSP (recommended uniform screening panel) in the US. Currently, 21 states have universal screening for MPS I, and 10 more states are working toward including MPS I in their newborn screening.

Currently, there is a growing movement promoting newborn screening for MPS disorders such as MPS I. It is now widely recognized that for many families, information about the diagnosis alone is helpful with the opportunity for genetic counseling, education about various and new treatment options, and improved quality of care with early medical help and therapy services.

Research into newborn screening for LSDs is still in early stages. Important questions remain about the screening process and the testing methods. There will likely continue to be debate over the appropriateness of screening. As a community, those whose lives have been touched by MPS I will likely continue to become more involved in the promotion of newborn screening.

Prenatal diagnosis

If you have a child with MPS I, it is possible to have tests during a subsequent pregnancy to find out whether the baby you are carrying is affected. It is important to consult your doctor early in the pregnancy if you wish to perform these tests. The decision to have prenatal testing is complex and personal. Talking with

your genetic counselor or doctor can help you explore these options and other strategies, such as egg or sperm donation, for having additional children while limiting the probability they will have or be carriers for MPS I.

Newborn screening and prenatal diagnosis for MPS I will help with early diagnosis in the future. Research is still being completed to measure the impact of newborn screening. Today, not all states are screening for MPS I, though it is federally mandated. Please check with your doctor for the options in your community.



FAMILY CONFERENCE, MINNEAPOLIS, MN

Living with MPS I

Living with MPS I or with an individual with MPS I can vary significantly depending on the severity of the disease. Individuals with severe MPS I (Hurler syndrome) may not be able to live independently,

whereas individuals with attenuated MPS I (Scheie syndrome) may be able to lead an almost normal life. Those with intermediate disease (Hurler-Scheie syndrome) fall between those two bookends.

Severe MPS I (Hurler syndrome)

Children with severe MPS I will vary considerably depending on which treatments they have received or are receiving, especially if they have had HSCT. Children with severe MPS I are usually happy, friendly, and mix well with others at school. They are much

loved by all who know them, and many are very easy to manage and to please. They are cheerful, with an infectious laugh. Crying as the child gets older may be linked to frustration at being unable to communicate.

Pain

It is very difficult to differentiate between pain and frustration when individuals, especially children, cannot express themselves due to disability caused by the severity of the disease. Individuals, especially children,

may have ear infections, a toothache, or aches and pains in their joints, or feel discomfort from a full stomach. Do not hesitate to ask your doctor to check whether or not there is a physical reason for the individual's distress.

Education

Individuals, especially children, with severe MPS I may benefit from having a mainstreamed education and enjoy the social interaction with peers. It is important to work with your school system and develop the best

Individualized Education Program for your child. For more information on education, see the booklet titled *A Guide for Parents: Education Strategies and Resources*, published by the National MPS Society.

Some, but not all, children with severe MPS I may benefit from attending mainstream school, but they need a multitude of resources from the school system, especially teachers.

Home adaptations

Individuals, especially children, with severe MPS I will become progressively less mobile and more dependent on their parents and/or caregivers to meet their everyday needs. The booklet *Daily Living with*

MPS and Related Diseases, published by the National MPS Society has many helpful suggestions for making adaptations in the home.

Taking a break

Caring for an individual or child with MPS is hard work. Parents and caregivers need a break to rest and enjoy activities, which may not be possible when their affected child or ward is with them. Siblings and others also need their share of attention and need to be taken

on outings that may not be feasible with an affected individual or child. Many parents and caregivers use some form of respite care or have someone come in regularly to help at busy times.

Palliative care

Palliative care is any form of medical care or treatment that concentrates on providing relief from symptoms due to the disease. The goals are to prevent suffering and to improve quality of life as best as possible for individuals facing serious, complex illnesses. This support encompasses aspects such as respite care, symptom management, and bereavement support. Palliative care may be short-term or extended, depending on the status of the patient.

is receiving hospice care, treatments intended to cure the disease are stopped, and only comfort measures are provided. For adults, hospice care is usually offered when the individual is expected to have fewer than 6 months to live. For children, hospice care may be offered as early as the diagnosis is made. This varies significantly between regions, states, and insurance providers. Often the differentiation between palliative and hospice care is one made by insurance companies as hospice may provide different billing for medical care and supplies.

Palliative care can be provided at any time it is needed by an individual with MPS I. Curative and preventative treatments continue as normal. This is in contrast to hospice care, which is also palliative, but is intended specifically to be end-of-life care. When an individual

With both palliative and hospice care, an assessment of medical need and a care plan can lead to support provided to the individual and family so that all can experience a better quality of life.

Attenuated MPS I

Education

The majority of children and older individuals with attenuated MPS I will attend mainstream school/university and achieve academically. In order for the individual to reach full academic potential, it is important to ensure the academic institution and associated personnel are aware of required resources. This may include a one-on-one classroom assistant, appropriate classroom furniture, and access to an individual

computer. Determination of modifications and correct supports will take place through meetings with the educational institution.

It may be helpful to have a Section 504 Plan in place in a school setting which allows for some modifications and supports as needed for those where an Individualized Education Program is not necessary.

The majority of individuals with attenuated MPS I will attend mainstream school and achieve academically.

Independence

Individuals with MPS I should be encouraged to be as independent as possible to lead full and enjoyable lives. The teenage years may be difficult if they have restrictions imposed by their disease. This may be helped by meeting or contacting other teenagers and adults who also have MPS I.

The Adult Resource Committee (ARC) exists to provide support for adults diagnosed with MPS and ML. Contact the ARC at arc@mpssociety.org for more information. Individuals with short stature may find additional support and helpful information through Little People of America, www.lpaonline.org.

Employment

The physical disabilities of those with MPS I should not prevent them from accessing meaningful employment. The Americans with Disabilities Act helps both employees and employers. Individuals with MPS I

Adaptations

Appropriately adapted living accommodations will greatly enhance the ability of an individual with MPS I to develop independent living skills. Where stature is severely restricted, kitchen and bathroom facilities set at a lower height will be required. If mobility is restricted to such an extent that a wheelchair is used, plans for any

Puberty

Adolescents with attenuated MPS I will go through the normal stages of puberty and are able to have children. Children born to a parent with MPS I are automatically carriers and can only be affected with the disease if the

Reproduction

Individuals with MPS I are fertile. Fertility studies in humans with any MPS type are rare. Spermatogenesis may be reduced among males with MPS I.



ADELE AND SAVANNAH

may find it helpful to contact their local Vocational Rehabilitation office, available in every state, (usually with multiple offices in each state) to provide information about and access to employment.

home adaptations will need to allow adequate space to accommodate this. Additional information about home adaptations can be found in the booklet titled *Daily Living with MPS and Related Diseases*, published by the National MPS Society.

other parent is a carrier of MPS I or has MPS I. Due to the physical effects of the disease, expectant mothers with MPS I must be closely monitored and will likely deliver via a Cesarean section.

Individuals with MPS I who have received allogeneic (from a donor with a different genetic background) HSCT often experience an adverse impact on fertility

due to the chemotherapy and radiotherapy associated with HSCT. Some hospitals, however, are now allowing families options to maintain fertility (through egg harvest or other methods) prior to transplant. Irradiation can also have adverse effects on the uterus including poor implantation, and poor fetal growth. Premature termination or birth may occur. Women whose stature is significantly restricted may be advised not to become pregnant because of risks to their health.

It is important to remember that all children born to a parent with MPS I are automatically carriers, but none will have the disease unless the other parent also is a carrier or has MPS I too. It is advisable for individuals with MPS I to take the following points into account when considering having a child:

- Preconception genetic counseling
- Preconception medical evaluation
- Preconception discussion of risks during pregnancy and delivery, e.g., high probability of a Cesarean delivery
- Health risks during pregnancy, e.g., difficulty with respiration due to the uterus pushing up, fluid overload, and cardiopulmonary complications
- Health risks during delivery, e.g., premature delivery due to skeletal limitations, anatomical differences making diagnosis of delivery process difficult, and problems with administering and managing anesthesia
- Newborns with skeletal problems will need immediate specialized medical care

All children born to a parent with MPS I are automatically carriers, but the disease cannot become dominant unless the other parent is also a carrier of MPS I, and then a child has only a 25% chance of inheriting the disease. There are considerable risks associated with pregnancy for individuals with MPS I. Please consult your doctor when making these reproductive decisions.

Healthcare information

Assistance may be available from specialized agencies for individuals with disabilities and from genetics clinics. Explore Social Services, Social Security, Medicaid Waivers, and the Katie Beckett Law. Investigate these options and others that may be available for you on federal, state, and local levels. In most states, it is beneficial to start with the Department of Social Services or Department of Health and Human Services for additional information. If you already have Medicaid, calling the phone number on the card will help to get

you connected with a social worker or case manager who will serve as a “point person” to help you get set up with things for which you qualify. If you do not have Medicaid or an established social worker, you can ask to speak with one through your healthcare provider. Many physicians have access to social workers, as do most hospitals. Your social worker should be able to locate additional information and/or resources for your family.

Assistance may be available from specialized agencies for individuals with disabilities and from genetic clinics.

General Management of MPS I

The primary goals of treatment and management of MPS I are to improve quality of life, slow disease progression, and prevent permanent tissue and organ damage. At present, there is no cure for MPS I. Early diagnosis and intervention may prevent irreversible damage in some individuals. Treatment options for MPS I comprise those aimed at disease management (including treating underlying enzyme deficiency), and

supportive or palliative care (care that focuses on comfort for an individual with an incurable disease). This section only briefly describes some management and treatment options. However, the decision of which interventions and treatments are best for the individual is an important and complex one that cannot be summarized here. These are best discussed with medical professionals with expertise in treating MPS I.

Importance of multidisciplinary care

As described earlier in this resource, individuals with MPS I usually have a wide range of signs and symptoms. As a result, they often need to be managed by many different medical specialists, including cardiologists, neurologists, pulmonologists, otolaryngologists, ophthalmologists, orthopedic surgeons, physical therapists, speech therapists, and occupational therapists. All healthcare professionals involved in the care of an MPS I patient should have a basic understanding of the disease and how the condition may affect treatment decisions.

Dealing with so many specialists can be overwhelming for individuals with MPS I and their caregivers. It can be very helpful to have a single physician with experience in MPS I, either as a primary care physician (who might be a pediatrician) or a geneticist, who will take responsibility for overseeing the overall care across medical specialties and keep track of the “big picture.” This physician can then refer the individual to other specialists as needed and help make sure they are receiving the best possible care. This physician might also become the main contact for coordinating disease and treatment-related information to the MPS I Registry.

A multidisciplinary approach to treatment and management coordinated by a single healthcare professional experienced in MPS I is recommended.

Diet

There is no scientific evidence that any symptoms of MPS I can be managed with a particular diet. Digestive system problems, such as diarrhea, tend to come and go naturally. Some individuals and parents, however, find that a change in the individual’s diet can ease problems, such as excessive mucus, diarrhea, or

hyperactivity. Reducing intake of milk, dairy products, and sugar, as well as avoiding foods with too many additives and coloring, have helped some individuals. It would be advisable to consult your doctor or a dietician if you plan major dietary changes to make sure the proposed diet does not leave out essential nutrients.

If your problems or the child's problems are eased, you could try reintroducing foods one at a time to test whether any particular item seems to increase their symptoms.

It is important to remember that GAGs are synthesized by cells as part of their natural process. This is not a disease caused by overproduction of GAGs, but rather by the inability to properly break them down. As such, there is no diet that can prevent GAG accumulation.

Please note: Consuming sugar or foods normally eaten will not affect the buildup of GAGs in the body.



MAKENZIE

There is no scientific evidence that diet has an effect on disease. However, it may help with symptom management for some individuals. Please consult your doctor or dietician when making dietary decisions.

Feeding tubes

Individuals with severe MPS I may have problems chewing and swallowing. If so, they are at risk for poor nutrition, choking, and aspiration (inhaling food or other substances into the lungs), which can lead to respiratory infections and pneumonia. During these episodes, the individual may need increasingly more time to be fed and may lose weight. One option to ensure such individuals receive the nutrition they need and prevent choking or aspiration is to use feeding tubes (also called “enteral nutrition”). These may also make it easier for a caregiver to feed the individual with MPS I. However, the decision to use feeding tubes is often a difficult one for family members and caregivers.

A flexible feeding tube is inserted that bypasses the mouth and throat and goes directly into the stomach or intestine. Nasogastric tubes are inserted through the nose and are usually a temporary measure lasting days to weeks. Longer-term feeding issues require surgical placement of a gastric (G)-tube, which is inserted into the stomach, or jejunal (J)-tube, which is inserted into the small intestine.

Because of special concerns regarding anesthesia in patients with MPS I, you or your doctor should consult with an anesthesiologist before surgery is done to insert the tube.

Feeding tubes may be an option if the individual with MPS I can no longer chew or swallow. These need to be inserted with care and training. Long-term feeding tubes require surgery. Please consult your doctor and anesthesiologist to ensure that feeding tubes are inserted and used correctly.

Physical therapy

Joint stiffness is a common feature of MPS I. Limitation of motion and joint stiffness can cause significant loss of abilities. Range-of-motion exercises (passive stretching and bending of the limbs) may offer some benefits in preserving joint function and should be started early. Exercises that cause pain should be avoided. Once significant limitation has occurred, increased range-of-motion may not be achieved, although further limitation

may be minimized. Individuals with MPS I should be as active as possible to maintain joint function and improve their general health. However, competitive or contact sports should be avoided. The doctor or physical therapist may be able to suggest ways of achieving this through a combination of daily activities and passive range-of-motion exercises.

Individuals with MPS I should be as active as possible to maintain joint function and improve general health. However, competitive or contact sports should be avoided. Please consult the doctor or physical therapist for ways of achieving this.

Occupational therapy

While physical therapy targets gross motor or “large” movements of the body (such as walking), occupational therapy focuses on fine motor movements and targets activities of daily living. It is important to consider occupational therapy following surgery or if there are difficulties with dressing, toileting, transitioning,

and other motions that involve the use of the hands. Occupational therapy may be helpful for young children with MPS I as well as their families to learn strategies for making adaptations early on, so that these become more natural.

Pain management

Pain management is an important topic for individuals with MPS I since many complications of the disease cause pain. Joint stiffness and pain, chronic headaches from increased intracranial pressure, hand or wrist pain from carpal tunnel syndrome, hip or back pain from abnormally shaped bones, mouth sores from dental cysts, and abdominal pain are just a few examples.

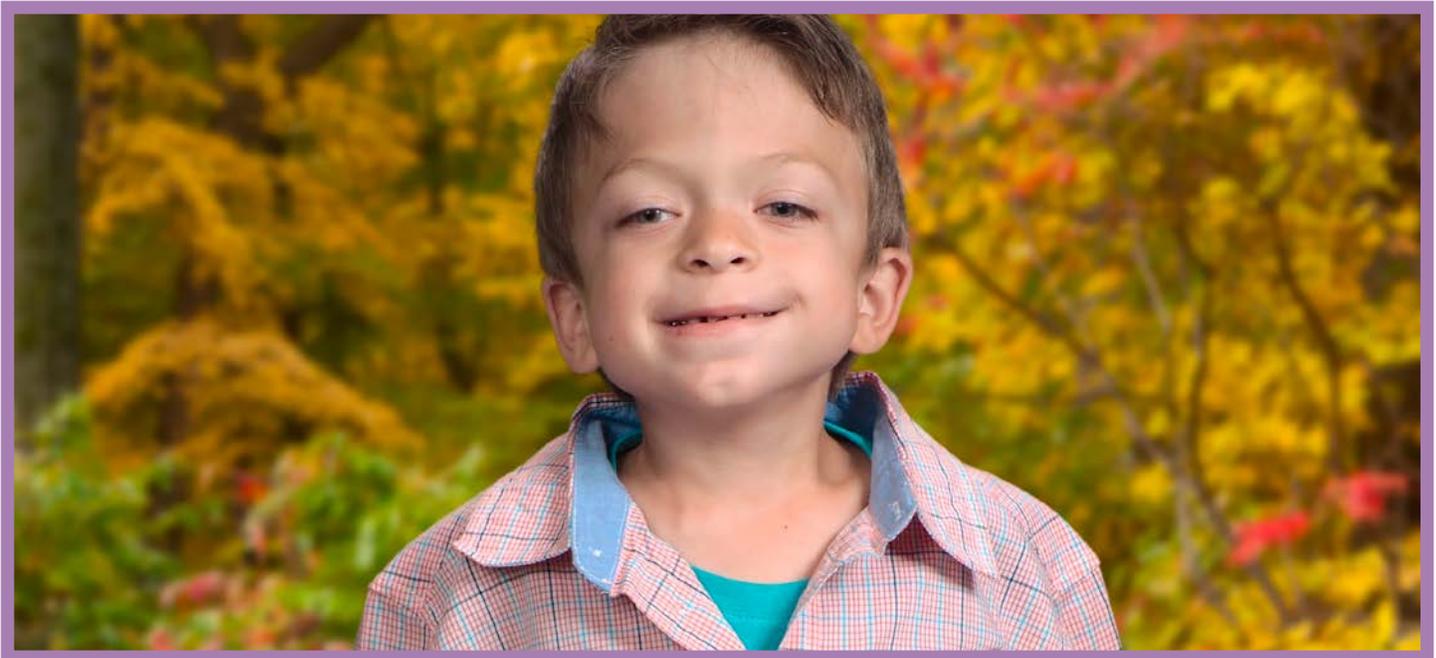
Many of the options to treat and/or manage the various symptoms have been discussed earlier in this resource, e.g., surgery to correct musculoskeletal issues, shunts to relieve hydrocephalus, and physical therapy. In addition to addressing the symptoms,

these procedures also help decrease and better manage the pain caused by the symptoms. In addition, pharmaceutical options, which include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen and naproxen), or narcotic pain relievers (such as codeine or morphine), can be prescribed for short-term quick relief. When pain is accompanied by muscle spasms, the doctor may recommend the addition of a muscle relaxant (such as methocarbamol, baclofen, or tizanidine). Special consideration should be taken with all pain medications to ensure they do not cause respiratory depression, causing difficulty in breathing.

The doctor can help you find an appropriate pain medication. Some people may need more than one pain medication to control their pain. If you are not getting the pain relief you need, speak to your doctor.

If you have trouble swallowing, some pain medications are available in liquid or patch form. Ask your doctor for more information on which pain control options are best for you or your child.

Managing pain is one of the primary issues for individuals with MPS I. Many of the treatments for specific symptoms also help with pain relief. Please consult your doctor for any additional medications needed to help alleviate the pain.



BRYSON

CPAP and BiPAP

Sleep apnea can be improved in some individuals with MPS I by opening the airway using CPAP or BiPAP machines during sleep. These machines distribute oxygen to a patient if needed, using a mask covering the face or nose. Both CPAP and BiPAP are noninvasive (no surgery, breaking the skin, or inserting a device into a body cavity). Both require the individual to wear a mask covering the nose, and sometimes the mouth, when sleeping. These may be used at times for some individuals when they are awake for additional respiratory support. Both types

of support can improve breathing using pressurized air. While both CPAP and BiPAP are very effective in managing sleep apnea, they do not treat the underlying problem of GAG accumulation. Occasionally, CPAP can increase the work involved in natural breathing. In these cases, it may be advisable to switch to a BiPAP machine. Individuals will need to get acclimated to using these devices. In cases where CPAP or BiPAP are not effective or are not appropriate, a tracheostomy (a surgical procedure to insert a breathing tube in the throat) may be used.

CPAP and BiPAP are noninvasive options usually sufficient to address sleep apnea, although they do not address the underlying GAG accumulation.



TALON

Tracheostomy

A tracheostomy (tray-kee-ossta-mee; also called an artificial airway or “trach,” pronounced “trake”) is a surgically created opening through the neck into the trachea (or the windpipe). A tube is usually placed through the opening into the trachea. This tube is referred to as a tracheostomy tube or a “trach” tube. The function of the tube is to open an airway and to remove secretions from the lungs. A tracheostomy is usually performed under general anesthesia (see below). After the area is cleaned, incisions are made to expose the outer wall of the trachea, which is made up of tough cartilage rings. A surgeon inserts the tracheostomy tube into the trachea after creating an opening through the cartilage rings.

It is important to discuss trach care in detail with the doctors. The surgical incision needs to be cleaned

frequently as it heals, perhaps as many as four to five times per day. Once the skin heals, it should be kept clean and dry. Most people use soap and water to clean the skin. Some people use a small amount of water-soluble antibiotic ointment around the skin incision. Mucus secretions or blood can block the tracheostomy tube and interfere with breathing. The tube may be blocked if you notice bubbles in the trach tube, if you hear loud gurgles coming from the trach tube, or if the individual with the tube seems to be having difficulty breathing (for babies, the signs may include agitation, flared nostrils, increased heart rate, or pale or blue-colored skin). If this occurs, the tube should be suctioned.

From time to time, the tracheostomy tube will need to be changed. Changing an old tube for a new, fresh tube

can be challenging but often becomes easier with time. Shortly after surgery, if the entry site has not healed properly, it may cave in and block the trachea when the tube is removed. There is also a risk of the new tube being inserted incorrectly. As the wound heals, the chance that either situation will occur will decrease.

One of the biggest challenges that people face following the insertion of the trach tube is adjusting to new breathing patterns and changes to the vocal cords. Communication is perhaps the biggest adjustment because it may be difficult for the individual to talk or make sounds. However, with proper training, many individuals can learn to speak with a tracheostomy tube.

Water-related activities can be hazardous to the person with a trach because there is not an easy way to hold their breath underwater, and water could enter their lungs. Special care needs to be taken during bathing to shield the tracheostomy tube opening from the water. A person with a trach may also benefit from using a cotton cover or scarf to protect from inhaling dust and other particles.

With proper planning, discussion with doctors, and after-surgery care, a tracheostomy may significantly help individuals with MPS I whose upper airway is blocked.



FAITH

A tracheostomy is generally a routine procedure, but as with any other surgical procedure, there are risks. With the anesthesia, there is a risk of adverse reactions to medications and problems with breathing. Because people with MPS I are at a higher risk for problems with anesthesia, the tracheostomy should be done in a hospital that is fully equipped to deal with these issues. Make sure that the anesthesiologist for the procedure has experience with MPS I.

Tracheostomy is an option to help with breathing when other methods have failed. It must be done in a hospital under anesthesia and the care of a surgeon who is knowledgeable in treating MPS.

Tracheostomies require a lifelong and specialized care of the tubes. This gets easier over time.

Anesthetics

Giving an anesthetic to an individual with MPS I requires skill and should always be undertaken by an experienced anesthetist. Inform your child's school or any other caregivers of this in case you cannot be contacted in the event of an emergency. If you must go to a different hospital in an emergency, be sure to tell the anesthetist there might be problems with intubation (placement of the breathing tube). The airway can be very small and may require a very small endotracheal tube. Placing the tube may be difficult and require the use of advanced intubation techniques, such as a flexible bronchoscope, laryngeal mask airway, or fiber optics.

In addition, the neck may be somewhat lax, and repositioning the neck during anesthesia or intubation

could cause injury to the spinal cord. For some individuals, it is difficult to remove the breathing tube after surgery is completed due to excessive swelling. It is important to advise physicians of the critical nature of these problems. Many problems, some fatal, have occurred during anesthesia of individuals with MPS.

For any elective surgery in a child with MPS, it is important to choose a pediatric anesthesiologist who has experience with difficult airways. This may require that the surgery be performed at a regional medical center instead of a local hospital. See additional information on anesthesia in the booklet titled *Is Your Child Having an Anesthetic?*, published by the National MPS Society.

Giving an anesthetic to an individual with MPS I requires advanced skill and should always be undertaken by an anesthetist experienced with difficult airways.

Research for the future

The mission of the National MPS Society is to find cures for MPS and mucopolipidosis (ML). As part of that mission, the Society funds research grants. The Society recognizes the need for targeted research for treatment of bone and joint problems and for treating the brain,

and Society research funding has focused on those areas. Information about Society-funded research and promising new areas of research can be obtained by contacting the Society's office.

This booklet is intended as an introduction into the nature of MPS I as well as to help individuals and families understand more about what is happening to those living with MPS I and what they can do to manage it. This booklet was updated by the National MPS Society in 2020.



Updates

Medical professionals and researchers are constantly learning new things about MPS I and treatments. Some of the information provided in this booklet may change over time. To keep up to date on the latest information on MPS I and its management, visit www.mpssociety.org.

We have reserved the space below to call out new developments or updates we think deserve your attention.

Update: Date: Link to more information:	

Benefits of the National MPS Society

Common bonds unite the lives of those affected by MPS and ML—the need for support and the hope for a cure.

The National MPS Society is committed to making a difference in the lives of MPS families through support, research, education, and advocacy. Families from around the world gain a better understanding of these rare genetic diseases through the Society's assistance in linking them with healthcare professionals, researchers, and, perhaps most importantly, each other.

The Adult Resource Committee (ARC) exists to provide support for adults diagnosed with MPS and ML. Contact the ARC at arc@mpssociety.org with any questions or for more information.

Individuals affected with an MPS or ML disorder and their families have a resource. One that stands ready to help—a resource that helps you take an active role in fostering the courage necessary to confront these diseases every day.

Benefits of membership in the National MPS Society:

- *eCourage*, our monthly newsletter containing stories and information about individuals with MPS and ML
- Educational materials such as syndrome booklets, fact sheets, and an MPS glossary
- Conference and education scholarships
- The Family Assistance Program, which provides financial support for durable medical goods
- News about various Society-sponsored conferences and gatherings, where families and leading MPS scientists, physicians, and researchers join together for a common cause
- Information on local events, such as regional social events and fundraisers. These events create opportunities for families to meet each other and help raise community awareness of these rare genetic diseases
- A listing in our membership directory that assists families with connecting with one another

Glossary

Term	Definition
Aspiration	To draw in or out by suction. For individuals with MPS, it most commonly means the accidental inhaling of a fluid or solid like saliva or food into the windpipe or lungs where it can lead to coughing, difficulty breathing, choking, or aspiration pneumonia.
Attenuated	Weakened, reduced, or diminished in size. Attenuated MPS means a less severe form of the disease.
Bronchoscopy	A medical procedure that lets a doctor look into the lungs and airways. The doctor inserts a thin tube with a light and camera through the nose or mouth down the throat and into the lungs.
Carpal Tunnel Syndrome	Thickening of the ligaments in the carpal tunnel (space in the wrist where the nerves pass between the carpal bones and the connective tissue) that causes pressure on the nerves. This can cause irreversible nerve damage if not surgically corrected. In children with MPS, carpal tunnel syndrome occurs because of the accumulation of GAG deposits.
Carrier	An individual who has a recessive, disease-causing version of a gene on 1 chromosome of a pair and a normal version of that same gene on the other chromosome. By definition, carriers of a recessive condition do not have clinical signs and symptoms of the condition.
Cerebrospinal Fluid (CSF)	The fluid that surrounds the brain and spinal cord which cushions them from shock, brings nutrients to the brain, and carries waste away. It is produced in the ventricles (cavities) of the brain and is reabsorbed into bloodstream.
Chromosomes	Linear, double-stranded structural units of genetic material consisting of DNA and supporting proteins called chromatin. Human cells contain 46 chromosomes identified as 23 pairs; 22 pairs are autosomes (the same from each parent) and 1 pair are the sex chromosomes.
Echocardiogram	Ultrasound of the heart to evaluate heart valve and heart muscle function.
Corneal Clouding	Cloudiness in the circular window at the front of the eye (cornea) due to a storage of GAGs.
Corneal Transplant	A surgical procedure where a damaged or diseased cornea is replaced by donated corneal tissue.

Enzyme	A protein that facilitates a biological reaction without itself being used up in the reaction (i.e. it acts as a catalyst). An enzyme acts by binding with the substance involved in the reaction (the substrate) and converting it into another substance (the product of the reaction).
Enzyme Replacement Therapy (ERT)	A medical treatment for a genetic disease whereby the missing protein (enzyme) is manufactured separately and given intravenously to the patient on a regular basis.
Gastrostomy Tube (G-Tube)	A tube surgically inserted through the abdomen into the stomach. It is used to deliver nutrition and/or medications directly into the stomach when swallowing is difficult because of disease or obstruction of the esophagus.
Gene	The basic unit of heredity. Genes are made up of sequences of DNA that code for specific proteins or other functional units. Hundreds of genes are arranged together in strings to form a chromosome.
Gene Therapy	A medical treatment for a genetic disease whereby normal genes are inserted into a patient's cells to replace or correct the effects of mutated or disease-causing genes.
Glycosaminoglycans (GAGs)	Complex linear sugar molecules that are widely found throughout the body in connective tissue, the area between cells, and secretions on the surfaces of many cell types. GAGs were previously called mucopolysaccharides.
Hernia	The bulging of an organ or tissue through some part of the body that should be containing it. Common examples are bulges in the umbilical (belly button) or inguinal (inner groin) regions of the body.
Hematopoietic Stem Cell Transplantation (HSCT)	A medical procedure that replaces enzyme-deficient cells with healthy enzyme-producing cells. Hematopoietic (blood) stem cells are capable of differentiating into a variety of specific cell types. The patient's bone marrow cells must first be eliminated by chemotherapy and/or radiation therapy. Then the healthy donor stem cells are infused into the bloodstream where they migrate into the bone marrow and multiply into new, healthy, enzyme-producing blood cells. These healthy cells migrate back to many parts of the body and brain where they produce properly functioning enzyme and "reboot" the immune system.

Hydrocephalus	A buildup of cerebrospinal fluid (CSF) in the cavities (ventricles) of the brain. This can put pressure on the brain and is sometimes characterized by an enlarged head in infants. Older children and adults can experience symptoms like headache, impaired vision, and cognitive difficulties. Communicating hydrocephalus can occur when the normal outflow of the fluid is blocked. It can be treated surgically by inserting a shunt into a ventricle to drain the excess fluid.
Individualized Education Program (IEP)	A specifically designed program for each child in the public school system who receives special educational services. The aim is to improve teaching, learning, and appropriate goal setting for each individual. A team including members from the school system and the family are generally involved in designing the IEP. Federal legislation is in place to guide the development of appropriate IEPs.
Kyphosis	An exaggerated, forward curve of the spine that causes a hunching of the back. (Similarly, a gibbus deformity is a type of kyphosis that involves a shorter section of the spine with a more angular curve.)
Lumbar Puncture	A lumbar puncture (also known as a spinal tap) is a procedure in which a needle is inserted into the space surrounding the spinal column in the lower back to withdraw cerebrospinal fluid (CSF) or to deliver medicine. This procedure may be performed to diagnose or treat a condition, but it is also used as a measure of intracranial pressure to aid in diagnosing hydrocephalus.
Lysosomal Storage Disorder (LSD)	An inborn error of metabolism, resulting in a particular lysosomal dysfunction. In the case of MPS disease, it is an inherited enzyme deficiency that blocks the natural breakdown of GAGs, causing a buildup of waste products in the lysosomes (specialized compartments within cells that contain the enzymes responsible for breaking down substances into smaller molecules so that they can be used again in various bodily processes).
Lysosome	Specialized compartments within cells that contain the enzymes responsible for breaking down substances into smaller molecules so that they can be either eliminated or used again in various bodily processes.
Mitral Valve Prolapse	When the flaps between the left atrium and the left ventricle of the heart don't close evenly or smoothly, the mitral valve that connects the two chambers forms a bulge (prolapse) into the left upper chamber (left atrium) as the heart contracts. This can lead to blood leaking backward into the left atrium, causing mitral valve regurgitation.

Mucopolipidosis (ML)	An inherited metabolic disease that affects the body's ability to break down various materials within cells. Patients with ML do not produce enough of one of the many enzymes required for a properly functioning lysosome. The name ML is used to classify all of the diseases with the clinical features common to both the mucopolysaccharidoses and the sphingolipidoses (diseases characterized by abnormal lipid or fat metabolism, affecting nerve tissue).
Mucopolysaccharidosis (MPS)	An inherited condition in which the body is unable to properly break down glycosaminoglycans (GAGs; formerly known as mucopolysaccharides). All of the various MPS diseases are characterized by defective lysosomal enzymes.
Mutation	Any change to the DNA sequence of a gene. Mutations are permanent alterations in the genetic code that can be passed down to future generations.
Otitis Media	Inflammation of the middle ear occurring commonly in children as a result of an infection, causing pain and temporary hearing loss.
Port-a-cath	A small medical device that allows easy access to a patient's veins. The port is installed beneath the skin and is connected to a catheter (a thin, flexible tube) that connects the port to a vein. A needle can be inserted through the skin into the port in order to draw blood or to give treatments, including drugs and blood transfusions. It can stay in place for months or years.
Scoliosis	A sideways curve of the spine.
Shunt	A passage that will allow fluids to move from one part of the body to another. It is often used to treat hydrocephalus, where a tube is surgically placed into the brain to help drain cerebrospinal fluid (CSF) and redirect it to another part of the body where it can be reabsorbed.
Sleep Apnea	A sleep disorder where breathing stops repeatedly during sleep. It is frequently caused by an obstruction of the airway.
Tracheostomy	A surgical procedure in which a hole is made into the trachea (windpipe) through the front of the neck and a tube is inserted to help a person breathe.
Vocational Rehabilitation	A series of services that are designed to help individuals with disabilities get or keep a job, or to return to work or other useful occupation. These services are often provided by federal- or state-run programs.

You can find a complete list of terms in our online glossary at mpssociety.org/fact-sheet-glossary.



For more information or to join the National MPS Society:

Visit www.mpsociety.org

Contact us at 877.MPS.1001

Or email us at info@mpsociety.org

This booklet is not intended to replace medical advice or care. The contents of and opinions expressed in *A Guide to Understanding Mucopolysaccharidosis (MPS)* do not necessarily reflect the views of the National MPS Society or its membership. This booklet may be reproduced, or copies can be made available upon request and written authorization from the National MPS Society.

ACKNOWLEDGEMENT

The National MPS Society would like to thank BioMarin, REGENXBIO, and Sanofi for their resources.