MUCOPOLYSACCHARIDOSES

Rare Diseases Unit of the Finnish Association of People with Physical Disabilities

Support for this guide was provided by Genzyme.

Publications of the Finnish Association of People with Physical Disabilities, O.58., 2013
ISBN 978-952-5548-54-9
ISSN 1457-1471

Printing location: N-PAINO 2013

Mucopolysaccharidoses

Mucopolysaccharidoses

Mucopolysaccharidoses are storage diseases

Mucopolysaccharidosis (MPS) is a group of rare, hereditary and incurable “storage diseases.” MPS is named after mucopolysaccharides (sugars bound to proteins), which are not broken down correctly in these diseases, causing the products of incomplete metabolism to accumulate in the body. The stored mucopolysaccharides, nowadays called glycosaminoglycans (GAGs), start to disrupt cellular functions. It is estimated that one in 25,000 newborn children has some type of mucopolysaccharidosis (an incidence of 1:25,000).

When maintenance systems fail

GAGs are constantly produced by the body and are needed as building blocks for bones, cartilage and tendons, for example. At the same time, old GAGs are broken down and eliminated from the body. The enzymes responsible for breaking them down are found in lysosomes, which are small components of cells. In MPS, the cycle fails: one of the lysosome enzymes needed for GAG metabolism is defective, deficient or absent, preventing the breakdown of GAGs. As a result, the body forms products that it cannot eliminate, most commonly dermatan, heparan or keratan sulfate. These products collect in different parts of the body, causing functional problems and symptoms in many different tissues and organs. Some of the products of incomplete metabolism are excreted in urine, which can be useful for diagnosis.

Many types of MPS

The seven main categories of MPS are determined by the enzyme deficiency involved. Many of the main categories also include named sub-categories, which were originally meant to describe the severity or typical symptoms of the disease (**Table).** Even cases that are categorized under the same name are different from each other. MPS is influenced by many variables that are not yet understood. One factor is that the necessary enzyme is sometimes present in a sufficient amount to alleviate symptoms.

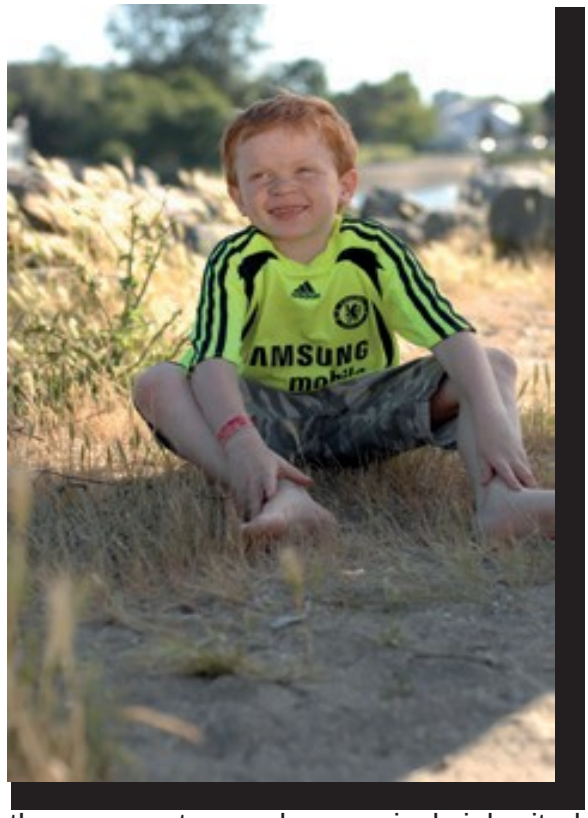
Generally speaking, the symptoms of MPS I, II, VI and VII are most clearly apparent in soft tissue and skeletal tissue, and often also in the brain (in severe MPS I or II and in MPS VII). The symptoms of MPS IV are primarily skeletal, whereas MPS III mostly affects the central nervous system.

The sub-categories are gradually being abandoned because the range of symptoms for each type of MPS covers a spectrum from less symptomatic forms to the most severe. For example, it is easier simply to refer to severe or milder forms of MPS I because the boundary between the Hurler and Hurler-Scheie form, or the Hurler-Scheie and Scheie form, is not clear.

Genetics of MPS

MPS diseases are hereditary. With one exception, they are inherited recessively in autosomes (chromosomes other than the sex-determining chromosomes).

A disease is recessively inherited when parents who are themselves healthy each contribute a “disease gene” to their child. The parents are said to be “carriers” of the disease gene. If one parent contributes a healthy copy of the gene instead, it “masks” the activity of its defective counterpart and prevents the disease from being expressed. Since autosomal inheritance is not sex-linked, girls and boys are equally likely to develop the disease.



We all have numerous disease genes that we are unaware of if they are paired with healthy genes.

When two parents each have the same autosomal, recessively inherited disease gene, they have a 75% chance of producing a healthy child (**Figure 1**).

MPS II (Hunter syndrome) is an exception because it is inherited recessively in sex chromosomes, specifically X chromosomes. Women have two X chromosomes (XX), but men have only one X chromosome along with a Y chromosome (XY). In women, one healthy X chromosome protects against MPS II even if the other X chromosome carries the disease gene. Men whose only X chromosome includes the defective gene will develop the disease.

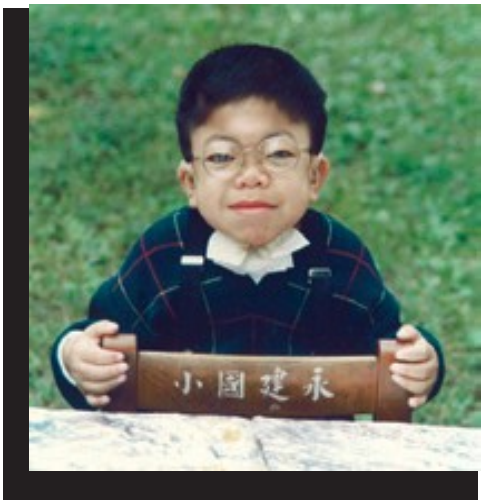
As a result, MPS II patients are practically always men. If a woman has an X chromosome with the MPS II genetic defect and gives birth to a boy, there is a 50% chance that her son will be healthy. All her daughters will be healthy,
but they could be carriers of the defective gene (**Figure 2**).

When a couple has a child with a recessively inherited disease for the first time, it usually comes as a surprise. If the couple plans to have more children, tests can be done in an early stage of pregnancy to find out whether the next child also has the disease.

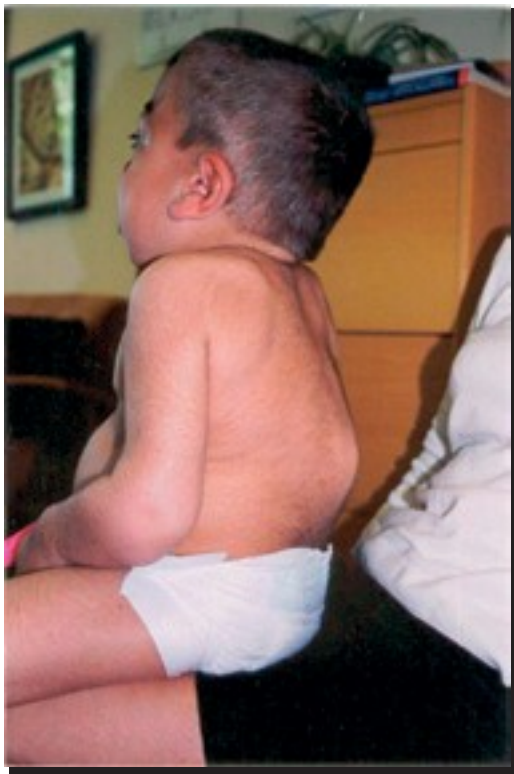
How the body is affected

In MPS and other storage diseases, metabolic products that have not been eliminated have an impact on the functioning of cells, tissues and organs. The products typically accumulate, and cause symptoms, in different parts of the body. Each case is unique, however, and may not involve all of the symptoms mentioned below. The severe form of MPS I (Hurler syndrome) is the most severe of the MPS diseases, so it is used as an example here.

Affected children appear normal at birth, but typical disease-related changes may already begin to occur during the first year of life. Abnormally rapid growth of the head, characteristic facial features, and the herniations developed by many of the children usually lead to further examinations and a diagnosis by the end of the first year. Typical facial features include a prominent forehead, depressed nasal bridge and wide nose, as well as plump cheeks and lips. At a later stage, the mouth is often open and the tongue may rest between the lips and teeth.



Severe MPS I increases susceptibility to ear and respiratory infections. Hearing becomes impaired as a result of recurrent ear infections and increased accumulations. Corneal clouding is one of the most typical problems causing visual impairment. The heart, too, is vulnerable: accumulations can cause narrowing of the coronary arteries or thickening of the heart valves, which often become leaky. The liver and spleen become enlarged.



The child may grow normally at first, but usually stops gaining height around three years of age. The hands are wide and the fingers are short due to abnormal skeletal development. Ribs are “oar-shaped,” the collarbones are short and thick, and the vertebrae are malformed. Vertebrae can easily slip out of place, especially in the neck area, something to keep in mind when moving or bending the patient’s head in connection with dental care or when administering anesthesia, for example. The spine does not stay straight (hump formation or scoliosis), the pelvic bones develop poorly, and the ends of long bones in the arms and legs are abnormal. Skeletal malformations and accumulations in the soft tissues around joints lead to joint stiffness and mobility impairment.

Increasing accumulations in the brain cause delayed mental development, which is usually noticeable by the age of 1–2 years, although development continues to occur. Skills begin to decline about 2–3 years later.

Similar and different disease features

MPS diseases have much in common in terms of the symptom spectrum, but MPS I progresses more quickly than any other form. There are differences in the symptoms as well. MPS III, in particular, is distinct from the other forms of MPS in many ways.

One very important difference is that mental development is not abnormal to a significant degree, if at all, in some forms of MPS (**Table**). The ultimate reason why some accumulations have more harmful effects than others is not known.

One way to distinguish between forms of MPS is that corneal clouding does not occur in MPS II (Hunter) or MPS III (Sanfilippo).

Short stature is a typical feature of MPS. Growth may even stop before the child is 3 years old, resulting in a final height of less than three feet. In MPS III, growth is more robust and continues until the child is about 10 years old. In the mildest cases, growth may continue until the child is nearly 5 feet tall.

Joint stiffness is typical for most forms of MPS, but is not consistent with the symptom profile of MPS IV (Morquio), in which joints are described as lax. One serious consequence for the cervical spine is that vertebrae may slip out of place, so special caution must be observed when bending the head. Joint stiffness is also not a typical feature of MPS III in the early stage; mobility is good initially and remains unimpaired for a fairly long time.

In MPS III, cognitive decline begins at the age of 1.5–3 years, often about ten years before motor skills begin to weaken. Sleep and behavioral problems begin at about 3–4 years of age. In MPS III, the typical facial features of MPS may be very mild. When a child who looks “normal” behaves quite abnormally, it can lead down the wrong diagnostic path; ADHD or autism spectrum disorders may be considered instead, delaying the correct diagnosis.

Treating symptoms versus the root cause

There is no curative treatment for any form of mucopolysaccharidosis. MPS diseases are progressive and usually life-limiting (**Table**). In the absence of an actual cure, the symptoms are treated instead. Examples of symptomatic treatment include hernia repair, surgical decompression of the spinal cord, removal of the tonsils and adenoids, ear tube placement in order to reduce infections, orthopedic procedures for skeletal problems, corneal transplants, etc. No two patients are alike, so symptomatic treatment is also individualized.

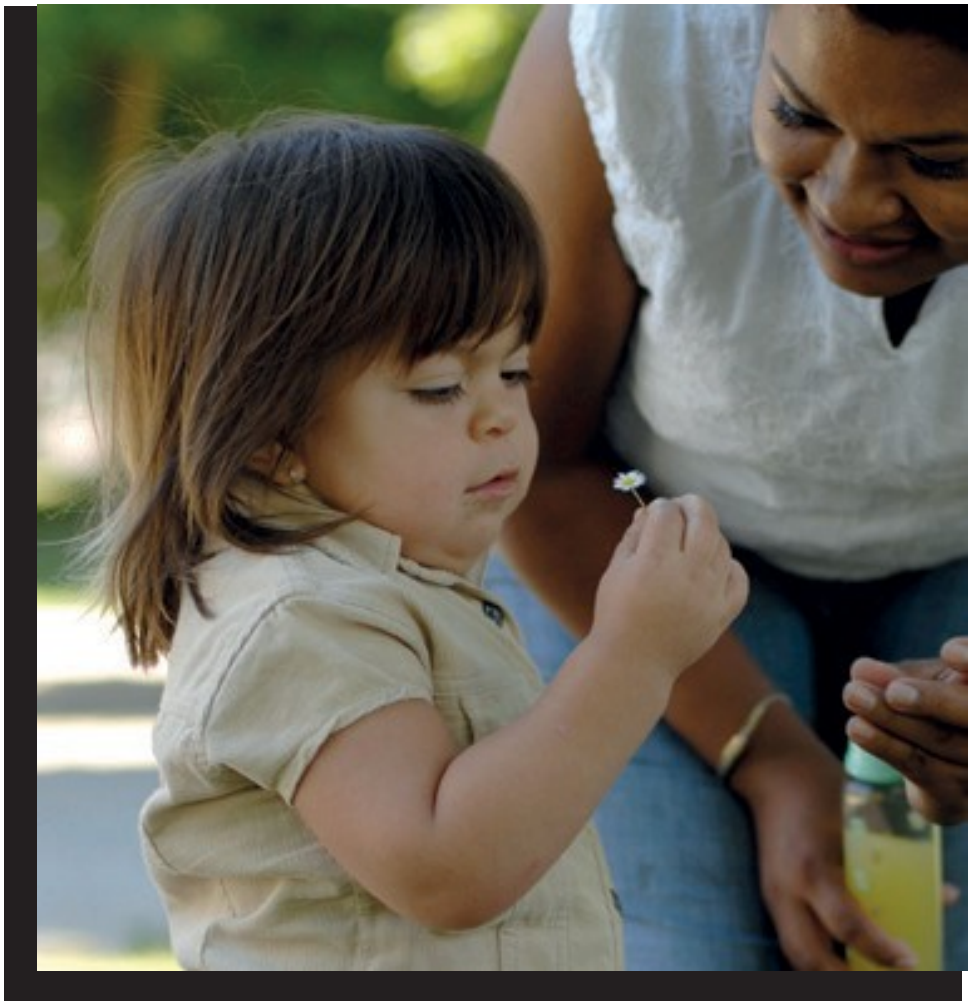
Due to the muscle and joint stiffness problems in most forms of MPS, physical therapy is essential for symptomatic treatment and for preventing functional impairment. Maintaining joint mobility as much as possible improves the patient's quality of life. Equipment that helps with everyday tasks serves the same purpose, along with identifying and removing obstacles in the patient's environment.

MPS treatment opportunities have improved in recent years. Although there has been no final breakthrough, treatment for a few types of MPS can already be aimed at the root cause, enzyme deficiency. These treatments have resulted in better quality of life and a longer lifespan.

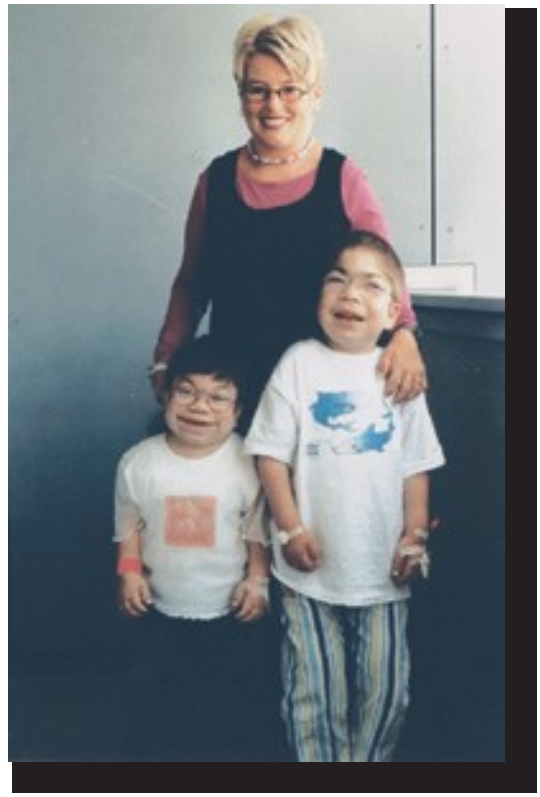
Blood stem cell transplant

Blood stem cell transplants were attempted as far back as the 1980s, the idea being that they could trigger production of the deficient enzyme. The treatment consists of transplanting stem cells from the blood of a healthy donor into the patient's body. If the procedure works, the donated cells "stick" and begin to multiply, producing all of the enzymes they produced in the donor, including the one that the transplant recipient lacked.

The treatments have been partially successful. Existing GAG accumulations in many tissues and organs have decreased after enzyme production is established, and the formation of new ones has slowed down. This has reduced symptoms. However, the brain has been largely unaffected by the positive influence of the enzyme. Symptoms of cognitive impairment have not been significantly reduced, although the rate of decline has been slowed. Stem cell transplantation should be done as early as possible, before significant accumulations have developed in the brain.



Stem cell transplants have not had enough effect on all forms of MPS to be considered a suitable treatment. Patients with severe MPS I or MPS II, as well as MPS VII, have benefited the most from stem cell transplants. Stem cell transplantation is a drastic treatment. In each individual case, careful consideration should be given to whether the potential benefits of a stem cell transplant are great enough to justify the risk of adverse effects.Another reason why this form of treatment has become less popular recently is that promising results have been obtained from enzyme replacement therapy.



Enzyme replacement therapy

The defective or absent enzyme is known for each of the various MPS types. It seems natural to suppose that if a “medicine” could be produced to replace the enzyme, and if this were supplied to people who need it, the disease could be controlled.

Indeed, enzyme (replacement) therapy has already been developed for MPS I, MPS II and MPS VI. The therapeutic products laronidase (for MPS I), idursulfase (for MPS II) and galsulfase (for MPS VI) are administered intravenously at a hospital once a week. The infusion takes several hours each time. Treatment continues throughout the patient’s life. As with drug treatments in general, adverse effects, such as allergic reactions, are possible.

Treatment results have been good, although the challenge for enzyme therapy has likewise been to extend the effect to the brain. The brain is protected by an important mechanism known as the blood-brain barrier, which prevents harmful substances in the bloodstream from entering the brain. The beneficial effect of the blood-brain barrier becomes a disadvantage when it is desirable for a substance to enter the brain, as in enzyme therapy. Though the therapy alleviates many other symptoms, it has little impact on accumulation that occurred in the brain and produced effects there before treatment began.

One way of trying to get around this limitation has been to administer enzyme therapy directly into the fluid space around the spinal cord, which in turn is connected to the brain. Good results have been obtained with this approach as well, but the treatment has not yet been officially registered. The safety and efficacy of a treatment must be proven in high-quality studies before registration can be completed, but for rare diseases, collecting such evidence takes time. Studies are still on-going, and it looks as if registration will eventually be accomplished also for administering enzyme replacement therapy into the fluid space around the spinal cord.

Other treatment possibilities are constantly being pursued with the help of animal testing and cell cultures. Though the path from such tests to established patient treatments is long, it is important to continue developing MPS treatments.

Special skills needed for treatment

MPS diseases are extremely rare, and it is understandable that individual healthcare providers are not necessarily knowledgeable or experienced in their treatment. Nevertheless, MPS in Finnish patients is often initially suspected at a child health clinic or public health center. Excessively rapid growth of the head, as well as persistent ear and respiratory infections, can point to the right diagnosis. Diagnosis and treatment, at least in the early stage, take place in a university hospital. Expertise in several different fields is needed. Neurologists, orthopedists, surgeons, stem cell transplant specialists, eye doctors, ear doctors, cardiologists, anesthesiologists, and dentists typically participate in treatment.

Centralized treatment is particularly important for rare diseases, contributing to cumulative knowledge and experience. This guarantees the best possible medical care for the patient.

Text, figures 1 and 2, and table:

Päivi Hölttä
Editor, Doctor of Dental Science, specialized dentist

Additional information about mucopolysaccharidoses is available in Finnish, Swedish and English on internet sites such as the following:
www.invalidiliitto.fi/harvinaiset
www.socialstyrelsen.se/ovanligadiagnoser
www.mpssociety.org
www.orpha.net
www.omim.org

Figure 1. Autosomal recessive disease inheritance. The disease is passed on to both girls and boys in the same way. Except for Hunter syndrome, all mucopolysaccharidoses are inherited as shown.

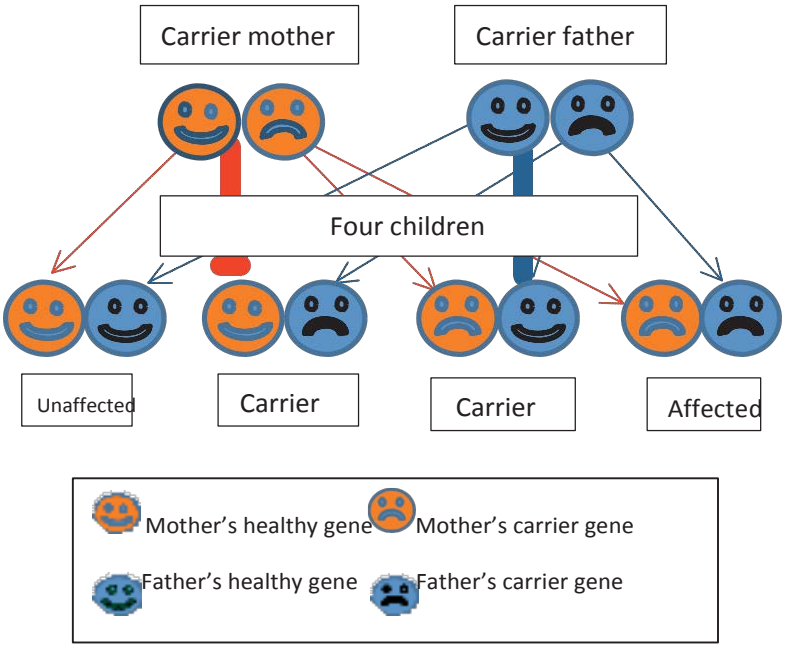


Figure 2. X-linked recessive disease inheritance, as in Hunter syndrome. Statistically, 50% of boys will be affected. Girls will be unaffected, although 50% of them will be carriers.

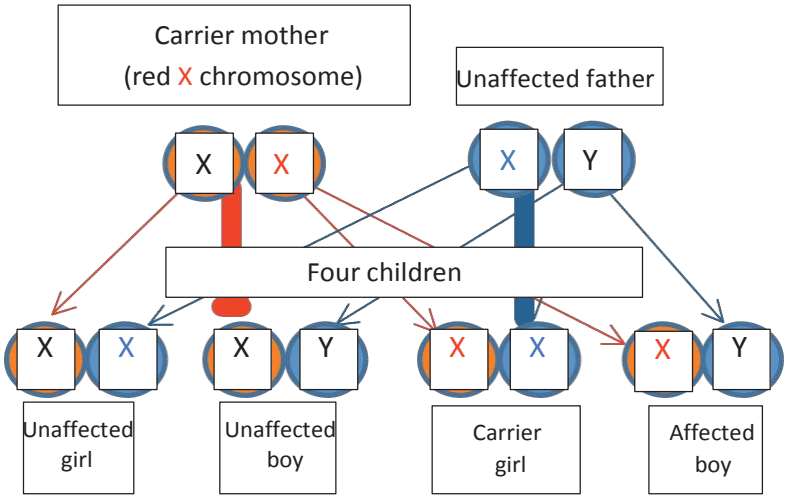


Table. Mucopolysaccharidoses are divided into seven main categories, which include sub-categories characterized by a spectrum of symptoms. In the literature, information about MPS incidence, projected lifespans, age at diagnosis, and treatments is absent or somewhat contradictory. The international statistics in the table are approximate and have been compiled from numerous sources. Separate statistics for Finnish patients are not available.

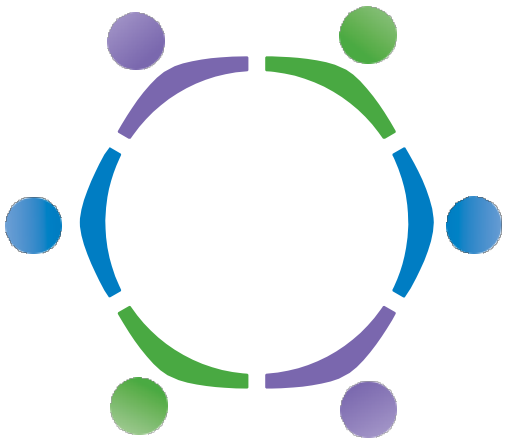
Mucopolysaccharidosis (MPS)	MPS sub-categories	Age at diagnosis	Projected lifespan (no SCT or ERT)	Incidence	Mental development	Treatment options; no curative therapy
MPS I	Hurler (MPS IH): severe	6–24 mos.	Usually ≤ 10 yrs.	1:100,000 (all forms together)	Impaired after about 3–4	SCT (< 2 yrs.), ERT, symptomatic
	Hurler-Scheie (MPS IH/S): less severe	3–8 yrs.	> 20 yrs.		Normal	ERT, symptomatic treatment
	Scheie (MPS IS): least severe	> 5 yrs.	Normal		Normal	ERT, symptomatic treatment
MPS II	Hunter, severe (MPS IIA)	18 mos.–4 yrs. depending on severity	10–15 yrs.	1:140,000–160,000 boys (A–B)	Impaired after about 2–3	ERT (SCT), symptomatic treatment
	Hunter, less severe (MPS IIB)		20–60 yrs.		Normal	Symptomatic treatment (ERT)
MPS III	Sanfilippo A (MPS IIIA)	1–2 yrs. for severe forms For milder forms, not until adulthood, perhaps even > 50 yrs.	For severe forms, 20–40 yrs. For mild forms, 40–70 yrs.	1:70,000–90,000 (A–D)	Impaired after about 2 yrs.	Symptomatic treatment ERT in development
	Sanfilippo B (MPS IIIB)					Symptomatic treatment
	Sanfilippo C (MPS IIIC)					Symptomatic treatment ERT in development
	Sanfilippo D (MPS IIID)					Symptomatic treatment
MPS IV	Morquio A (MPS IVA)	1–3 yrs.	For severe forms, 2–3 yrs.; for mild forms, 60–70 yrs.	1:200,000 (A–B)	Normal	Symptomatic treatment, ERT
	Morquio B (MPS IVB)					Symptomatic treatment
MPS VI	Maroteaux-Lamy (MPS VI)	2–3 yrs.	About 20 yrs. for severe forms, more for milder forms	1:240,000–300,000	Normal	ERT (SCT), symptomatic treatment
MPS VII	Sly	0–7 yrs. depending on	From a few months up to 20–40 yrs.	< 1:250,000	Impaired early	Symptomatic treatment, SCT
MPS IX	Hyaluronidase deficiency	?	Not known; only 1 patient described	Extremely rare	?	Symptomatic treatment

Abbreviations: SCT = blood stem cell transplant, ERT = enzyme replacement therapy

The Rare Diseases Unit of the Finnish Association of People with Physical Disabilities (FPD) provides guidance and support for rare musculoskeletal injuries and diseases. The unit publishes a series of Rare Diseases guides, including this Mucopolysaccharidoses guide. The guide was prepared by Päivi Hölttä (editor, Doctor of Dental Science, specialized dentist) and funded by Genzyme. FPD guides are used to help disseminate information about specific diagnoses that is not readily available in the Finnish language. The guides are intended for people who have rare musculoskeletal injuries or diseases, their loved ones, and professionals in the social services and healthcare fields.

FPD Rare Diseases Unit guides and orders:
www.invalidiliitto.fi/harvinaiset

Specialized skills and rehabilitation for patients with rare conditions:
www.lahdenkuntoutuskeskus.fi



Rare Diseases Unit of the Finnish Association of People with Physical Disabilities
Launeenkatu 10, 15100 Lahti, tel. +358 (03) 812 811
www.invalidiliitto.fi/harvinaiset