A Guide to Understanding Mucopolysaccharidosis (MPS) III

Canadian MPS Society
for Mucopolysaccharide & Related Diseases

Founded in 1984, The Canadian Society for Mucopolysaccharide and Related Diseases Inc. (The Canadian MPS Society) is committed to providing support to individuals and families affected with MPS and related diseases, educating medical professionals and the general public about MPS, and raising funds for research so that one day there will be cures for all types of MPS and related diseases.

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Introduction

Mucopolysaccharidosis III (MPS III, pronounced **mew**·ko·**pol**·ee·**sak**·ah·ri·**doh**·sis three), also called Sanfilippo syndrome, is a mucopolysaccharide storage disease named after Dr. Sylvester Sanfilippo, who described the condition in 1963. MPS III is characterized by developmental delay and cognitive regression, with usually mild physical problems.

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

All individuals with MPS III have a deficiency of one of four enzymes which results in the accumulation of glycosamino-glycans (GAG), pronounced **gly**·cose·a·**mee**·no·**gly**·cans), previously called mucopolysaccharides, inside special parts of the cell called lysosomes. This is why MPS III is part of a larger family of diseases called the lysosomal storage diseases (LSDs). The accumulation of GAG is responsible for numerous problems that affect individuals with MPS III.

As yet, there is no cure for individuals affected by these diseases, but there are ways to manage the challenges they will have, and ensure an improved quality of life. Scientists who study MPS continue to look for better and more effective ways to treat these diseases. As a result, patients will likely have more options available to them in the future.

Children with MPS III will have lives that are different from the majority of children, but they have delightful personalities and are extremely lovable. Children affected by MPS III will give you love that is totally unconditional. They will make you laugh when you think you may never laugh again. Their love is infectious to everyone around them. They communicate with you even when they lose their verbal skills. Their eyes will beguile you, their smiles will entice you and their spirit will raise yours when you think nothing else can.

What causes MPS III?

As mentioned previously, all MPS disorders are caused by the storage of complex molecules called glycosaminoglycans (GAG). GAG are long chains of sugar molecules used in the building of bones, cartilage, skin, tendons and many other tissues in the body. These sugar chains are submicroscopic and cannot be seen with the eye, but can be studied using special scientific instruments and analytical methods.

GAG form part of the structure of the body and also give the body some of the special features that make it work. For example, the slippery, gooey fluid that lubricates your joints contains GAG. The rubbery resilient cartilage in your joints is another example. All tissues have some of this substance as a normal part of their structure; however, individuals with MPS have too much GAG accumulation.

To understand how GAG accumulation causes MPS III, it is important to understand that in the course of the normal life process, there is a continuous process of building new GAG and breaking down the old - a recycling process. This ongoing recycling process is required to keep the body healthy. The breaking down of GAG occurs in a part of the cell called the lysosome. Lysosomes are basically bags full of digestive enzymes which break down worn-out cellular components. This is why MPS III is considered one of the approximately 40 different kinds of lysosomal storage diseases (LSDs). All LSDs are caused by a deficiency of an individual enzyme – a biochemical tool. The breakdown and recycling process requires a series of special enzymes. To break down GAG, a series of enzymes works in sequence one after another.

The GAG chain is broken down by removing one sugar molecule at a time starting at one end of the GAG chain. Each enzyme in the process has its special purpose in the body and does one very specific action - just like a screw-driver works on screws and a hammer works on nails.

Individuals with MPS III have a defect in the gene that instructs the body to make one of four specific enzymes, each of which is essential in the breakdown of certain GAG called heparan sulfate (HS). The incompletely broken down heparan sulfate remains stored inside cells in the body and begins to build up, causing progressive damage. The GAG are not toxic, but the amount and the effect of

Shawn

storage in the body lead to many physical problems. There is also evidence that GAG are bioactive. This means that their accumulation can cause activation of other chemical reactions in the body (i.e. they may trigger inflammation in joints).

Babies may show little sign of the disease, but as more and more GAG accumulate, symptoms start to appear. Sugar or foods normally eaten will not affect whether there is more or less build-up of GAG.

Sophie

Are there different forms of MPS III?

There are four different enzyme deficiencies that have been found to cause MPS III; the disease is described as type A, B, C or D. The names of the deficient MPS III enzymes are heparan N-sulfatase (type A), alpha-N-acetylglucosaminidase (type B), acetyl-CoA-glucosaminide acetyltransferase (type C) and N-acetylglucosamine-6-sulfatase (type D). There is little clinical difference among the four types of MPS III, since all four types accumulate the same GAG, heparan sulfate. Heparan sulfate is primarily found in the central nervous system and its accumulation in the brain is responsible for the numerous problems that affect individuals with all types of MPS III.

How common is MPS III?

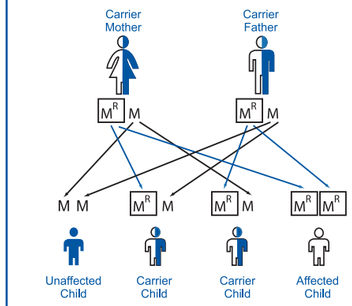
The estimated incidence of MPS III (all four types combined) based upon published studies is 1 in 70,000 births. Type A is the most common in northwestern Europe, type B in south-eastern Europe, and types C and D are rare everywhere. Although MPS III is individually rare, the incidence of all MPS diseases combined is 1 in 25,000 births and the larger family of lysosomal storage diseases collectively occur in about 1 in every 5,000 to 7,000 births.

How is MPS III inherited?

MPS III is a genetic disease. When most individuals think of genetic disease, they think of a health problem that gets passed down from father or mother to child and so on. While many genetic diseases are passed down through generations in an obvious way, some genetic diseases are “hidden,” or recessive, and only show up when both genes in an individual are affected. MPS III is that type of genetic disease. Most families who have a child with MPS III do not have a family history of genetic problems. MPS III seems to show up suddenly even though the genetic mutation can be traced up the family tree to earlier generations through DNA testing.

Individuals with MPS III are missing one of four specific enzymes that are essential to the breakdown of one of the GAG called heparan sulphate. Heparan sulphate is primarily found in the central nervous system and its accumulation in the brain is responsible for the numerous problems that affect individuals with all types of MPS III.

To understand this better, it is important to understand some basic concepts about genetics. DNA, or deoxyribonucleic acid, is the hereditary material in humans; nearly every cell in a person’s body has the same DNA. Most DNA is located in the cell nucleus, but a small amount of DNA can also be found in the mitochondria. A gene mutation is a permanent change in the DNA sequence that makes up a gene. A gene is the basic physical and functional unit of heredity, and genes act as instructions to make molecules called proteins. All humans are formed with two complete sets of genes - one set from each parent. So every individual has half his genes from his mother and half from his father. Enzymes are made from the instructions found in the genes.



Courtesy of Genzyme Corporation

Legend:

M – copy of gene that properly controls production of the enzymes that break down GAGs

M^R – faulty copy of gene, one that does not properly control production of the enzymes that break down GAGs in MPS III

MPS III is a genetic recessive disease. All relatives of affected individuals should seek further information from their medical/genetics doctor or from a genetic counsellor if they have questions about the risk for recurrence of the disease in their family, or other questions related to inheritance of MPS diseases.

As each enzyme in the body is produced by two genes, one from the mother and one from the father, if one gene happens to be non-functioning (as is the case for a carrier parent), then the body may produce only 50 percent of the normal level of enzyme associated with that gene. However, 50 percent of the normal enzyme level is enough to keep the individual who is a carrier from having any symptoms of MPS III. If, however, the genes inherited from both the mother and the father are not functioning correctly, the individual will have little or no enzyme in the body and will experience symptoms of MPS III.

This is why MPS III is a genetic recessive disease. Both parents of an affected child are “carriers” of the disease. Each parent has one normal copy of the gene that produces the enzyme and one non-functioning copy of the gene that cannot properly produce the enzyme. However, one functioning copy of the gene allows the carrier parents to be symptom free.

It’s important to note that we are all carriers of 6-10 different conditions and it is important to know that there is nothing we have done or not done in our own health or during a pregnancy, for example, that has caused this.

For each child born to carrier parents there is a one out of four chance of having MPS III and thus a three out of four chance of not having MPS III. The non-affected children of carrier parents have a 2 out of 3 chance of being carriers, like the parents.

Anyone with an affected sibling or family member should consider seeking further information from their medical genetics doctor or from a genetic counsellor if they have questions about the risk for recurrence of the disease in their family or other questions related to inheritance of MPS diseases.

Elisa with her cousin

How is MPS III diagnosed?

Doctors may consider testing for MPS III 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 III, a 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 various ages. Most, but not all, individuals with an MPS disorder have GAG levels in their urine that are higher than those of individuals without an MPS disorder.

A urine test is only one of the first steps in diagnosing MPS III; 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 III, the enzyme activity levels are much lower or absent. If the urine GAG test is normal but there is a strong suspicion of MPS III, enzyme testing should be considered.

Of all the MPS diseases, MPS III (Sanfilippo) produces the mildest physical abnormalities. Since the early symptoms are also common in unaffected children, diagnosis is often delayed.

Early diagnosis of MPS III is critical. The earlier MPS III is diagnosed, the sooner a comprehensive medical care plan and supportive care can be implemented to ensure the best possible quality of life. As treatments are developed for MPS III, early diagnosis will be critical in potentially preventing some of the permanent damage the disease may cause.

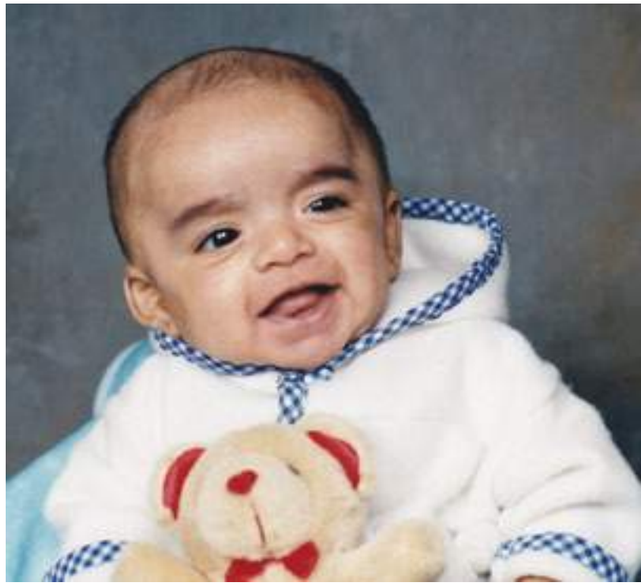
Prenatal diagnosis

If you have a child with MPS III, it is possible to have tests during a subsequent pregnancy to find out whether the baby you are carrying is affected. It is essential to know the type of MPS III (type A, B, C or D), because each one requires a specific test. 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 counsellor or doctor can help you explore these options and other strategies for having additional children, such as egg or sperm donation, which limit the probability that the children will have or be carriers for MPS III.

How does the disease progress?

MPS III affects children differently, and its progress will be faster in some than in others. Babies usually show no signs of the disease, but symptoms start to appear from 2 to 6 years of age. Change will usually be very gradual and, therefore, easier to adjust to. Affected children's preschool years may be very frustrating for parents. They may begin to worry as their children start to lag behind their friends' children in development, and they may feel they are being blamed for their children's overactive and difficult behaviour.

Diagnosis may be delayed, as some children do not have abnormal features, and their symptoms are very non-specific with little evidence to suggest an MPS disease. A doctor has to be perceptive enough to recognize that something is seriously wrong and ask for urine and blood tests to determine a diagnosis. Some families have had one or more additional children, who are sometimes also affected, before a diagnosis is established.



Raza

As the disease progresses, children develop extreme activity, restlessness and often very difficult behaviour. Some children sleep very little at night. Many will get into everything. Sadly, language and understanding will gradually be lost. Some children never become toilet trained, and those who do will eventually lose this ability.

Over time children with MPS III begin to slow down. They become more unsteady on their feet, tending to fall frequently as they walk or run. Eventually they lose the ability to walk. Some parents report episodes of muscle spasms, dystonia (sustained muscle contractions) or continuous jerking movements. These may or may not be linked to seizures and can be difficult to treat. Parents will need help with the physically tiring task of caring for an immobile child or teenager with severe developmental delay.

Clinical concerns related to MPS III

Of all the MPS diseases, MPS III produces the mildest physical abnormalities. It is important, however, that simple and treatable conditions such as ear infections and toothaches not be overlooked because of behaviour problems that make examination difficult. Children with MPS III often have an increased tolerance of pain. Bumps and bruises or ear infections that would be painful for other children often go unnoticed in children with MPS III. Parents may need to search for a doctor with a patience and interest in treating a child with a long-term illness. Do not hesitate to consult a doctor if you think your child might be in pain.

Some children with MPS III may have a blood-clotting problem during and after surgery. It is advised that pre-operative tests be done to see if this might be a problem for your child. Discuss this with your surgeon.

Physical appearance	Children with MPS III grow to a fairly normal height, and changes in appearance may be less than in other MPS diseases. The hair tends to be thick and there may be more hair than usual on the body. The eyebrows are often dark and bushy and may meet in the middle, and the bridge of the nose can be flattened.
Nose, throat and chest concerns	The problems described in this section are common to children with MPS diseases, but occur less often in individuals with MPS III. The severity of the problems depends greatly on the individual child.
Runny nose	The bridge of the nose can be flattened and the passage behind the nose may be smaller than usual due to poor growth of the bones in the mid-face and thickening of the mucosal lining. This combination of abnormal bones, with storage in the soft tissues in the nose and throat, can cause the airway to become easily blocked. Some children with MPS III have chronic drainage of clear mucus from the nose (rhinorrhea). This chronic nasal discharge is due to the abnormal drainage of normal secretions and chronic ear and sinus infections.
Throat	The tonsils and adenoids often become enlarged and partly block the airway. The windpipe (trachea) becomes narrowed by storage material and may be floppy, or softer than usual, due to abnormal cartilage rings in the trachea.

Medications often affect individuals with MPS III differently, so it is essential to consult your doctor rather than using over-the-counter medications.

Breathing difficulties	Many individuals with MPS III have frequent coughs and colds. At night they may be restless and awaken frequently. Sometimes the individual may stop breathing for short periods while asleep (sleep apnea). Pauses of up to 10 to 15 seconds may be considered normal. This noisy breathing, which stops and starts, can be very frightening for parents to hear and may mean that the child's oxygen level may be low when sleeping, which can damage the heart over time. If a parent notices significant choking or episodes of interrupted breathing, the child should be evaluated by a sleep specialist using a polysomnogram (sleep study). It is important to know that many individuals may breathe like this for years. Sleep apnea, which rarely occurs in MPS III, can be treated in some individuals by removing the tonsils and adenoids (adenoids may re-grow), opening up the airway with nighttime continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) or tracheotomy, as discussed in the following paragraphs.
Management of breathing problems	Affected children may be admitted to the hospital overnight for a sleep study. 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 monitors of the body's function. From this study, doctors can assess how much blockage to breathing is present, how much trouble a child is having moving air into the lungs during sleep, and the effect this is having on his or her body.
Treatment of respiratory infections	Medication often affects individuals with MPS III differently, so it is essential to consult your doctor rather than using over-the-counter products. Medications for controlling mucous production may not help. Medications such as antihistamines may dry out the mucous, making it thicker and harder to dislodge. Decongestants usually contain stimulants that can raise blood pressure and narrow blood vessels, both undesirable for individuals with MPS. Cough suppressants or medications that are too sedating may cause more problems with sleep apnea by depressing muscle tone and respiration. Although most normal individuals with colds do not require antibiotics, individuals with MPS III almost always end up with secondary bacterial infections of the sinuses or middle ear. These infections should be treated with antibiotics. Poor drainage of the sinuses and middle ear make overcoming infections difficult. Therefore, it is common to have infections improve on antibiotics and then promptly recur after the antibiotic course is over. Chronic antibiotic therapy may be used to help some individuals with recurring ear infections. Ventilation tubes can be used to improve drainage from the ear and speed resolution of infections. It is important to consult with an ear, nose and throat (ENT) specialist experienced with MPS diseases to determine which tube is best. Many individuals with MPS III become allergic to antibiotics or may acquire resistant infections. Your doctor can prescribe other antibiotics to help manage this problem. While overusing antibiotics is not advised, most individuals with MPS will require some type of treatment for most infections. You will need a doctor with whom you can develop a good working relationship to manage the frequent infections.

Clinical concerns related to MPS III

Mouth

Individuals with MPS III may have an enlarged tongue. Gum ridges can be broad. The teeth can be widely spaced and poorly formed with fragile enamel. It is important that the teeth are well cared for, as tooth decay can be a major cause of pain. Teeth should be cleaned regularly, and if the water in your area has not been treated with fluoride, consult your dentist about giving your child daily fluoride tablets or drops. 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. Even with the best dental care, an abscess around a tooth can develop due to abnormal formation of the tooth. Irritability, crying and restlessness can sometimes be the only sign of an infected tooth in a severely involved individual.

If an individual with MPS III has a heart problem, it may be advised that antibiotics be given before and 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. If teeth need to be removed while under an anesthetic, it should be done in a hospital that has experience working with patients affected with MPS disorders, and under the care of both an experienced anesthetist and a dentist, never in the dentist's office.

Heart

Heart disease is common in most MPS diseases, but serious heart problems rarely occur in individuals with MPS III. If heart problems develop, they may not cause any real problems until later in the individual's life. Medications are available to help manage the heart problems that occur in MPS III.

Your doctor may hear heart murmurs (sounds caused by turbulence in blood flow in the heart) if the valves become damaged by stored GAG. Heart valves are designed to close tightly as blood passes from one chamber of the heart to another in order to stop blood from flowing back in the wrong direction. If a valve is weakened, it may not shut firmly enough and a small amount of blood may shoot backward, leading to turbulence and a murmur. Most individuals with MPS III have some degree of heart valve leakage or blockage, but the problem is usually mild and surgery is rarely needed. They may have slowly progressive valvular heart disease for years without any apparent clinical effects. If the condition worsens, medications can be used to lessen the effect on the heart. However, an operation may be required to replace the damaged valves.

Although major heart problems are rare in MPS III, individuals should have an echocardiogram (ECHO) annually (or as often as your doctor thinks necessary) to show whether any problems are beginning. 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, especially coronary artery disease.

Because of the unusual problems that can occur in these diseases, you should select a cardiologist with some knowledge of MPS III. At a minimum, you should inform the doctor about the heart problems experienced by individuals with MPS III.

Liver and spleen

In individuals with MPS III, the liver and spleen may become slightly enlarged due to storage of GAG (hepatosplenomegaly), but this does not usually cause problems.

Abdomen and hernias

In most individuals with MPS III, the abdomen bulges out due to posture, weakness of the 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. A hernia can come from behind the navel (umbilical hernia) or in the groin (inguinal hernia). Inguinal hernias should be repaired by an operation, but hernias will sometimes recur. Umbilical hernias are not usually treated unless they are small and cause entrapment of the intestine or are very large and are causing problems. It is very common to have a recurrence of an umbilical hernia after a repair has been made.

Bowel problems

Many individuals with MPS III suffer periodically from loose stools and diarrhea. The cause of this is not fully understood. Occasionally, the problem is caused by severe constipation and leakage of loose stools from behind the solid mass of feces. More often, however, parents describe it as "coming straight through." It is thought there may be a defect in the autonomic nervous system, the system that controls those bodily functions usually beyond voluntary control. Studies have found storage in the nerve cells of the intestine and it seems likely that abnormal motility in the bowel is the cause of diarrhea.

An examination by your pediatrician, who may use an additional test like an x-ray, may establish the cause of diarrhea. The problem may disappear as the child gets older, but it can be made worse by antibiotics prescribed for other problems. The episodic diarrhea in some individuals with MPS III appears to be affected by diet; elimination of some foods can be helpful.

If antibiotics are the cause, treatment may involve eating plain live-culture yogurt to change the bacterial make-up in the intestines. This provides a source of lactobacillus to help prevent the growth of harmful organisms within the bowel, which can cause diarrhea or make it worse. A diet low in roughage also may be helpful.

Constipation may become a problem as the child gets older and less active and as 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.

Bones and joints

Individuals with MPS III tend to have minimal problems with bone formation and growth. Features of osteoporosis can, however, develop as early as the teen years. As the bones become fragile and brittle there is increased risk of fractures, and the decrease of overall stability increases the risk of falling. Prolonged use of seizure medication combined with decreased mobility can lead to brittle bones. Recent research has shown that high-dose vitamin D therapy can improve bone mineral density.

Joints

Joint stiffness occurs in all types of MPS, and the maximum range of movement of all joints may become limited. Individuals with MPS III tend to have minimal problems with joints. Later in life joint stiffness may cause pain, which may be relieved by heat and ordinary painkillers. Limited movement in the shoulders and arms may make dressing and grooming difficult. Anti-inflammatory drugs, such as ibuprofen, can help with joint pain, but their use should be monitored closely to make sure irritation and ulcers in the stomach do not occur.

Clinical concerns related to MPS III

Hands	Individuals with MPS III have fingers that occasionally become bent due to contractures, and they may not be able to fully extend their arms.
Hips	In some individuals with MPS III, the hips may become dislocated, but this is often not a problem and treatment may not be necessary.
Legs and feet	Many individuals with MPS III stand and walk with their knees and hips flexed. This, combined with a tight Achilles tendon, may cause them to walk on their toes. They sometimes have knock-knees but this is very unlikely to need treatment. Severe knock-knees can be treated by surgery on the tibia bones, but this is not common in MPS III. The feet are broad and may be stiff with the toes curled under, rather like the hands.
Cold hands and feet	Cold hands and feet may occur in MPS III as the disease progresses, resulting from disruption of the normal neurologic regulation of blood vessels (autonomic dysfunction). It may not bother the child, but if it does the obvious remedies of heavy socks and warm gloves may be useful. Late in the disease, the temperature control mechanism in the child may become damaged and the child may sweat at night, as well as having cold hands and feet by day. Some children have episodes when their body temperature drops (hypothermia). If this happens, keep your child warm and ask your doctor for advice on the best ways of managing the problem.
Skin	Individuals with MPS III tend to have thickened and tough skin, making it difficult to draw blood or place intravenous catheters. Excess hair on the face and back occurs in some individuals with MPS III.

Neurological problems: brain, senses and nerves

Seizures	At a later stage of the disease, individuals with MPS III can have frequent, minor seizures, during which they momentarily lose the ability to focus and concentrate (petit mal). When this is occurring, the child may seem more out of touch or harder to feed. Some may have generalized seizures (grand mal), which can be controlled by medications. During the seizure you should place your child on his or her side to prevent the inhalation of vomit and leave him or her in that position until the seizure is over. Check that the airway is clear, and do not put anything in the mouth. Seizures can usually be prevented or reduced in frequency with conventional anti-seizure medications. It is not unusual to try several medications before finding what works best. Some doctors may recommend the individual wear a helmet to prevent head injury.
Eyes	There may be problems with vision caused by changes to the retina. GAG storage in the retina can result in loss of peripheral vision and night blindness. Night blindness can result in an individual not wanting to walk in a dark area at night or waking up at night and being afraid. Sometimes the addition of a night light in a hall or bedroom is beneficial. If you have concerns about your child's vision, an ophthalmologist can perform special studies to help determine whether the problem is due to how the retina responds to light.
Ears	Deafness is common in all types of MPS III. It may be conductive or nerve deafness or both (mixed deafness) and may be made worse by frequent ear infections. It is important that individuals with MPS III have their hearing monitored regularly so problems can be treated early to maximize their ability to learn and communicate.
Conductive deafness	Correct functioning of the middle ear depends on the pressure behind the eardrum being the same as that in the outer ear canal and in 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. This is called middle ear effusion. 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 T-tubes, 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, the cause of nerve deafness is damage to the tiny hair cells in the inner ear. It may accompany conductive deafness, in which case it is referred to as mixed deafness. Nerve or conductive deafness can be managed by the fitting of a hearing aid or aids. In general, it is felt that hearing aids are under-utilized in MPS diseases.
Sleep	Sleeping difficulties are extremely common in children with MPS III. This may mean that your child has problems falling asleep, or may wake frequently throughout the night. See the section below on how to cope with sleeping problems, and for more practical advice, read the section on sleep in our "Daily Living with MPS & Related Diseases" booklet, which is posted on the Canadian MPS Society's website.

General treatment and management

Diet

There is no scientific evidence that a particular diet has any helpful effect on individuals with MPS III, and symptoms such as diarrhea tend to come and go naturally. Some parents, however, find that a change in their child's diet can ease problems such as excessive mucous, diarrhea or hyperactivity. Reducing intake of milk, dairy products and sugar, as well as avoiding foods with too many additives and colouring, have helped some individuals. Consult your doctor or a dietician if you plan major dietary changes to make sure the proposed diet does not leave out essential items. If your child's problems are eased, try reintroducing foods one at a time to test whether any particular item seems to increase the child's symptoms.

Early feeding of children with MPS III usually causes few problems, but some do not progress to eating food that needs chewing. Others learn to chew but find it increasingly difficult to eat "lumpy" foods, particularly if they are mixed with food of a smooth texture. Many become quite picky and reject a number of foods for no clear reason.

As affected children lose the rhythm of swallowing, they may start to splutter and cough while eating. It is better to serve food of a mashed consistency. Meat will be tolerated more easily if it is made through slow cooking rather than just chopped into small pieces. You can help by moving your hand gently backward under the chin and slowly down the throat to help move the tongue and encourage swallowing. Choking is frightening and you can provide reassurance by rubbing your child's back and holding his or her hands.

Swallowing becomes more difficult as a child with MPS III gets older and the disease progresses. When this occurs, the individual may choke or aspirate food or liquids into the lungs, which can result in recurrent pneumonia. During this time, there also may be a decrease in weight and feeding can take more and more time. Families often consider alternate means of feeding, such as through a gastrotomy tube (G-tube). Consultation with your medical geneticist and pediatric surgeon can help with your decision making.

It is important to note there is no diet that can prevent the storage of GAG, because they are actually made by the body. So reducing sugar intake or other dietary components cannot reduce GAG storage.

Choking

When children cannot chew and have difficulty swallowing, there is a risk of choking. Even when food is cut up into very small pieces, children may still start to choke. If this happens, act quickly: turn the child upside down, or lay the child head down over your knee and pound sharply between the shoulders three or four times. Pounding on the back while the child is upright can make things worse by causing the child to breathe in rather than cough out the food. If necessary, put your finger down his or her throat to try to dislodge the food item, but beware of reflexive biting. Consider registering for first aid and safety courses.

Choking also can occur with liquids, including secretions made by the body such as saliva. As swallowing becomes more difficult, affected individuals may begin drooling and may need to be suctioned.

If an affected individual develops a fever within a few days of a choking episode, consult your doctor. It is possible that some food particles entered the lungs (aspiration); treatment is required for pneumonia that may have developed.

You can help your child swallow by moving your hand gently backward under the chin and slowly down the throat to help move the tongue.

Chewing

As they become more out of touch with their environment, many individuals with MPS III will entertain themselves by rocking or chewing on their fingers, clothes or whatever they can lay their hands on. Because there is little one can do to stop this behaviour, it is best to provide the individual with a wide range of safe items on which to chew such as rubber toys, teething rings or soft cloths.

If the problem is severe and the affected individual starts to injure his or her fingers, elbows may be splinted for periods of the day so hands cannot reach the mouth.

Physiotherapy

When a child with MPS III is young and mobile, physiotherapy may not be needed, although regular exercise is important. Chest physiotherapy may be needed later to help clear an infection.

As an affected child gets older, joints of the feet and ankles may become tight and spastic. Hydrotherapy may be helpful in keeping joints mobile. Some range-of-motion physical therapy may be useful but need not be intensive. Exercises that cause pain should be avoided.

When a child or adult with MPS III is immobile, it is important to ensure that he or she is sitting with proper support to avoid uneven pressure on particular joints. If a deformity at the ankle joint develops, making walking difficult, special braces may help.

Anesthetics

Giving an anesthetic to an individual with MPS III 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 have to go to a different hospital in

Consider registering your family members and other carers in first aid and CPR (cardiopulmonary resuscitation) courses.

an emergency, tell the anesthetist there might be problems with intubation (placement of the breathing tube). The airway can be 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 it during anesthesia or intubation could cause injury to the spinal cord. For some individuals, it is difficult to remove the breathing tube after surgery due to excessive swelling. Advise physicians of the critical nature of these problems and that many problems have occurred during anesthesia of MPS individuals. For any elective surgery in an MPS child, it is important to choose a pediatric anesthesiologist who has experience with difficult airways. This may require the surgery be performed at a regional medical centre instead of a local hospital. Generally, individuals with MPS III have fewer problems with anesthesia than other individuals with MPS. See additional information on anesthesia in the booklet "Is Your Child Having an Anesthetic?" published by the Canadian MPS Society.

Education

It is important to work with your school system and develop the best Individualized Education Program (IEP) possible for your child. Inclusive education is legally required in Canada; therefore, schools must have a means of identifying those students who are not completely able to adjust to a standard classroom situation as a result of a disability. Canadian human rights laws specify "a right to reasonable accommodation for a disability" which ensures that schools and other educational authorities have a legal obligation to take appropriate steps to eliminate discrimination resulting from a rule, practice, or barrier that has, or can have, an adverse impact on individuals with disabilities. This is referred to as the "duty to accommodate." For more information on education, see the Education Strategies section of the binder "MPS III: A resource for individuals and families affected by MPS III", which is posted on the Canadian MPS Society's website.

Puberty

Children with MPS III will go through the normal changes associated with puberty.

Life expectancy

Life expectancy in MPS III is extremely varied. Individuals with MPS III typically live into their teenage years. Some children will not live this long, while others will live into their twenties. Mildly affected individuals have lived into their thirties, and in a few rare cases, into their forties. Though parents understandably worry about their child's death, it is usually a peaceful event. You may find it helpful to prepare yourself in advance for the time of your child's death. The Society has a book available called "Choices – When Your Child is Dying," written by its founder Sheila Lee. Please contact the Society office to receive a complimentary copy of this guide for parents dealing with the grief associated with the impending loss of a child.

Ways of making life more tolerable

The behaviour problems seen in children with MPS III are generally not altered by medications or behavioural therapy. It is helpful to adapt family life as much as possible, and to seek regular breaks for parents and other family members.

Some parents may try to modify their child's behaviour with the support of a local psychologist, and a few have reported some limited success. However, the child's behaviour will continue to change as the disease progresses, and the usefulness of a particular behaviour modification technique may be short-lived.

Some parents find it very helpful to designate a room or part of a room in the house especially for their child with MPS III.

Adapting the house

Parents find it very helpful to designate a room or part of a room for their child with MPS III. The room should be within a caregiver's hearing distance and be made safe for the child to play without constant supervision, so parents can interact with other children or deal with household tasks. Ensure small objects, such as coins, hair clips and elastic bands, are out of reach. Furniture that is fragile or has sharp edges should be removed and replaced by large cushions on the floor. Windows may need to be fitted with strengthened glass or Plexiglas, and the floor should be easy to clean. Replacing the door to the room with a Dutch door allows the child to see the parents, increasing the child's sense of security while keeping him or her safe. Favourite durable toys and playthings should be accessible to the child. A television or stereo speakers can be placed high on a shelf or suspended from the ceiling and operated by the parents using remote control. Additional information about home adaptations can be found in the booklet "Daily Living with MPS and Related Diseases", published by the Canadian MPS Society, and funding for home renovations or adaptations is available through the Society's Family Assistance Program.

Sleeping difficulties

Many children with MPS III are very restless at night, not sleeping for more than a couple of hours at a time. The reason for this is unknown. It is sometimes possible to improve this situation with medications, but it may take you and your physician a period of trial and error to establish which drug will work best, and drugs often lose their effect after a while. Some parents choose to ration their use to a few nights a week or accept that after a few weeks the medication will have to be discontinued for a while. It is vital for parents to sleep if they are to cope during the day; do not hesitate to ask your doctor for help.

Some parents find they can achieve a longer period of unbroken sleep by putting their children to bed later and following a regular routine. The thought of a child getting up in the middle of the night and having an accident while the rest of the household is asleep worries many parents. Some find it helps to put a lock on the outside of their child's bedroom door, to replace the bedroom door with a Dutch door and locking the bottom section, to fit a stair gate in the doorway, or to place special pads under the carpet by the door which cause a bell to ring if the child leaves his or her room.

Some parents find that removing furniture and using only a mattress on the floor helps to prevent falls or injuries during the night. Some also find that special containment beds are helpful.

More practical advice from parents on dealing with issues surrounding sleep can be found in our booklet "Daily Living with MPS & Related Diseases".

Hyperactivity

Most children with MPS III go through a hyperactive stage where they get into everything, are difficult to control and are unaware of danger. Medications used to treat hyperactivity generally do not modify this behaviour in children with MPS III; instead, it is better to adapt houses as previously described. Fenced yards where children can run around safely are great assets.

It is most helpful if affected children can join play groups or attend schools or after-school programs where a variety of activities occupy them. Ideally there should be space for children to run around and keep fit for as long as possible. Many affected children are calmed by the movement of cars and travel well.

Enjoying your child

Children with MPS III will have lives that are different from the majority of children, but they have delightful personalities and are extremely lovable.

Children affected by MPS III will give you love that is totally unconditional. They will make you laugh when you think you may never laugh again. Their love is infectious to everyone around them. They communicate with you even when they lose their verbal skills. Their eyes will beguile you, their smiles will entice you and their spirit will raise yours when you think nothing else can.

Taking a break

Caring for a severely affected child is hard work. Parents will need regular breaks so they can continue caring for their child(ren) with MPS III without becoming exhausted. Brothers and sisters also need to have their share of attention, and to be taken on outings that are not feasible with an affected child.

Financial support and supportive care

Individuals with MPS III and their families may need help from case managers and support workers to access a variety of healthcare and supportive care services, including physical supportive care, emotional support, and financial assistance.

Families may benefit from financial assistance from health insurance or government programs to help cover the costs of medical treatment and devices. Health Canada's Service Canada website provides links to a number of programs for financial support of people with disabilities (www.servicecanada.gc.ca/eng/audiences/disabilities/index.shtml). Visit the Canadian MPS Society's website for a list of more links to programs which provide financial assistance (or refer to the lists included in the Society's MPS III resource binder "MPS III: A resource for individuals and families living with MPS III"). You may also wish to investigate private agencies and foundations. The Canadian MPS Society's Family Assistance Program provides financial aid and respite funding when it is not available through insurance or other sources - please contact the Canadian MPS Society office or visit www.mpssociety.ca for more details.

Specific treatment of MPS III

Overview

The goals of managing MPS III are to improve quality of life and to slow down the progression of the disease. Currently there is no cure for MPS III. Treatment options for MPS III include those aimed at disease management and supportive or palliative care (care that makes a person with a disease that cannot be cured more comfortable).

Hematopoietic Stem Cell Transplant (HSCT)

The goal of HSCT is to restore the activity of the deficient enzyme. The initial transplants in children with MPS III using stem cells from bone marrow did not improve the neurological deterioration. In recent years transplants have been performed using stem cells from umbilical cord blood. Long-term data is not available to show the benefits of this procedure. For parents 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 Canadian MPS Society can put you in touch with physicians and families so you can become better informed before reaching a decision.

Enzyme replacement therapy (ERT)

Because ERT does not cross the blood-brain barrier at normal doses and the physical problems in children with MPS III are less severe than other forms of MPS, it is unlikely this intravenous (IV) treatment will be developed for MPS III. Research is being conducted to assess the benefit of IV injection of ERT into cerebral spinal fluid.

Genistein

Genistein from soy isoflavone extracts are being widely used in the treatment of MPS III patients in an attempt to reduce the amount of GAG produced and stored; however, long-term prospective placebo controlled studies are needed to asses clinical benefit of genistein in MPS diseases. Please speak with your physician about genistein before considering it as a treatment for your child.

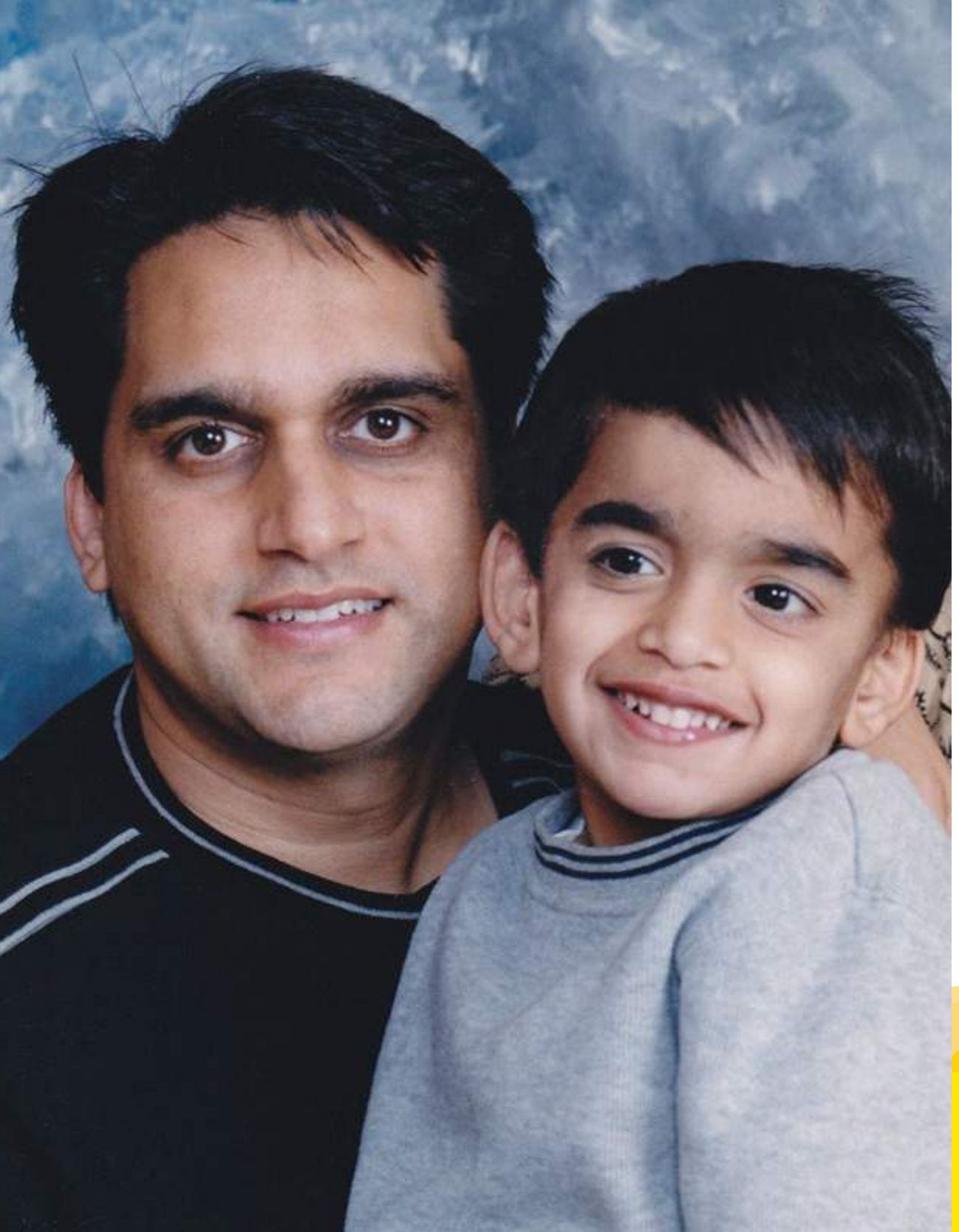
Sophie

Living with MPS III

Disease severity varies significantly for individuals with MPS III, and it is not possible to predict the expected life span for a given individual. However, the availability of new and ever-improving treatments, as well as other surgical procedures, provides hope for better future outcomes for all individuals affected by MPS III.

Research for the future

The Canadian MPS Society is committed to finding cures for MPS and related diseases, and therefore funds research grants (as do other foundations, such as the Sanfilippo Children's Research Foundation, which specifically funds research into MPS III). 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.



There are several different types of mucopolysaccharide (MPS) diseases. This booklet is intended as an introduction to mucopolysaccharidosis, type III (MPS III). A more thorough resource binder entitled “MPS III: A resource for individuals and families living with MPS III” is available for affected individuals and families through the Canadian MPS Society’s office.

This booklet was updated in 2013 by the Canadian MPS Society with help from the National MPS Society (USA), experts in the field, and parents of those with MPS III. This booklet is not intended to replace medical advice or care. The contents of and opinions expressed in “A Guide to Understanding MPS (Mucopolysaccharidosis) III” do not necessarily reflect the views of the Canadian MPS Society or its membership. This booklet may be reproduced and copies can be obtained through the Canadian MPS Society’s office or its website.

Raza and his Dad

Common bonds unite the lives of those affected by MPS and related diseases – all have a need for support and hope for a cure.

The Canadian MPS Society is committed to making a difference in the lives of families affected by MPS and related diseases through support, research, education and advocacy. Families gain a better understanding of these rare genetically determined diseases through the Society's assistance in linking them with health care professionals, researchers and, perhaps most importantly, each other.

Join the Canadian MPS Society and enjoy a variety of benefits, including:

- Our quarterly newsletter, the Connection, a valuable resource that helps members stay current on MPS-related news and events and stay in touch with each other, and our monthly e-newsletter, the e-Connection
- Our Family Referral Directory (Membership Directory): connecting families affected with the same syndrome or living in the same region
- Our Family Assistance Program: providing financial aid to affected families
- Advocacy support: to ensure our members receive the treatment and care they need
- Family conferences and regional meetings: providing families an opportunity to learn more about new research, treatments and care strategies, and to meet with other families, share experiences and form life-long friendships
- Bereavement support: for families dealing with the devastating loss of a child or family member to MPS or a related disorder

For more information or to join the Canadian MPS Society:
visit www.mpssociety.ca
contact us at **604-924-5130** or **1-800-667-1846**
or email us at **info@mpssociety.ca**