A Guide to Understanding Mucopolysaccharidosis (MPS) IV

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.

Table of Contents

Introduction

Mucopolysaccharidosis type IV (MPS IV, pronounced **mew**·ko·**pol**·ee·**sak**·ah·ri·**doh**·sis **four**) is a mucopolysaccharide storage disease, also known as Morquio syndrome. MPS storage diseases are included in a family of inherited disorders called lysosomal storage disorders (LSDs). Morquio syndrome takes its name from Dr. Morquio, a pediatrician in Montevideo, Uruguay, who in 1929 described a family of four children affected by this condition. As the same condition was also described in the same year by Dr. Brailsford from Birmingham, England, it is sometimes known as Morquio-Brailsford syndrome. MPS IV is characterized by short stature, severe bone disease and preservation of intelligence. Two different enzyme deficiencies can cause two different types of MPS IV, each having a wide spectrum of clinical severity from mild to very severe disease.

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).

If you are the parent of a newly diagnosed child, it is important to remember that MPS IV comprises a wide spectrum of severity and that individuals may be categorized anywhere from severe (or "rapidly progressing") to attenuated (less severe or "slowly progressing"). Even children from the same family may be affected differently. A range of possible problems is described in this booklet; however, this does not mean that your child will experience them all. Some complications arise early in childhood, while other present much later or may never occur.

As yet, there is no cure for individuals affected by this disease, but there are ways to manage the challenges they will have, and to ensure the best quality of life. Hematopoietic stem cell transplant (HSCT) has been attempted to treat MPS IV with little success. Enzyme replacement therapy (ERT), although not a cure, is a potential treatment, but data from ongoing clinical trials will have to be analyzed before determining the safety and efficacy of this treatment. Scientists who study MPS continue to look for better and more effective ways to treat these diseases, and it is likely that individuals will have more options available in the future.

What causes MPS IV?

All MPS disorders are caused by the storage of complex molecules called glycosaminoglycans. Glycosaminoglycans (GAG, pronounced **gly**·cose·a·**mee**·no·**gly**·cans), previously called mucopolysaccharides, 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 IV have too much GAG accumulation.

Individuals with MPS IV have a deficiency of an enzyme which results in the accumulation of glycosaminoglycans (GAG). This accumulation of GAG is responsible for the numerous problems that affect patients with MPS IV.

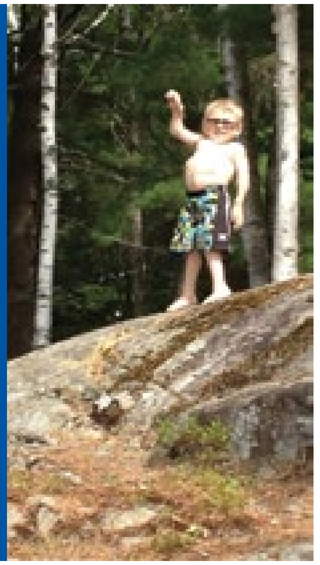
To understand how GAG accumulation causes MPS IV, it is important to understand that in the course of the normal life process, there is a continuous process of building new GAG and breaking down the old - a recycling process. This ongoing recycling process is required to keep the body healthy. The breaking 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 IV is considered one of the approximately 40 different kinds of lysosomal storage diseases (LSDs). All LSDs are caused by an inherited 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 screwdriver works on screws and a hammer works on nails.

Amy

Individuals with MPS IV are missing one of two specific enzymes which are essential in the breakdown of certain GAG called keratan sulfate (KS) and chondroitin-6-sulfate (CS). MPS IVA is caused by a defect in the gene that instructs the body to make the enzyme N-acetyl-galactosamine-6-sulfate sulfatase (GALNS, pronounced en-a·**see**·tyl·ga·lak·**tose**·amine-six-**sul**-fate **sul**·fa·tace), which is also called galactosamine-6-sulfatase. MPS IVB is caused by a defect in the gene that instructs the body to make the enzyme beta-galactosidase (GLB1). Because of this gene defect, cells either produce the enzymes in low amounts or not at all, and incompletely broken down GAG remains stored inside cells in the body and begins to build up, causing progressive damage. GAG are not toxic, but the amount and the effect of 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 accumulates, symptoms start to appear. Sugar or foods normally eaten will not affect whether there is more or less buildup of GAG.

Are there different forms of MPS IV?



Zane

It is important to understand that MPS IV has a broad clinical spectrum, ranging from severe (rapidly progressing) to attenuated (slowly progressing).

There are two different enzyme deficiencies that have been found to cause MPS IV; the disease is described as type A or B. As mentioned earlier, the names of the deficient enzymes are N-acetylgalactosamine-6-sulfate sulfatase, also called galactose 6-sulfatase (MPS IV A), and beta-galactosidase (MPS IV B). An individual affected by MPS IV cannot have both types. MPS IV A, the most common form, was first recognized to be a severe disease, and MPS IV B was initially considered to be an attenuated form or late onset variant. It is now recognized that both forms of MPS IV have a wide spectrum of clinical severity and are each viewed as a continuous spectrum of disease, with the most severely affected ("rapidly progressing") individuals on one end, the less severely affected (attenuated or "slowly progressing) individuals on the other end, and a range of severities in between.

In general, individuals with MPS IV B have similar problems, but tend to be mildly affected compared to individuals with MPS IV A. Both diseases result from an inability to break down keratan sulfate and chondroitin-6 sulphate (types of GAG). Keratan sulfate is primarily found in the bones and connective tissues. Chondroitin-6 sulphate accumulates in cartilage, bone and the heart valves. This GAG accumulation is responsible for the majority of problems that affect individuals with both types of MPS IV. Individuals with MPS IV B also store oligosaccharides.

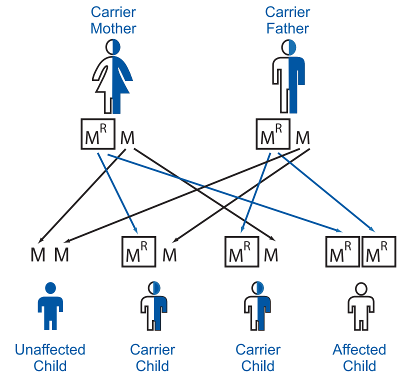
How common is MPS IV?

Reliable incidence figures are not available for MPS IV, but estimates have varied between 1 in 200,000 live births to 1 in 300,000 live births. Although MPS IV is individually rare, the incidence of all MPS diseases is 1 in 25,000, and the larger family of LSDs collectively occurs in about 1 in every 5,000 to 7,000 births.

How is MPS IV inherited?

MPS IV 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 IV is that type of genetic disease. Most families who have a child with MPS IV do not have a family history of genetic problems. MPS IV seems to show up suddenly even though the genetic mutation can be traced up the family tree to earlier generations through DNA testing.

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. Together, the individual has 100 percent of the genes required to live.



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 IV

Olivier

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 IV. 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 IV.

This is why MPS IV is a genetic recessive disease. Both parents are "carriers" of the non-functioning gene - 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.

Any child born of carrier parents has a three out of four (75 percent) chance of having at least one functioning gene and therefore no disease. Each child also has a one in four (25 percent) chance of inheriting the non-functioning gene from both the mother and from the father and thus being affected with MPS IV. There is a two in three (67 percent) chance that unaffected brothers and sisters of individuals with MPS IV will be carriers of the non-functioning gene that causes MPS IV.

MPS IV is a genetic recessive disease.

Anyone with an affected sibling or family member 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.

Christopher

How is MPS IV diagnosed?

Doctors may consider testing for MPS IV 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 IV, 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 IV; 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 IV, the enzyme activity levels are much lower or absent. If the urine GAG test is normal but there is a strong suspicion of MPS IV, enzyme testing should be considered.

MPS IV is a highly variable disease

MPS IV has a highly variable phenotype. This means that some children may have many of the symptoms described below and may be severely affected while others may not experience all of the symptoms and have a milder presentation. There is currently no reliable way of telling from biochemical diagnostic tests how severe the disease will be. Detailed studies have shown that in individuals with attenuated, or slowly progressing, MPS IV, a very small amount of active enzyme is working. This small amount of enzyme will digest some of the accumulating GAG, resulting in the disease being less severe than in an individual who has almost no enzyme activity.

DNA tests do not always correctly determine the severity of MPS IV. Many different kinds of mutations (permanent changes) in the gene that produces the enzyme deficiency have been identified. The gene has been studied extensively to see if there is any relationship between specific genetic mutations and the symptoms of the disease. There are some common mutations of the gene that 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 the individual's condition is likely to be at the severe end of the spectrum. Other common mutations of the gene cause very small amounts of defective enzyme to be produced, and still other mutations are not common at all and may only occur in a single known family. In these cases, it is virtually impossible to predict severity of disease using DNA analysis.

There is therefore no perfectly reliable way to determine the exact course of disease for individuals with MPS IV. Even with the same small amount of enzyme activity, and even within the same family, there can be variations in severity that cannot be explained by the enzyme level or DNA mutation. It is important to remember that whatever name is given to your child's condition, MPS IV is a spectrum with a variety of symptoms, and is extremely varied in its effects. This booklet addresses a wide range of possible symptoms that individuals with MPS IV may encounter; however, parents should be aware that their child(ren) may not experience them all or to the degree described.

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

Prenatal diagnosis

If you have a child with MPS IV, 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 counsellor 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 that they will have or be carriers for MPS IV.

Zane and Lucas

Clinical concerns related to MPS IV

Growth	Children with MPS IV usually grow normally at first, but growth may start to slow down around 18 months of age. Those who are severely affected usually stop growing around the age of 8 and full height may be between 90 cm and 120cm. Other individuals with MPS IV continue growing into their teens and can reach 150 cm. The torso is relatively shorter than the limbs.
Intelligence	There is no storage of GAG in the brain of individuals with MPS IV; therefore intelligence is not usually affected.
Physical appearance	The face of someone affected by MPS IV is altered to a certain extent by the disease. The mouth tends to be wide, the jaw square and the bridge of the nose flattened. The neck is very short, but the texture of the hair is not affected as it is in other MPS diseases. Individuals with MPS IV may develop prominent tummies and a characteristic way of walking and holding their arms due to joint contractures at their shoulders, elbows, hips, knees and ankles.
Eyes	The circular window at the front of the eye (cornea) can become cloudy due to storage of GAG, which disrupts the clear layers of the cornea. Corneal clouding tends to be mild and not particularly noticeable in most individuals with MPS IV and rarely interferes with vision. If corneal clouding is severe, it may reduce sight, especially in dim light. Some individuals cannot tolerate bright lights as the clouding can cause uneven refraction of light. Wearing caps with visors, or sunglasses, can help.
Ears	Some degree of deafness is common in both types of MPS IV disease. 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 IV have their hearing monitored regularly so that problems can be treated early to maximize the individuals' 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 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.

Zane

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 most individuals. In general, it is felt that hearing aids are underutilized in MPS diseases.
Mouth and teeth	Individuals with MPS IV may have a prominent chin, wide mouth and enlarged tongue. 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 cause of pain. Teeth should be cleaned regularly, and if the water in your area has not been treated with fluoride, daily fluoride tablets or drops should be given. Even with the best dental care, an abscess around a tooth can develop due to abnormal formation of the tooth. If an individual with MPS IV has a heart problem, such as a leaking valve, it may be advised by the individual's cardiologist 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. If teeth need to be removed while under an anesthetic, this 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.
Chest	Normally, the breastbone (sternum) is joined to the spine by the ribs. In MPS IV, the growth of the spine is affected. The breastbone continues to grow more normally, but as it is joined to the spine, it is forced to buckle outward in a rounded curve or sometimes in a prominent beak shape. The chest is bell-shaped and the ribs are held fixed in a horizontal position, causing restriction of efficient breathing. A breathing test, called a pulmonary function test, can be used by a lung specialist or respirologist to assess the amount of restriction caused by the abnormal bones.
Breathing difficulties	The windpipe (trachea) continues to grow while in some cases the cervical spine does not. This can mean that older teenagers and adults may need to tip their heads back to keep the trachea extended and prevent it from kinking and blocking off the airway. This can cause problems when the head needs to be bent forward, for example while getting a haircut. The heart and lungs in older teenagers and adults are compressed within a small thorax. This can lead to difficulties with the exchange of gases in the lungs, and restrictive respiratory failure can occur. As this is a difficult complication to treat, it is important to treat additional chest problems, such as infections, very seriously. Restrictive lung disorder can result from abnormal bone growth and /or decreased lung space. A respirologist is the best person to determine any possible therapy, including the use of BiPAP or CPAP at night or during the day. Upper airway obstruction, caused by enlarged adenoids or tonsils, can cause noisy breathing. Individuals with MPS IV may also have sleep apnea. Sleep apnea is a sleep disorder in which there are moments when a person stops breathing during sleep. This is caused by upper airway blockage caused by the position of the neck during sleep. Some relief can be found by sleeping on a flat bed with no pillows.

Clinical concerns related to MPS IV

Respiratory infections

Although children with MPS IV are not necessarily more prone to respiratory infections, their restricted chests mean they are less able to cope with an infection if it involves the lungs. Your doctor may advise you to contact him or her immediately if you think an infection might be starting so that an antibiotic can be prescribed if necessary.

Cases have been reported of individuals with MPS IV suffering severe breathing problems after spending several days at high altitude. It would be wise to check with your doctor if you are planning a long airplane flight or a vacation in the mountains.

Treatment of respiratory infections

Although most individuals with colds do not require antibiotics, individuals with MPS IV 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 makes it more difficult to overcome infections, and it is common to have infections respond to antibiotics then promptly recur after the course of antibiotics 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 an ears, nose and throat (ENT) specialist experienced with MPS diseases to determine which tube is best.

Many people with MPS IV 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 people with MPS will require some treatment for most infections. You will need a doctor with whom you can develop a good working relationship to manage the frequent infections.

Heart

Heart disease can occur in people with MPS IV but may not develop or cause any real problems until later in the individual's life. Medications are available to help manage the heart problems that occur in MPS IV. 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 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. Many individuals with MPS IV have some degree of heart valve leakage or blockage. Some individuals with MPS IV may develop problems with the aortic or mitral valves. They may have slowly progressive valvular heart disease for years without any apparent clinical effects. If the condition worsens, an operation may be needed to replace the damaged valves.

As heart problems can occur in MPS IV, individuals should have a test known as 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.

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

Abdomen and hernias

Individuals with MPS IV develop an enlarged liver and spleen (hepatosplenomegaly) due to the storage of GAG. The enlarged liver does not cause problems or lead to liver failure but its volume can interfere with eating and breathing.

Occasionally part of the abdominal contents may 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 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.

Bones and joints

People with MPS IV tend to have significant problems with bone formation and growth. The bone disease in MPS IV is different from that seen in other MPS diseases. The major clinical features of MPS IV are those related to the bones and their effect on the nervous system if nerves are compressed by abnormal bone movement.

Structure of bone

Since MPS IV primarily affects bone, it is helpful to understand the structure of bone in relation to your child's symptoms. Children grow because bones grow. Bones are like poles, and they elongate only at the ends. The region at each end of a long bone is called the epiphysis. At the appropriate times in life when we have growth spurts, our bodies first make connective tissue which is laid down at the epiphysis. The connective tissue at the epiphysis is then replaced by bone, which results in the total bone becoming longer. It is like adding another section onto the end of the pole. In MPS IV, because the GAG are not properly broken down, they cannot help contribute to the production of normal connective tissue.

A lack of normal connective tissue, therefore, results in a lack of bone production at the epiphysis tips which is required for normal growth. Abnormal bone development is called dysplasia. As a result of dysplasia, individuals with MPS IV have very slow growth and their bones remain permanently shorter.

Spine

The bones of the spine (vertebrae) normally line up from the neck to the buttocks. In individuals with MPS IV, the spine tends to be severely affected and its bones or vertebrae are abnormally flattened (platyspondyly). The vertebrae are often poorly formed and may not stably interact with each other. If this happens, the vertebrae can compress and injure the spinal cord. Symptoms such as urinary incontinence (after toilet training) could be a clue that some damage has been done to the spinal cord and should be properly investigated by a doctor. One or two of the vertebrae in the lower back are sometimes slightly smaller than the rest and set back in line. This backward slippage of the vertebrae can cause an angular curve (kyphosis or gibbus). If curvature is not severe, then bracing may be suggested. There are different opinions on whether surgery is needed or whether a brace can be used either to correct a curve or to support the back. If a brace is used, it should not be the kind that restricts the movement of the chest even further.

Clinical concerns related to MPS IV

Neck (cervical spine)

Problems in this area are perhaps the most serious for individuals with MPS IV. Neck problems need to be discussed at the time of diagnosis as serious problems can occur before 5 to 6 years of age. The difficulties arise from a structural defect in the upper vertebrae of the spine, which is worsened by very loose ligaments. The bones that stabilize the connection between the head and neck are usually malformed in people with MPS IV (odontoid dysplasis). There should be a piece of bone called the odontoid process sticking up between the first and second vertebrae which gives support as the head moves backward and forward. With odontioid dysplasia, the neck can become unstable, which places the spinal cord at risk to life-threatening injury. The spinal cord is a big bundle of nerves that carries messages between the brain and the rest of the body. If the cord is compressed or squeezed (cervical myelopathy), there will be gradual worsening effects on the child, with paralysis or death occurring if left untreated.

Children with MPS IV should be referred to an orthopedic surgeon who specializes in spines from an early age to monitor the condition of the cervical spine. MRI studies or X-rays will be performed with the head bent forward (flexion view) and with the neck straight (extension view) and will be repeated from year to year to monitor the situation. A baseline study of the neck is recommended at the time of diagnosis. If severe pain or pain associated with weakness or tremors in the lower legs, or tingling in fingers or upper limbs occurs, the child should have studies of the neck (MRI and flexion-extension X-rays) to evaluate for slippage of the neck vertebrae or a decrease in the opening size of the vertebrae around the spinal cord. A neurologist may suggest an “evoked potentials test” to determine a nerve conduction baseline and to determine any future changes to the baseline.

Parents may be alarmed that their child may have weakness in such a vital place as the cervical spine, and may be worried about their child being harmed by a severe fall. The surgeon will be able to advise you on the risks. It is important to keep a balance between avoiding risks and letting the child lead as normal a life as possible, however activities such as somersaults, head stands, contact sports, trampoline, or diving should be avoided completely.

Some problems with the cervical spine can be corrected by an operation called decompression surgery. This procedure involves operating on the upper neck vertebrae (C1 – C4) to enlarge the opening through which the spinal cord travels. It is a surgery only to be undertaken by neurosurgeons familiar with this procedure. Recuperation may involve the patient wearing a neck brace or “halo” for some weeks as the vertebrae heal and the muscles adjust to being moved around during surgery.

Other problems with the cervical spine can be corrected by an operation called a cervical fusion. Small pieces of bone are taken from the legs and fixed into the neck where they eventually grow to form a firm support, joining the top two vertebrae to the base of the skull. Fusion operations are often carried out on patients with other conditions, but there are special problems with individuals with MPS IV and common methods may fail. Most orthopedic surgeons have minimal or no experience with patients with MPS IV; however, surgeons at some hospitals have performed a number of fusion operations. The Canadian MPS Society has information about orthopedic surgeons and hospitals where successful cervical fusions have been performed.

After cervical fusion, it is essential to immobilize the neck in the correct position (reduced) for more than four months while the grafted bone grows up to join the base of the skull. One method of achieving this successfully is known as the “halo” method.

A metal “halo” ring is attached to the skull, and bars leading from it are fixed to the body by a plaster cast. The operation involves a hospital stay of usually no more than one week. The halo is typically required for three to four months to allow healing and fusion of the spine. Although caring for a patient in a halo is hard work, patients adjust remarkably well.

Scoliosis	Abnormal sideways curvature of the spine, or scoliosis, also can occur and, if severe, may require intervention. In general, fusion with bone is the best alternative and hardware-like rods are not well tolerated. In any case, the soft bone makes the surgery and recovery difficult. Many patients need multiple procedures. Bracing may be an option prior to surgery as movement of the chest should not be restricted.
Hips, knees and ankles	Bones can be broken and realigned by an orthopedic surgeon to permit correct alignment at the hips, knees and ankles. Simple leg casts, full body casts, or external fixatures may be used after these surgeries to keep bones in appropriate positions for optimal healing. External fixatures are stainless steel posts which are screwed into bone and protrude from the skin. These posts must be carefully attended to as they increase the chance of infection during healing.
Hips	It is common for the hips to become dislocated, but this is often not a problem and treatment may not be necessary. It is important to discuss this with an orthopedist comfortable with MPS IV disorders. If the individual continues to be able to walk and pain occurs later in life, surgery may be considered.
Knock knees (Genu Valgum)	As a child with MPS IV grows older, the knees gradually become more “knocked” (genu valgum). It is sometimes possible for the legs to be straightened by an operation, but it is usually considered best to wait until the child has stopped growing. Joints are held in place by strong bands of protein fibre called ligaments. Individuals with MPS IV have ligaments that are often very lax. If this is the case, surgery may not achieve any noticeable improvement.
Ankles and feet	The ankles of those with MPS IV may be weak and turn inward as a result of ligaments being lax. Occasionally ankle-foot orthotics (AFOs) or knee-ankle-foot orthotics (KAFOs) are worn, but firm supportive shoes may be equally adequate. The bones composing the arches in the feet are held in position by ligaments and tendons. These are likely to be weakened resulting in flat feet. The toes may be misshapen.
Shoulders	The shoulders of those with MPS IV are often partially dislocated downward (subluxed) so the arms cannot be raised straight above the head. This rarely causes any discomfort, but can make dressing or attracting a teacher’s attention more difficult.
Wrists	The wrists of those with MPS IV are enlarged and curved. They may become very loose and floppy as the tiny carpal bones fail to develop properly, and the ligaments are lax. This can mean considerable loss of strength in the hands. Attempts have been made to correct this problem surgically by grafting bone from another part of the body to the wrists, but unfortunately the technique has not yet been successful. Small plastic splints with wrist bands may be helpful in some cases. Writing may be difficult and some individuals may find it easier to use a computer. Carpal tunnel syndrome is common in most forms of MPS diseases, but has not been a frequently reported problem in MPS IV. If your child seems to have pain or numbness in the hands, particularly at night, it would make sense to have an electrical test called a nerve conduction study performed. This test will show whether carpal tunnel syndrome is the cause or if there is a problem with nerve conduction in the neck or spine. If your child has any weakness at all in the hand or has decreased muscle mass at the base of the thumb, ask for the test from your neurologist. Be persistent, as many physicians may not believe that carpal tunnel syndrome is present without the classic symptoms. Most individuals affected by MPS do not have the classic symptoms of carpal tunnel syndrome, even with severe nerve entrapment and damage.
Pain	Many individuals with MPS IV complain of pain. Pain may be caused by problems with bone formation and growth as mentioned above, but may also be due to inflammation (similar to arthritis). Pain management is important as it can help to improve general quality of life. Children and adults can benefit from seeing a pain specialist, such as a rheumatologist.

General management of MPS IV

Diet

There is no scientific evidence that a particular diet has any helpful effect on people with MPS IV. 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. It is advisable to consult your doctor or a dietician if you plan major dietary changes to make sure the proposed diet does not omit essential nutrients. If your child's problems are eased, you might try reintroducing foods one at a time to test whether any particular item appears to increase the child's symptoms.

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

Individuals with MPS IV should be as active as possible to maintain muscle strength and general health. Your child's doctor or physical therapist may be able to suggest ways of achieving this.

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Vomiting

Some individuals with MPS IV have a tendency to vomit easily, especially first thing in the morning, perhaps because mucus has built up overnight. Restricted space for internal organs in a small body can mean the stomach may be constricted and discomfort may be experienced after a large meal, resulting in vomiting. Sometimes there is a feeling of finding it hard to breathe as lungs are also constricted. A few children have had episodes of vomiting to the extent that they have become dehydrated. Consult your doctor if vomiting continues over several hours.

Medications

Children with MPS IV may be affected differently by medications, so it is essential to consult your doctor rather than using over-the-counter drugs. Medication may be tried for controlling mucus production, but some may make the mucus thicker and harder to dislodge or make the child more irritable. Decongestants usually contain stimulants that can raise blood pressure and narrow blood vessels, both undesirable for people with MPS IV. Cough suppressants or medication that is too sedating may cause more problems with sleep apnea by depressing muscle tone and respiration. Swallowing large pills may be difficult for children with MPS IV due to their small tracheas, so liquid medication may be preferable. It is now recognized that frequent use of antibiotics can make them less effective when really needed.

Physical therapy

Joint stiffness is not a feature of MPS IV, but loose joints can be a problem. Intensive physical therapy will be needed to help an individual with MPS IV start walking again after neck, spine or leg surgery. Individuals with MPS IV should be as active as possible to maintain muscle strength and general health. Your child's doctor or physical therapist may be able to suggest ways of achieving this. It is important to keep a balance between avoiding risks and letting your child lead as normal a life as possible. Activities such as somersaults, head stands, contact sports, trampoline or diving should be avoided completely because of risk to the neck.

Individuals with MPS IV should be as active as possible to maintain muscle strength and general health.

Mobility

Many individuals with MPS IV remain ambulatory into their teens and adult life. Others may need to use a wheelchair from an early age, at least for getting around outdoors or for periods of longer activity. An electric wheelchair is vital to encourage independence. Consult your physical therapist or occupational therapist for advice.

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Anesthetics

Various management options and surgical procedures to manage the symptoms of MPS IV require that the person being treated be given an anesthetic. General anesthesia uses a medication or gas that "puts the person to sleep" before surgery. To make sure the person under anesthesia receives enough oxygen during surgery, a laryngeal mask airway (LMS) is used, if possible. In some cases, a LMA may not be possible and a tube is placed into the throat and connected to a machine that helps the person breathe.

Giving an anesthetic to an individual with MPS IV requires skill and should always be undertaken by an experienced anesthetist familiar with MPS IV. If the cervical spine is unstable, the individual with MPS IV is at risk if the neck is flexed while unconscious, and special precautions must be taken. Inform your child's school or any other caregivers of this in case you cannot be contacted in the event of an emergency. Consider an emergency letter or a medical bracelet to indicate potential difficulties with intubation (placement of the breathing tube). If you have to go to a different hospital in an emergency, tell the anesthetist there may be problems with the neck and possibly with intubation. 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 a flexible bronchoscope to place it gently. 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 with MPS IV, it is difficult to remove the breathing tube after surgery is completed. Advise physicians of the critical nature of this difficulty, and that many problems have occurred during anesthesia of individuals with MPS IV.

Giving an anesthetic to an individual with MPS IV requires skill and should always be undertaken by an experienced anesthetist familiar with MPS IV.

For any elective surgery in a child or adult with MPS IV, it is important to choose a pediatric or general anesthesiologist who has experience with difficult airways. This may require that the surgery be performed at a regional medical centre instead of a local hospital.

Topical anesthetics, such as "Emla" cream, used to freeze skin in order to more comfortably insert an IV line, may not be effective in individuals with MPS IV. Use of nitrous oxide (laughing gas) for initial anesthesia in the operating room should be discussed with the operating surgeon and anesthesiologist.

See additional information on anesthesia in our booklet entitled "Is Your Child Having an Anesthetic?" or in the Anesthesia Considerations section of the binder entitled "MPS IV: A resource for individuals and families affected by MPS IV".

Living with a child or adult with MPS IV

Education

Most children with MPS IV attend mainstream school and succeed academically. Achieving post-secondary education is highly possible; however, it is important to ensure that the school is aware of the resources required. 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 IV: A resource for individuals and families affected by MPS IV”, which is posted on the Canadian MPS Society’s website.

Puberty and reproduction

Adolescents with MPS IV will go through normal developments of puberty, although the onset of periods in girls may be delayed. Individuals with MPS IV are fertile. Women whose stature is significantly restricted may be advised not to become pregnant because of health risks. All children born to a parent with MPS IV are automatically carriers but none will have the disease unless the other parent also is a carrier.

Transition to independence

More information on medical transition is available in our binder “MPS IV: A resource for individuals and families affected by MPS IV”.

Individuals with MPS IV should be encouraged to be as independent as possible so that they can lead full and enjoyable lives. The teenage years may be difficult if those affected have restrictions imposed by their disease, but meeting or contacting other teenagers and adults who also have MPS IV may help. A power wheelchair may be a helpful mode of transportation and provide further independence and an adapted vehicle can help teens achieve independence through driving. Learning to use the bus will also help affected teens and adults get around in their communities. It is a good idea for teens and adults to wear “Medic-Alert” bracelets and carry medical wallet-cards to ensure medical personnel are aware of any crucial health concerns in the case of an emergency.

Employment

Many individuals with MPS IV do well at a variety of different jobs. Some advice: Begin your search for the right job by assessing your physical capabilities. It’s important to be practical about what you can and cannot do. Instead of using your limitations as a restriction, use them as a guide to finding the right career. A career counsellor can help you explore a type of work that you might enjoy and that is well suited to your individual strengths and interests. Section 15 of the Canadian Charter of Rights and Freedom guarantees equality rights plus freedom from discrimination for people who have a physical or mental disability. The Employment Equity Act (EEA) of 1995 ensures that persons with disabilities are granted full and equal access to employment and opportunity. An employer must accommodate the disabilities of employees, prospective employees, and clients or customers. More information is available in our binder “MPS IV: A resource for individuals and families living with MPS IV”.

Compassionate leave legislation is overseen in Canada at the provincial level. A summary of the elements of the compassionate care leave provisions in employment standards in legislation published by Human Resources and Skills Development Canada can be found online at www.hrsdc.gc.ca/eng/labour/labour_law/esl/compass.shtml.

Home adaptations

Appropriately adapted living accommodations will greatly enhance the ability of an individual with MPS IV to develop independent living skills. Where stature is severely restricted, kitchen and bathroom facilities at a low level will be required. If mobility is restricted to such an extent that a wheelchair is used, plans for any home adaptations will need to allow adequate space to accommodate this. Additional information about home adaptations can be found in the booklet published by the Canadian MPS Society, “Daily Living with MPS and Related Diseases”.

Psychosocial issues

To date, there has been no research carried out exploring the psychosocial development of individuals affected with MPS IV, so it is not possible to make definitive statements about this subject. As a parent of a child or young adult with MPS IV, it is important to consider how their disability may cause them to experience additional challenges in life.

Some children and young adults with MPS IV may adapt socially and emotionally by becoming socially inhibited, or by internalizing problems or developing an aggressive, outgoing personality. Adolescence may be more of a challenge as they have to experience all of the physiological and psychosocial changes as well as any disease-related changes or limitations. Developing the necessary skills to lead independent adult lives can be challenging although important to achieving social maturity. Referral for counselling is recommended if problems such as depression are seen in teenagers and young adults with MPS IV.

Parents and family members may need emotional support to help them cope. Families may need access to respite care, individual counselling, and support groups. The Canadian MPS Society has respite funding available through its Family Assistance Program. Please visit the Society’s website or call its head office for more information.


Matt

Melanie

Financial support and supportive care

Individuals with MPS IV 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 IV resource binder "MPS IV: A resource for individuals and families living with MPS IV"). You may also wish to investigate private agencies and foundations. The Canadian MPS Society's Family Assistance Program provides financial aid 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.

Living with MPS IV

Disease severity varies significantly for individuals with MPS IV, and it is not possible to predict the expected life span for a given individual. Those on the more slowly progressing end of the disease spectrum may have a reasonably normal lifespan. However, the availability of new and ever-improving treatments as well as other surgical procedures provides hope for better future outcomes for individuals affected by MPS IV.

The Canadian MPS Society has funding, including respite funding, available through its Family Assistance Program. Please visit the Society's website or call its head office for more information.

Specific treatment of MPS IV

Overview

The goals of managing MPS IV are to improve quality of life, to slow down the progression of the disease, and to prevent permanent tissue and organ damage. Currently there is no cure for MPS IV; however, early intervention may help prevent irreversible damage. Treatment options for MPS IV 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. HSCT does not, however, correct the skeletal structural defects, so at this time HSCT is not recommended for MPS IV.

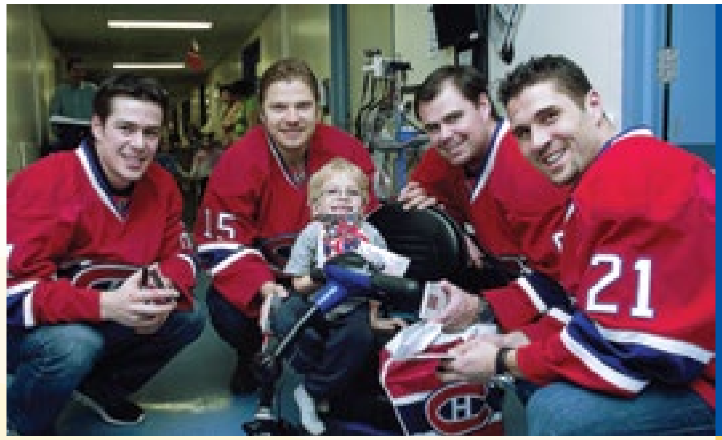
Enzyme replacement therapy (ERT)

Enzyme replacement therapy (ERT), although not a cure, is a potential treatment, but data from ongoing clinical trials will have to be analyzed before determining the safety and efficacy of this treatment.

The goals of managing MPS IV are to improve quality of life, to slow down the progression of the disease, and to prevent permanent tissue and organ damage.

Research for the Future

The Canadian MPS Society is committed to finding cures for MPS and related diseases, and therefore 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.



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There are several different types of mucopolysaccharide (MPS) diseases. This booklet is intended as an introduction to mucopolysaccharidosis, type IV (MPS IV). A more thorough resource binder entitled "MPS IV: A resource for individuals and families living with MPS IV" 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 IV. This booklet is not intended to replace medical advice or care. The contents of and opinions expressed in "A Guide to Understanding MPS (Mucopolysaccharidosis) IV" 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.

Melissa and Papuk

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
- Bereavements 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**