A Guide to Understanding Mucopolysaccharidosis (MPS) VI

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 VI (MPS VI, pronounced **mew**·ko·**pol**·ee·**sak**·ah·ri·**doh**·sis six) is one of the rarer mucopolysaccharide diseases. It takes its name from two French doctors, Dr. Maroteaux and Dr. Lamy, who first described the condition in 1963. Historically, MPS VI has been divided into severe and mild forms. It is now clear that this disease is more complex and more variable than was previously assumed. It is now perhaps more appropriate to view MPS VI as a continuous spectrum of disease, with the most rapidly progressing individuals on one end and the more slowly progressing individuals on the other end, and a wide range of different severities in between. The term attenuated instead of mild is used to describe the less severe (slowly progressing) patients because the effects of the disease on a less severe patient are too significant to be considered mild. MPS VI varies enormously in the severity of the problems it causes. It is important to remember this variation if you are the parent of a newly diagnosed child.

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

This booklet describes most of the possible problems that may arise for an individual with MPS VI; however, your child may not experience them all, or be severely affected by them. In fact, some individuals have very few physical problems and are able to lead relatively normal lives.

All individuals with MPS VI have deficiency of the enzyme arylsulfatase B (ASB, pronounced **ar**·il·**sul**·fa·tace **B**), which results in the accumulation of glycosaminoglycans (GAG, pronounced **gly**·cose·a·**mee**·no·**gly**·cans), previously called mucopolysaccharides, inside special parts of the cell called lysosomes. This is why MPS VI 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 patients with MPS VI.

As yet, there is no cure for individuals affected by MPS VI, but there are ways to manage the challenges they will have, and to help them enjoy life. Hematopoietic stem cell transplant (HSCT) has been used to treat some patients with MPS VI successfully. Enzyme replacement therapy (ERT), approved by the FDA in 2005, is another available treatment. Scientists who study MPS continue to look for better and more effective ways to treat these diseases, and it is likely that individuals with MPS VI will have more options available to them in the future.

Individuals with MPS VI have a deficiency of the enzyme arylsulfatase B, which results in the accumulation of glycosaminoglycans (GAG). This accumulation is responsible for numerous problems that affect individuals with MPS VI.

What causes MPS VI?

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 VI, 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 VI 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 screw-driver works on screws and a hammer works on nails.

Individuals with MPS VI have a defect in the gene that instructs the body to make a specific enzyme called arylsulfatase B (ASB), which is essential in the breakdown

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of certain GAG called dermatan sulfate (DS). The incompletely broken down dermatan sulfate remains stored inside cells in the body and begins to build up, causing progressive damage. The GAG itself is not toxic, but the amount of it and the effect of storing it 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.

Is it possible to predict the severity of MPS VI?

All individuals with MPS VI lack the same enzyme, and currently there is no reliable way of telling how severe the disease will be from biochemical tests. Detailed studies have shown that in individuals with attenuated MPS VI, a very small amount of active enzyme is working as it should, resulting in the attenuated form of MPS VI.

Jasper

How common is MPS VI?

It has been estimated that about 1 in 215,000 births is affected by MPS VI. Although MPS VI 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 VI inherited?

MPS VI 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 copies of the gene in an individual are affected. MPS VI is that type of genetic disease. Most families who have a child with MPS VI do not have a family history of genetic problems. MPS VI seems to show up suddenly even though the genetic mutation (the actual "spelling mistake" in the genetic code) 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.

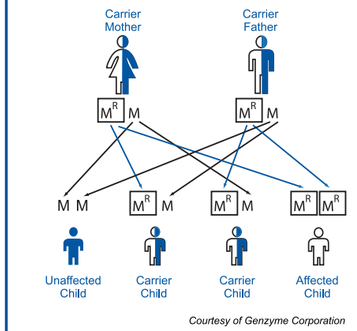
Each enzyme in the body is produced by two copies of a gene - one from the mother and one from the father. If one gene happens to be non-functioning (as is the case for a carrier parent), then the body may produce only 50 percent of the normal level of enzyme associated with that gene. However, 50 percent of the normal enzyme level is enough to keep the individual who is a carrier from having any symptoms of MPS VI. 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 VI.

This is why MPS VI is a genetic recessive disease. Both parents of an affected individual are "carriers" of this 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 VI and thus a three out of four chance of not having MPS VI. The non-affected children of carrier parents have a 2 out of 3 chance of being carriers, like the parents.

All family members 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.

MPS VI is a genetic recessive disease. All families 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.



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 VI

How is MPS VI diagnosed?

Doctors may consider testing for MPS VI 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 VI, the doctor will typically first do a urine test to look for GAG levels that are higher than normal. The results are compared to GAG levels that are known to be normal for 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 VI; 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 VI, the enzyme activity levels are much lower or absent. If the urine GAG test is normal but there is a strong suspicion of MPS VI, enzyme testing should be considered.

Violet

MPS VI is a highly variable disease

MPS VI has a highly variable phenotype (phenotype refers to the clinical features of the condition). Key variable features include the age at which symptoms and signs develop as well as the rate of progression of these symptoms. 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. There is currently no single reliable way of telling how severe the disease will be. The age at which a child begins to develop symptoms, as well as the types of gene changes that an individual with MPS VI has, are clues to the severity of the disease, but only after detailed assessment and testing of a child can a physician make an educated guess as to where the child falls on the disease spectrum.

DNA tests do not always provide the information that leads to the determination of the severity of MPS VI. Many different kinds of mutations (permanent changes) in the gene that produces the enzyme (ASB) 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 can be difficult or impossible to predict expected severity of disease.

There is therefore no perfectly reliable way to determine the exact course of disease for individuals with MPS VI. 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 VI 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 VI 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 VI is critical. The earlier MPS VI is diagnosed, the sooner potential treatment options can be explored and supportive care started to help you or your loved one, and potentially prevent some of the permanent damage the disease may cause.

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.

Prenatal diagnosis

If you have a child with MPS VI, or if you and your partner are known to carry MPS VI, 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 for having additional children, such as egg or sperm donation, while limiting the probability that they will have or be carriers for MPS VI.

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Clinical concerns related to MPS VI

The section below highlights the clinical features of MPS VI disease and is largely based on historical data from patients. It does not take into account the impact of the recent emergence of treatments for MPS VI, either enzyme replacement or other symptom-based management approaches.

Growth	Growth in height is usually significantly less than normal for individuals with rapidly progressing MPS VI, but varies according to the severity of the disease. Individuals with the most severe form of MPS VI may not grow taller than 91 – 122 cm (3 to 4 feet). In contrast, individuals with attenuated MPS VI usually grow to a relatively normal height, reaching 152 cm (5 feet) or more.
Intelligence	Intelligence is not affected by MPS VI; many affected individuals are of above-average intelligence.
Physical appearance	Individuals with MPS VI, particularly those with severe disease, look remarkably similar due to their large heads, short necks, chubby cheeks, broad noses with a flat bridge and wide nostrils. Their shoulders are narrow and rounded and their stomachs tend to protrude. The hair on their bodies is coarser and more abundant than usual, and their eyebrows are bushy. Their skin may become thickened and less elastic than usual.
Nose, throat, chest and ear problems	The problems described in this section occur more commonly in rapidly progressing individuals. Individuals with attenuated MPS VI are likely to have fewer and less severe symptoms.
Runny nose	Typically, the bridge of the nose is 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. One of the common features of individuals with severe MPS VI is the chronic discharge of thick mucous from the nose (rhinorrhea), and chronic ear and sinus infections.
Throat	The tonsils and adenoids often become enlarged and can partly block the airway. This, combined with a short neck, contributes to problems in breathing. The windpipe (trachea) becomes narrowed by storage material and may be more floppy, or softer than usual, due to abnormal cartilage rings in the trachea. Nodules or excess undulations of tissue can further block the airway.
Chest	The shape of the chest is frequently abnormal and the junction between the ribs and the breastbone (sternum) is not as flexible as it should be. The chest is therefore rigid and cannot move freely to allow the lungs to take in a large volume of air. The muscle at the base of the chest (diaphragm) is pushed upward by the enlarged liver and spleen, further reducing the space for the lungs. When the lungs are not fully cleared, there is an increased risk of infection (pneumonia).
Breathing difficulties	Many affected individuals breathe very noisily even when there is no infection. At night they may be restless and snore. Sometimes the individual may stop breathing for short periods while asleep (sleep apnea). Pauses of up to 10-15 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 is 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 can be treated in some patients by removing the tonsils and adenoids (adenoids may re-grow), opening up the airway with night time ventilation such as 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 oxygen levels 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 the breathing is blocked, how much air the child is taking into the lungs during sleep, and how much effect this has on his or her body. CPAP or BiPAP can open the airway at night using air pressure. A mask is placed on the face each night and air is pumped into the airway to keep it from collapsing. This may seem to be an extreme measure, but many individuals are able to tolerate it; it can greatly improve the quality of sleep, and prevent or reduce the risk of heart failure caused by low night time oxygen levels. In severe cases of sleep apnea, a tracheotomy (a hole in the airway made in the front of the neck) may be needed. Most families will try to avoid a tracheotomy because it is invasive and disruptive; however, many doctors feel that many individuals with MPS VI would benefit from receiving a tracheotomy earlier to improve their night time breathing and overall health. Chest postural drainage can be helpful in clearing secretions from the lungs. A physiotherapist can teach parents and someone at the child's school how to do this.

Clinical concerns related to MPS VI

Treatment of respiratory infections

Medication often affects individuals with MPS VI differently, so it is essential to consult your doctor rather than using over-the-counter products. Medication for controlling mucous production may not help. Medication 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 VI 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 VI 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.

Mouth

Individuals with MPS VI generally have thick lips and an enlarged tongue. Gum ridges are broad. The teeth are 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, give your child daily fluoride tablets or drops. For severely affected individuals, 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.

Since individuals with MPS generally have heart problems, 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, 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 all individuals with MPS VI, severe to attenuated; however, heart disease may not develop or cause any real problems until later in the individual's life. Heart disease is a major cause of death in individuals with MPS VI. Medications are available to help manage the heart problems that occur with MPS VI. Cardiomyopathy (weak heart muscle) and endocardiofibroelastosis (stiff heart) are conditions that can occur in young individuals with severe MPS VI. Coronary artery disease caused by GAG storage in the heart blood vessels is similar to that seen in older adults and can lead to death. Some individuals with attenuated MPS VI may develop problems with the aortic or mitral valves; they may have slowly progressive valvular heart disease for years without any apparent clinical effects. As 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.

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 and a small amount of blood may shoot backward, leading to turbulence and a murmur. Most individuals with MPS VI have some degree of murmur or leakage.

Since heart problems occur so frequently in MPS VI, all individuals with MPS VI 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.

In individuals who are severely affected, the muscle of the heart may be damaged by storage of GAG (cardiomyopathy) and the heart may also be put under strain by having to pump blood through abnormal lungs (corpulmonale or right heart failure). A number of affected individuals have high blood pressure.

Occasionally the coronary arteries of individuals with moderate to severe MPS VI may become narrowed and cause episodes of chest pain (angina). If your child is distressed and crying and is at the same time pale and sweating while keeping still, you should consult your doctor who may refer your child for an electrocardiogram (ECG or EKG).

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

Liver and spleen

Individuals with MPS VI usually have enlarged livers and spleens (hepatosplenomegaly). caused by accumulation of GAG. The enlarged liver does not usually cause liver problems, but it can interfere with eating and breathing.

Clinical concerns related to MPS VI

Abdomen and hernias

In most individuals with MPS VI, 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 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 VI 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, which 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, supplemented by an X-ray if necessary, 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. As the episodic diarrhea in some individuals with MPS VI appears to be affected by diet, elimination of some foods can be helpful.

If antibiotics are the cause, eating plain, live-culture yogurt is often helpful during episodes of diarrhea. This provides a source of lactobacillus to help prevent the growth of harmful organisms within the bowel wall, which can cause diarrhea or make it worse. A diet low in roughage may also 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, your doctor may prescribe laxatives or a disposable enema.

Bones and joints

Individuals with MPS VI tend to have significant problems with bone formation and growth. This leads to bone problems (dysostosis multiplex) as well as neurological problems if nerves are compressed by bone.

Spine

The bones of the spine (vertebrae) normally line up from the neck to the buttocks. Individuals with MPS VI often have poorly formed vertebrae that may not stably support each other. One or two of the vertebrae in the middle of the back are sometimes slightly smaller than the rest and set back in line. This backward slippage of the vertebrae can cause an angular curve (kyphosis or gibbus) to develop, but does not usually require treatment. In the attenuated form of MPS VI, spinal cord compression is common. The compression is due to accumulation of GAG in the membrane surrounding the spinal cord. Doctors will want to monitor this carefully and arrange surgical treatment if necessary.

Neck

The neck is short and sometimes restricted in movement. The bones that stabilize the connection between the head and neck can be malformed (odontoid dysplasia) in individuals with the severe form of MPS VI, making the neck unstable. Fusion surgery is required to connect all the bones to each other so they do not slip further. If severe pain or pain associated with weakness or tremors in the lower legs occurs, the child should have studies of the neck (MRI and flexion-extension X-rays) to evaluate for slippage of the neck vertebrae, which can cause spinal cord compression.

Parents of children with MPS VI should be cautious when handling the area of the spine around the neck. Children with MPS VI should avoid high risk activities such as contact sports and gymnastics, including trampolines.

Scoliosis

Abnormal curvature of the spine, or scoliosis, can also occur and, if severe, may require intervention. In general, fusion with bone is the best alternative as hardware-like rods are not tolerated well. Soft bone makes the surgery and recovery difficult and many patients need multiple procedures.

Joints

Joint stiffness is common in MPS VI and the maximum range of movement of all joints may become limited. Later in the individual’s life joint stiffness may cause pain, which may be relieved by 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 avoid stomach irritation and ulcers.

Clinical concerns related to MPS VI

Hands	The shape of the hands in children with MPS VI is very noticeable; the hands are short and broad with stubby fingers. The fingers stiffen and gradually become curved, and the tips of the fingers can become permanently bent over. Finger joints may become locked, called trigger finger. Trigger fingers may be corrected with heat and massage or, if necessary, surgery. Individuals with MPSVI may also experience pins and needles/numbness in the hands from carpal tunnel syndrome (see below).
Legs and feet	Many individuals with MPS VI stand and walk with their knees and hips flexed. This, combined with tight Achilles tendons, may cause them to walk on their toes. They sometimes have knock-knees but this is very unlikely to need treatment, although severe knock-knees can be treated by surgery on the tibia bones. The feet are broad and may be stiff with the toes curled under, rather like the hands. Lack of flexibility in the hips and legs often prevents children from sitting cross-legged (the seating position of choice for most kindergarten teachers) or putting on their own socks and shoes.
Skin	Individuals with MPS VI tend to have thickened and tough skin, making it difficult to draw blood or place intravenous catheters. Excess hair on the face and back is common in severely affected individuals. Sweating and cold hands and feet are also common problems, and are possibly related to the heart, circulation, or other mechanisms that control temperature regulation. Periodic blue or cold hands or feet should be evaluated by a cardiologist to determine if the heart or the aorta might be responsible for the problem.

Neurological problems: brain, senses and nerves

Brain	The brain and spinal cord are protected from jolting by the cerebrospinal fluid that circulates around them. In some individuals with MPS VI, particularly those with severe MPS VI, circulation of the fluid can slowly (over months to years) become blocked so that it cannot be taken back into the bloodstream. The blockage (communicating hydrocephalus) causes increased pressure inside the head, which can press on the brain and cause headaches, incontinence, delayed development, expansion of the skull and ultimately blindness. If hydrocephalus is suspected, an imaging study of the brain (CT or MRI scan) should be performed. A lumbar puncture with pressure measurement (ideally pressure monitoring) is another way to assess if hydrocephalus exists. If a doctor confirms an individual has communicating hydrocephalus, it can be treated by the insertion of a thin tube (shunt) that drains fluid from the brain into the abdomen (ventriculoperitoneal or VP shunt). The shunt has a pressure-sensitive valve that allows spinal fluid to be drained when the pressure around the brain becomes too high. The lack of papilledema (swelling around the optic disk) or normal-sized ventricles does not rule out hydrocephalus in individuals with MPS VI.
Eyes	The eye problems described here are common in MPS VI. The circular window at the front of the eye (cornea) becomes cloudy due to storage of GAG, which disrupts the clear layers of the cornea. If corneal clouding is severe it may reduce sight, especially in dim light. Some individuals with MPS VI cannot tolerate bright lights, as the clouding causes uneven refraction of the light. Wearing caps with visors, or sunglasses, can help. A corneal transplant can result in improved vision for most individuals with MPS VI; however, the transplant may need to be repeated over time. Changes to the retina or glaucoma (increased pressure) should be checked during an eye examination. Storage in the retina can result in loss of peripheral vision and night blindness. It is often difficult to determine which combination of problems is responsible for a decrease in eyesight. An ophthalmologist can perform special studies to help determine whether the problem is caused by how light gets in the eye (the cornea) or to how the eye responds to light (the retina or optic nerve disease).
Ears	Some degree of deafness is common in MPS VI. It may be conductive or nerve (sensorineural) deafness or both (mixed deafness) and may be made worse by frequent ear infections. Individuals with MPS VI should have their hearing monitored regularly so that problems can be treated early, in order to maximize learning and communication.
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 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 is made through the eardrum (myringotomy) to remove the fluid by suction. A small ventilation tube is then 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 fall out. If this happens, the surgeon may decide to use T-tubes, which usually stay in place much longer. Once the 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. This may accompany conductive deafness, in which case it is referred to as mixed deafness. Nerve or conductive deafness can be managed with hearing aids in most patients. Hearing aids are generally underutilized in MPS diseases.

Clinical concerns related to MPS VI

Carpal tunnel syndrome and other nerve entrapments or compression

Individuals with MPS VI sometimes experience pain and loss of feeling in the fingertips caused by carpal tunnel syndrome. The wrist, or carpus, consists of eight small bones known as the carpals, which are joined by fibrous bands of protein called ligaments. Nerves have to pass through the wrists in the space between the carpal bones and the ligaments. Thickening of the ligaments causes pressure on the nerves, which can cause irreversible nerve damage. The nerve damage will cause the muscle at the base of the thumb to waste away and will make it difficult for a child to oppose his or her thumb in a position for a normal grasp. Although your child may not complain of pain, carpal tunnel syndrome may be severe. If your child seems to have pain in the hands, particularly at night, an electrical test called a nerve conduction or electromyograph study should be performed, which 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 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. Uncorrected carpal tunnel syndrome may result in the loss of sensation in the hands and fingers. Carpal tunnel syndrome can be corrected through surgery; however, it may return in the future requiring additional surgeries.

A similar type of nerve compression can happen elsewhere in the body, such as the feet, and cause localized weakness or pain.

Individuals with MPS VI sometimes experience pain and loss of feeling in the fingertips caused by carpal tunnel syndrome.

Isaac

General treatment and management

Diet

There is no scientific evidence that a particular diet has any helpful effect on individuals with MPS VI, and symptoms such as diarrhea tend to come and go naturally. Some parents 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, has 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, foods can be reintroduced one at a time to test whether any particular item seems to increase the child's symptoms.

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

Swallowing may become difficult as an individual with MPS VI gets older and the disease progresses. If 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. It is often difficult for a family to consider alternate means of feeding, such as a gastrotomy tube (G-tube), and consultation with your medical geneticist and pediatric surgeon can help with your decision making.

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Physiotherapy/sports

Joint stiffness is a common feature of MPS VI. Limitation of movement and joint stiffness can cause significant loss of function. Range-of-motion exercises (passive stretching and bending of the limbs) may offer some benefits in preserving joint function, and should be started early although exercises that cause pain should be avoided. Once there is significant limitation of movement, it may not be possible to increase range-of-motion, but it may minimize further limitation. Individuals with MPS VI should be as active as possible to maintain joint function and improve their general health; however, contact sports should be avoided. Your child's doctor, a physical therapist, or a recreation therapist may be able to suggest ways of achieving optimal fitness through a combination of daily activities, adapted sports and passive range-of-motion exercises.

Individuals with MPS VI should be as active as possible to maintain joint function and improve general health; however, contact sports should be avoided. Your child's doctor or physical therapist may be able to suggest ways of achieving this.

Mobility

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

Pain

Many individuals with MPS VI 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 or joint specialist such as a rheumatologist.

Anesthetics

Various management options and surgical procedures to manage the symptoms of MPS VI 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 (LMA) is used, if possible. In some cases, a LMA may not be possible and an endotracheal (ET) tube is placed into the throat and connected to a machine that helps the person breathe.

Giving an anesthetic to an individual with MPS VI requires skill and should always be undertaken by an experienced anesthetist familiar with MPS VI. If the cervical spine is unstable, the individual with MPS VI 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 VI, 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 VI.

For any elective surgery in a child or adult with MPS VI, 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. It may also be helpful to meet with the anesthetic team to plan the procedure prior to the surgical date.

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 VI. 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 "Is Your Child Having an Anesthetic?" or in the Anesthesia Considerations section of our binder "MPS VI: A resource for individuals and families affected by MPS VI".

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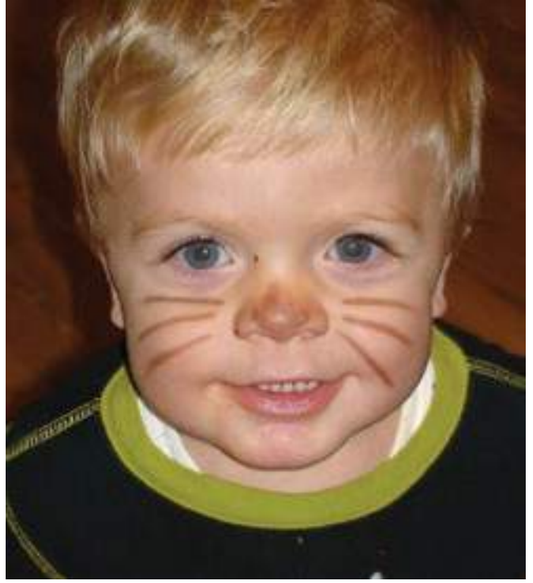

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Education

The majority of children with attenuated MPS VI 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 VI: A resource for individuals and families affected by MPS VI", which is posted on the Canadian MPS Society's website.

Puberty and reproduction

Adolescents with MPS VI will go through normal developments of puberty, although the onset of periods in girls may be delayed. Individuals with MPS VI 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 VI are automatically carriers but none will have the disease unless the other parent also is a carrier.

Transition to independence

As those with attenuated MPS VI reach their teen years, it is helpful for them to start a gradual transition to advocate for their own medical care. More information on medical transition is available in our binder "MPS VI: A resource for individuals and families affected by MPS VI". Individuals with MPS VI 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 VI may help. If needed, a power wheelchair may be a helpful mode of transportation and provide further independence, and an adapted vehicle can help teens and young adults with significant mobility issues 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

Most individuals with attenuated MPS VI 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 VI: A resource for individuals and families living with MPS VI".

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.

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Home adaptations

Appropriately adapted living accommodations will greatly enhance the ability of an individual with MPS VI 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 Canadian MPS Society's booklet "Daily Living with MPS and Related Diseases", and funding is available through the Society's Family Assistance Program.

Psychosocial issues

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

Some children and young adults with MPS VI 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 VI.

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.

Isaac

Taking a break

Caring for a severely affected child is hard work. Parents need a break to rest and enjoy activities, and this may not be possible when their affected child is with them. Brothers and sisters need their share of attention, and need to be taken on outings that may not be feasible with a severely affected child. Many parents use some form of respite care or have someone come to help at busy times.

Financial support and supportive care

Individuals with MPS VI 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. If a social worker is attached to your medical team, he or she can also help you with useful resources.

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 VI resource binder "MPS VI: A resource for individuals and families living with MPS VI"). 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 VI

Overview

The goals of managing MPS VI 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 VI; however, early intervention may help prevent irreversible damage. Treatment options for MPS VI 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), as well as those aimed at treating the underlying enzyme deficiency.

Hematopoietic Stem Cell Transplant (HSCT)

The goal of HSCT for MPS VI is to restore the activity of the deficient enzyme, which may improve such symptoms as enlarged liver and spleen, joint stiffness, sleep apnea, heart disease, hydrocephalus and hearing loss. HSCT does not correct bone or eye problems, however, so post-transplant, individuals frequently require further therapies and treatments. Bone marrow and cord blood transplants are types of HSCT. 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)

ERT for MPS VI was approved by the FDA in 2005. Naglazyme® is a manufactured version of the body's natural ASB enzyme. Naglazyme improves endurance (walking ability and stair climbing) and decreases the levels of GAG in the urine. Treatments of Naglazyme are given weekly through intravenous infusions. For parents to fully understand the risks, benefits and limitations of ERT, it is important to talk with physicians familiar with MPS VI ERT and families undergoing this treatment. The Canadian MPS Society can put you in touch with physicians and families so you can become better informed before reaching a decision.

Living with MPS VI

Disease severity varies significantly for individuals with MPS VI, 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 all individuals affected by MPS VI.

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.

Violet

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

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**