National MPS Society

Support for Families. Research for a Cure.

A Guide to Understanding MPS VII

Sly Syndrome

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

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Pictured on the cover: ALISYNN, MATTHEW

Introduction

Mucopolysaccharidosis (MPS) VII is a mucopolysaccharide disease originally described by Dr. William Sly in 1972. Also referred to as Sly syndrome, MPS VII is caused by a deficiency of the lysosomal enzyme, β-glucuronidase. Though it is the rarest of the MPS diseases, it shares many features common to other MPS diseases—it is progressive in nature and affects many of the body's systems. Because it is so rare a disease, there are few detailed reports about affected individuals in medical literature. However, like all other MPS diseases, the clinical course of MPS VII can vary greatly from very severe to mild. In the most extreme case, children are born with a condition called hydrops fetalis. This is a very severe condition in which the child retains an enormous amount of fluid throughout the body. Infants with hydrops fetalis rarely survive beyond a few weeks to a few months of age. Most individuals with MPS VII are less severely affected and have clinical symptoms similar to several other MPS diseases. It is now clear, based on current understanding of the enzyme and its gene, that MPS VII comprises a wide spectrum of severity from very severe (hydrops fetalis) to attenuated disease. The term "attenuated" instead of "mild" is used to describe less severe individuals because the effects of the disease on a less severe individual are too significant to be considered mild.

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).

All individuals with MPS VII have a deficiency of the enzyme β-glucuronidase, which results in the accumulation of β-glycosaminoglycans (GAG), previously called mucopolysaccharides, inside special parts of the cell called lysosomes. This is why MPS VII is part of a larger family of diseases called the lysosomal storage diseases (LSDs). The accumulation of GAG is responsible for numerous problems that affect individuals with MPS VII.

Individuals with MPS VII have a deficiency of the enzyme β-glucuronidase, which results in the accumulation of glycosaminoglycans. This accumulation is responsible for numerous problems that affect individuals with MPS VII.

As yet, there is no cure for individuals affected by these diseases, 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 other types of MPS diseases, but there has been little or no experience in individuals with MPS VII. Experiments in mouse and dog models of MPS VII suggest that HSCT may be an effective form of therapy. Enzyme replacement therapy (ERT) has been developed for several of the MPS diseases. ERT helps the physical problems in individuals with MPS, but it does not help the central nervous system. However, ERT is not yet available to individuals with MPS VII. Scientists who study MPS VII continue to look for better and more effective ways to treat these diseases, and it is likely that individuals will have more options available to them in the future.

What causes MPS VII?

Glycosaminoglycans (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 accumulates and causes MPS VII , 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 old ones—a recycling process. The breaking down of GAG occurs in a part of the cell called the lysosome. That is why MPS VII is considered one of the approximately 40 different kinds of LSDs. All LSDs are caused by the inherited deficiency of individual enzymes and are very rare. This ongoing recycling process is required to keep your body healthy. The breakdown and recycling process requires a series of special biochemical tools called 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.

Individuals with MPS VII are missing one specific enzyme called β-glucuronidase, which is essential in the breakdown of certain GAG called dermatan sulfate and heparan sulfate. The incompletely broken down dermatan sulfate and heparan sulfate remain stored inside cells in the body and begin 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.

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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.

How common is MPS VII?

MPS VII is one of the least common forms of MPS with an estimated frequency of less than 1 in 250,000 births. Although MPS VII is individually rare, the incidence of all MPS diseases 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.

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

How is MPS VII inherited?

MPS VII is a genetic disease. When most people 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 VII is this type of genetic disease. Most families who have a child with MPS VII do not have a family history of genetic problems. MPS VII 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. All humans are formed with two complete sets of genes—one set from each parent. So any individual has half of his or her genes from his or her mother and half from his or her father. Together, the individual has 100 percent of the genes required to live.

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 defective (as is the case for a carrier), 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 enzyme to keep the individual who is a carrier from having any symptoms of MPS VII. If, however, the genes 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 VII.

This is why MPS VII is a genetic recessive disease. Both parents are "carriers" of the defective gene—each parent has one normal copy of the gene that produces the enzyme and one defective copy of the gene that cannot properly produce the enzyme. However, one normal 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 normal gene and therefore no disease. Each child also has a one in four (25 percent) chance of inheriting the defective gene from both the mother and from the father and thus being affected with MPS VII. There is a two in three (67 percent) chance that unaffected brothers and sisters of individuals with MPS VII will be carriers of the defective gene that causes MPS VII. This is why individuals who are related to each other should not conceive children. The probability of related parents having similar recessive gene mutations increases dramatically.

How is MPS VII diagnosed?

Doctors may consider testing for MPS VII 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 VII, the doctor will typically first do a urine test to look for levels of GAG that are higher than normal. The results are compared to levels of GAG that are known to be normal for various ages. Most, but not all, individuals with MPS have GAG levels in their urine that are higher than those of individuals without MPS.

A urine test is only one of the first steps in diagnosing MPS VII; 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 VII, the enzyme activity levels are much lower or absent.

Early diagnosis of MPS VII is critical. The earlier MPS VII 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 VII, it is possible to have tests during a subsequent pregnancy to find out whether the baby you are carrying is affected. It is important to consult your doctor early in the pregnancy if you wish to perform these tests. The decision to have prenatal testing is complex and personal. Talking with your genetic counselor or doctor can help you explore these options and other strategies, such as egg or sperm donation, for having additional children while limiting the probability they will have or be carriers for MPS VII.

Clinical problems in MPS VII

Growth

Growth in height is usually significantly less than normal but varies according to the severity of the disease.

Intelligence

Individuals with the severe form of MPS VII experience progressive storage of GAG in the brain that is primarily responsible for the slowing of development by 1–3 years of age, followed by a progressive regression in skills until death. There is a great variation in the

severity of the condition, however; some children with MPS VII may say only a few words, others learn to walk well and to read a little. They can enjoy nursery rhymes and simple puzzles. Parents emphasize that it is important to help babies and children affected by MPS VII learn as much as they can before the disease progresses. Even when the child starts to lose the skills he or she has learned, there may still be some surprising abilities left. Children will continue to understand and to find enjoyment in life even if they lose the ability to speak.

It is important to remember that MPS VII is a spectrum. Some individuals have milder physical problems and learning disabilities, while others have more severe physical problems and normal intelligence.

Individuals with MPS VII commonly have other medical problems that can hamper their learning and performance, including chronic ear infections, poor vision, poor hearing, communicating hydrocephalus and sleep apnea. Adequate treatment of these medical problems can improve their function; therefore, comprehensive medical assessments should be performed in individuals with significant developmental decline.

Some individuals with MPS VII may have normal or near normal intelligence with mild physical involvement. It is important to remember that MPS VII is a spectrum. Some individuals with attenuated MPS VII have milder physical problems and learning disabilities, while others have more severe physical problems and normal intelligence.

Physical appearance

Individuals with MPS VII look remarkably similar to others with MPS diseases due to the coarsening of their facial features, short noses, flat faces and large heads. Their heads tend to be longer than normal from front to back with a bulging forehead (scaphocephalic).

To understand the reason for the abnormal skull shape, it is important to understand more about how the bones of the skull form to create the shape of the skull. Babies' skulls are soft and the individual cranial bones are separated by thin fibrous tissue called sutures. In the front above the forehead and in the back near the hair whorl are the anterior (front) and posterior (back) fontanelles, or soft spots, which close during the first few years. In MPS VII, the suture along the top of the head fuses earlier than normal so that the skull expands more in the front and the back creating the long

head shape and prominent forehead. There is often a ridge across the forehead where the skull has closed prematurely.

The nose is broad with a flat bridge and wide upturned nostrils. The eye sockets are shallow and the eyes protrude slightly. The tongue is enlarged and may stick out. The hair on the body is coarser and more abundant than usual. They have protruding bellies and stand and walk with a bent-over stance due to joint contractures at the hips, shoulders, elbows and knees.

The appearance of individuals with attenuated MPS VII is extremely variable. Adults are often stocky in build and their trunks are shorter than their limbs. The neck may be short and stiff.

Nose, throat, chest and ear problems

The problems described in this section generally occur in more severely affected individuals. Individuals with attenuated MPS VII 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. Individuals with MPS VII may have chronic discharge of thick mucus from the nose (rhinorrhea) and chronic ear and sinus infections.

Throat

The tonsils and adenoids often become enlarged and 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 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. They may fear their child is dying. If this is happens, the child's oxygen level may be low when sleeping which can damage the heart over time. If a parent notices significant choking or episodes of interrupted breathing, the child should be evaluated by a sleep specialist using a polysomnogram. 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, opening up the airway with nighttime continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) or tracheotomy, as discussed in the following paragraphs.

Many affected individuals breathe very noisily even when there is no infection.

Management of breathing problems

The doctor may want the child to be admitted to the hospital overnight for a sleep study. Monitors are placed on the skin and connected to a computer to measure the levels of oxygen in the blood, breathing effort, brain waves during sleep and other monitors of the body's function. From this study, the doctors can assess how much blockage to breathing is present, how much trouble your child is having moving air into the lungs during sleep, and how much effect this has on his or her body.

Removal of tonsils and adenoids will help in some cases to lessen the obstruction and make breathing easier, but adenoid tissue may grow back.

CPAP or BiPAP can open the airway at night using air pressure. This treatment involves placing a mask on the face each night and having air 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 because it can greatly improve the quality of sleep, as well as help prevent or reduce the risk of heart failure caused by low oxygen levels at night. In severe cases of sleep apnea with heart failure, a tracheotomy (a hole into the airway made in the front of the neck) may be needed. Most families will try to avoid a tracheotomy because it is so invasive and disruptive. However, many doctors feel that individuals with MPS VII would benefit from receiving a tracheotomy earlier than they generally do for improving their nighttime breathing and overall health.

Chest postural drainage can be helpful in clearing secretions from the lungs. A physiotherapist will be able to teach parents and someone at the child's school how to do this.

Treatment of respiratory infections

Drugs often affect individuals with MPS VII differently, so it is essential to consult your doctor rather than using over-the-counter medications. Drugs for controlling mucus production may not help. Drugs, such as antihistamines, may dry out the mucus making it thicker and harder to dislodge. Decongestants usually contain stimulants that can raise blood pressure and narrow blood vessels, both undesirable for individuals with MPS VII. Cough suppressants or drugs 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 VII 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 VII 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 VII 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.

Mouth

Individuals with MPS VII 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. Cleaning inside the mouth with a small sponge on a stick soaked in mouthwash will help keep the mouth fresh and help avoid bad breath. Even with the best dental care, an abscess around a tooth can develop due to abnormal formation of the tooth. Irritability, crying and restlessness can sometimes be the only sign of an infected tooth in a severely involved individual.

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. 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.

Since individuals with MPS VII generally have heart problems, antibiotics should be given before and after any dental treatment. This is because certain bacteria in the mouth may get into the bloodstream and cause an infection in the abnormal heart valve, potentially damaging it further. If teeth need to be removed while under an anesthetic, it should be done in the hospital under the care of both an experienced anesthetist and a dentist—never in the dentist's office.

Heart

Heart disease is common in individuals with the severe form of MPS VII, 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 individuals with MPS VII. Coronary artery disease caused by GAG storage in the heart blood vessels may occur and can lead to death. Some individuals with attenuated

MPS VII may develop problems with the heart 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.

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Your doctor may hear heart murmurs (sounds caused by turbulence in blood flow in the heart) if the valves become damaged by stored GAG. Heart valves are designed to close tightly as blood passes from one chamber of the heart to another in order to stop blood from flowing back in the wrong direction. If a valve is weakened, it may not shut firmly enough and a small amount of blood may shoot backward, leading to turbulence and a murmur. Most individuals with MPS VII have some degree of murmur or leakage.

Since heart problems occur so frequently in MPS VII, individuals with MPS VII should have a test known as an echocardiogram 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 GAG storage (cardiomyopathy). The heart also may be put under strain by having to pump blood through abnormal lungs (corpulmonale or right heart failure).

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

Liver and spleen

In individuals with MPS VII, both liver and spleen become enlarged (hepatosplenomegaly) by accumulation of GAG. The large liver does not usually cause liver problems, but it can interfere with eating and breathing and the proper fitting of clothes.

Abdomen and hernias

In most individuals with MPS VII, the abdomen bulges out due to posture, weakness of the muscles and the enlarged liver and spleen. Frequently, part of the abdominal contents will push out behind a weak spot in the wall of the abdomen. This is called a hernia. A hernia can come from behind the navel (umbilical hernia) or in the groin (inguinal hernia). Inguinal hernias should be repaired by an operation but hernias will sometimes recur. Umbilical hernias are not usually treated unless they are small and cause entrapment of the intestine or are very large and are causing problems.

Bowel problems

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

An examination by your pediatrician, 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. Episodic diarrhea in some individuals with MPS VII appears to be affected by diet; elimination of some foods can be helpful.

If antibiotics are the cause, eating plain, live-culture yogurt often is 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 also may be helpful.

Constipation may become a problem as the child gets older and less active and as the muscles weaken. If an increase in roughage in the diet does not help or is not possible, the doctor may prescribe laxatives or a disposable enema.

Bones and joints

Individuals with MPS VII tend to have significant problems with bone formation and growth. This leads to bone problems (called 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 the severe form of MPS VII may 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 it usually does not require treatment.

Neck

The bones that stabilize the connection between the head and neck may be malformed (odontoid dysplasia) in individuals with the severe form of MPS VII, making the neck unstable. If this occurs, fusion surgery may be required to connect all the bones to each other so they do not slip further. Some severely affected individuals appear to have occasional pain in the back of the neck. Rubbing may help this, and the child may enjoy having his or her neck gently massaged. If severe pain or pain associated with weakness or tremors in the lower legs occur, 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.

It is recommended that children with MPS VII avoid high-risk activities such as contact sports and gymnastics, including trampolines.

Parents of children with MPS VII should be cautious about how the area of the spine around the neck is handled. It is recommended that children with MPS VII avoid high-risk activities such as contact sports and gymnastics, including trampolines.

Scoliosis

Abnormal curvature of the spine, or scoliosis, also can occur and, if severe, may require intervention. In general, fusion with bone is the best alternative because hardware-like rods are not well tolerated. In any case, the soft bone makes the surgery and recovery difficult.

Joints

Joint stiffness is common in MPS VII 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 make sure irritation and ulcers in the stomach do not occur.

Hands

The shape of the hands in children with MPS VII is very noticeable. The hands are short and broad with stubby fingers. The fingers stiffen and gradually become curved, usually due to limited joint movement. The tips of the fingers can become permanently bent over. Finger joints may become locked—called trigger finger. Trigger fingers may be resolved with heat and massage or by surgery, if necessary.

Legs and feet

Individuals with MPS VII may stand and walk with their knees and hips flexed. This, combined with a tight Achilles tendon, may cause them to walk on their toes.

Skin

Individuals with the severe form of MPS VII tend to have thickened and tough skin, making it difficult to draw blood or place intravenous catheters. Excess hair on the face and back may occur in individuals with the severe form of MPS VII. Sweating and cold hands and feet may occur, 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 decline in developmental function in individuals with the severe form of MPS VII may be related to storage in the neurons in the brain. Other aspects of MPS VII can affect brain function, including inadequate oxygen levels, sleep deprivation due to sleep apnea, increased fluid pressure in and around the brain (hydrocephalus), and effects on the eyes and ears that affect the ability of the individual to see and hear normally.

The brain and the spinal cord are protected from jolting by the cerebrospinal fluid that circulates around them. In individuals with MPS VII, circulation of the fluid becomes blocked over time 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 MRI should be performed. However, a lumbar puncture with pressure measurement (ideally pressure monitoring) is the best way to assess if hydrocephalus exists. If your doctor confirms the individual has communicating hydrocephalus, it can be treated by the insertion of a thin tube (shunt), which drains fluid from the brain into the abdomen (ventri-culoperitoneal or VP shunt). The shunt has a pressure-sensitive valve that allows spinal fluid to be drained to the abdomen 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 VII.

Eyes

The eye problems described here can occur in MPS VII. 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. If corneal clouding is severe it may reduce sight, especially in dim light. Some individuals with MPS VII 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 VII. However, the transplant may need to be repeated over time.

There may be problems with vision caused by changes to the retina or glaucoma (increased pressure) which should be checked during an eye examination. GAG storage in the retina can result in loss of peripheral vision and night blindness. Night blindness can result in an individual not wanting to walk in a dark area at night or waking up at night and being afraid. Sometimes the addition of a night light in a hall or bedroom is beneficial. It is often difficult to determine which combination of problems is responsible for the decrease in eyesight. An ophthalmologist can perform special studies to help determine whether the problem is due to an effect on how light gets in the eye (the cornea) or on how the eye responds to light (the retina or optic nerve disease).

Ears

Some degree of deafness may occur in MPS VII. 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 VII have their hearing monitored regularly so that problems can be treated early to maximize their ability to learn and communicate.

Conductive deafness

Correct functioning of the middle ear depends on the pressure behind the eardrum being the same as that in the outer ear canal and the atmosphere. This pressure is equalized by the Eustachian tube, which runs to the middle ear from the back of the throat. If the tube is blocked, the pressure behind the eardrum will drop and the drum will be drawn in. If this negative pressure persists, fluid from the lining of the middle ear will build up and in time become thick like glue. This is called middle ear effusion.

If it is possible for the child to have a light general anesthetic, a small incision through the eardrum can be made (myringotomy) to remove the fluid by suction. A small ventilation tube may then be inserted to keep the hole open and allow air to enter from the outer ear canal until the Eustachian tube starts to work properly again. The tubes placed in the eardrum may quickly fall out. If this happens, the surgeon may decide to use larger T-tubes, which usually stay in place much longer. It is expected that 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. 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. Hearing aids are generally underutilized in MPS diseases.

Carpal tunnel syndrome and other nerve entrapments or compression

Individuals with MPS VII may 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; this 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 nerve conduction or electromyograph study should be performed. This test will show whether carpal tunnel syndrome is the cause. 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.

General treatment and management

Diet

There is no scientific evidence that a particular diet has any helpful effect on individuals with MPS VII, 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 mucus, diarrhea or hyperactivity. Reducing intake of milk, dairy products and sugar, as well as avoiding foods with too many additives and coloring, have helped some individuals. It would be advisable to consult your doctor or a dietician if you plan major dietary changes to make sure the proposed diet does not leave out essential items. If your child's problems are eased, you could 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 there is no diet that can prevent the storage of GAG because they are actually created by the body. So reducing sugar intake or other dietary components cannot reduce GAG storage.

Physical therapy/sports

Joint stiffness is a common feature of MPS VII. Limitation of motion 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. Exercises that cause pain should be avoided. Once significant limitation has occurred, increased range of motion may not be achieved, although further limitation may be minimized. Individuals with MPS VII should be as active as possible to maintain joint function and improve their general health. However, competitive or contact sports should be avoided. Your child's doctor or physical therapist may be able to suggest ways of achieving this through a combination of daily activities and passive range-of-motion exercises.

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Anesthetics

Giving an anesthetic to an individual with MPS VII requires skill and should always be undertaken by an experienced anesthetist. Inform your child's school or any other caregivers of this in case you cannot be contacted in the event of an emergency. If you must go to a different hospital in an emergency, be sure to tell the anesthetist there might be problems with intubation (placement of the breathing tube). The airway can be very small and may require a very small endotracheal tube. Placing the tube may be difficult and require the use of advanced intubation techniques, such as a flexible bronchoscope, laryngeal mask airway or fiber optics. In addition, the neck may be somewhat lax, and repositioning the neck during anesthesia or intubation could cause injury to the spinal cord. For some individuals, it is difficult to remove the breathing tube after surgery is completed due to excessive swelling. It is important to advise physicians of the critical nature of these problems, and that many problems have occurred during anesthesia of individuals with MPS. For any elective surgery in a child with MPS, it is important to choose a pediatric anesthesiologist who has experience with difficult airways. This may require that the surgery be performed at a regional medical center instead of a local hospital. See additional information on anesthesia in the booklet titled *Is Your Child Having an Anesthetic?* published by the National MPS Society.

For any elective surgery in a child with MPS, it is important to choose a pediatric anesthesiologist who has experience with difficult airways.

Living with a child with MPS VII

Children with MPS VII are usually happy, friendly children who mix well and are popular at school. They are much loved by all who know them and many are very easy to manage and to please. They are cheerful, with an infectious laugh. Crying as the child gets older may be linked to frustration at being unable to communicate.

Pain

It is very difficult when a child cannot express him or herself to know whether the crying is from pain or frustration. Children may have ear infections, toothache, aches and pains in their joints or feel discomfort from a full stomach. Do not hesitate to ask your doctor to check whether there is a physical reason for your child's distress.

Education

Children with MPS VII may benefit from having a mainstreamed education and enjoy the social interaction with peers. It is important to work with your school system and develop the best Individualized Education Program (IEP) for your child. For more information on education, see the booklet titled *A Guide for Parents: Education Strategies and Resources* published by the National MPS Society.

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Home adaptations

Children with MPS VII will become progressively less mobile and more dependent on their parents to meet their everyday needs. The booklet *Daily Living with MPS and Related Diseases*, published by the National MPS Society, has many helpful suggestions for making adaptations to the home.

Taking a break

Caring for a severely affected child is hard work. Parents need a break to rest and enjoy activities, which may not be possible when their affected child is with them. Brothers and sisters also need their share of attention and need to be taken on outings that may not be feasible with an affected child. Many parents use some form of respite care or have someone come in regularly to help at busy times. Individuals with attenuated MPS VII may need help to become more independent from their families and may benefit from a vacation, perhaps with others who have disabilities.

Palliative care

Palliative care is any form of medical care or treatment that concentrates on reducing the severity of disease symptoms. The goal is to prevent and relieve suffering and to improve quality of life for people facing serious, complex illness. This support encompasses aspects such as respite care, symptom management and bereavement support and many extend over a period of time. An assessment of medical need and a care plan can lead to support provided to the child and family so both can experience a better quality of life.

Healthcare information

Assistance may be available from specialized agencies for the disabled and from genetic clinics. You might want to look into Social Services, Social Security, Medicaid Wavers and the Katie Beckett Law. Investigate these options and others in your state or with your Department of Health. If you have a social worker assigned to you, he or she should be able to help locate additional information and/or resources for your family.

Life expectancy

Life expectancy in MPS VII is varied. Infants with hydrops fetalis rarely survive beyond a few weeks to a few months of age. Individuals with attenuated MPS VII can have a reasonably normal life span while severely affected individuals may die before becoming teenagers. Moderately affected individuals may live to be young adults. Though parents often worry about their child's death, it is usually a peaceful event. Parents may find it helpful to prepare themselves in advance for the time of their child's death.

Specific treatment of MPS VII

Although MPS VII is one of the least common lysosomal storage diseases, it is one of the most extensively studied. This is due to the availability of several authentic animal models of this disease. These animal models have enabled scientists to not only better understand the natural history of the disease but also to develop therapies for this disease. A great deal of work has been done with Hematopoietic Stem Cell Transplant (HSCT), enzyme replacement and gene therapy for the treatment of MPS VII. Currently, HSCT is the only recommended therapy for MPS VII, although experience is very limited. However, enzyme replacement and gene therapy have been shown to be effective in the animal models.

The goals of managing MPS VII 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 VII. However, early intervention may help prevent irreversible damage. Treatment options for MPS VII include those aimed at disease management and supportive or palliative care (care that makes a person with a disease who cannot be cured more comfortable), as well as those aimed at treating the underlying enzyme deficiency.

Hematopoietic Stem Cell Transplant

The goal of HSCT for MPS VII is to restore the activity of the deficient enzyme, β-glucuronidase, which may improve such symptoms as enlarged liver and spleen, joint stiffness, sleep apnea, heart disease, hydrocephalus and hearing loss. If a child with MPS VII receives HSCT from an unaffected individual (parent, sibling or unrelated matched donor), the affected child will now have the hematopoietic (blood) system of the donor. In this scenario, the blood cells circulating through the child's body are from the normal donor and, therefore, have normal levels of the deficient lysosomal enzyme. As the cells circulate they can secrete some of their enzymes and potentially correct the defect in some tissues.

MATTHEW

HSCT does not correct bone or eye problems, frequently requiring future therapies and surgeries. HSCT in children with MPS VII does not generally have central nervous system benefit. Bone marrow and cord blood transplants are types of HSCT. Unfortunately, there has been little or no experience with bone marrow transplantation in patients with MPS VII. However, experiments in mouse and dog models of MPS VII suggest it may be an effective form of therapy for the systemic disease. 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 National 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)

Enzyme replacement therapy has been approved for several of the MPS diseases. The recombinant enzyme is typically given by weekly intravenous infusion. Although ERT has not been attempted in patients with MPS VII, this approach has been shown to be very effective in animal models of this disease. There is reason to hope that ERT will help some of the physical problems, but the blood-brain barrier may prevent enzyme therapy from directly helping the brain.

Gene therapy

Gene therapy research conducted in animals with MPS VII has shown positive results. There are plans to begin a clinical gene therapy trial in individuals with MPS VII. The National MPS Society can provide you with more information about this research.

Research for the Future

The mission of the National MPS Society is to find cures for MPS and related diseases. As part of that mission, the Society funds research grants. The Society recognizes the need for targeted research for treatment of bone and joint problems and for treating the brain, and Society research funding has focused on those areas. Information about Society funded research and promising new areas of research can be obtained by contacting the Society's office.

This booklet is intended as an introduction to the nature of the disease, as well as to help families understand more about what is happening to those with MPS VII and what they can do to manage it. This booklet was updated by the National MPS Society in 2008.

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

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

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

Benefits of membership in the National MPS Society:

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

National MPS Society

For more information or to join the National MPS Society:

Visit **www.mpssociety.org**
Contact us at **877.MPS.1001**
Or email us at **info@mpssociety.org**