



National
MPS
Society

Support for Families. Research for a Cure.



A Guide to Understanding ML II and III

I-Cell Disease and Pseudo-Hurler Polydystrophy

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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2 Introduction

Mucopolysaccharidoses (ML) II (I-Cell disease) and ML III (Pseudo-Hurler polydystrophy) are closely related diseases, first described in the 1960s. The more severe of the two, I-Cell disease, was named by Jules Leroy, a Belgian pediatrician, for the inclusions he saw in his patients' cells under a microscope. Pseudo-Hurler polydystrophy was described by the French physicians Maroteaux and Lamy, who found the disease reminiscent of severe MPS I, though milder in its manifestations. Both diseases were assigned to the class of mucopolysaccharidosis, I-Cell disease as mucopolysaccharidosis II and Pseudo-Hurler polydystrophy as mucopolysaccharidosis III (or simply, ML II and III). Recent molecular studies identified mutations that correlate with the phenotypes (characteristics) seen in the spectrum of ML II and III, leading to revised classification.

Revised Classification of ML II and III

	<i>Past Nomenclature</i>	<i>Current Nomenclature</i>
I-Cell disease	ML II	ML II alpha/beta
Pseudo-Hurler polydystrophy	ML III A	ML III alpha/beta
ML III variant	ML III C	ML III gamma

As yet, there is no cure for individuals affected by these diseases. Natural history studies are providing comprehensive information about the disease symptoms and management, disease progression and future research opportunities. Treatments are available to manage the challenges and improve the quality of life of individuals affected with ML II and III. Scientists who study ML diseases continue to look for better and more effective ways to treat them, and it is likely that individuals will have more options available to them in the future.

What causes ML II and III?

Both ML II and III are diseases of the lysosomes. Lysosomes are the recycling plants of our cells—places where large and complex molecules are broken down to constituent parts, to be reused or disposed. Within the lysosomes, there are several dozen enzymes that carry out this breakdown of complex molecules.

In ML II and III, many of the enzymes are either missing completely from the lysosomes or are present in inadequate amounts. Instead, they are found outside of the cell in excessive amounts in the blood. That happens because, when they are first made (in other parts of the cell), these enzymes must be equipped with a signal that guides them to lysosomes. In ML II and III, signals are not attached to enzymes and, failing to reach lysosomes, are secreted out of the cell instead. The major problem is the deficiency of these enzymes within lysosomes causes an accumulation of molecules that should have been broken down. The accumulation, in turn, causes progressive damage to cells and organs. The inclusions that Dr. Jules Leroy had observed as black dots under the microscope, and for which ML II was named, are lysosomes engorged with stored material.

The biochemical cause of ML II and III is therefore different from that of other lysosomal storage diseases, such as the mucopolysaccharide (MPS) diseases. In the latter, there is only one lysosomal enzyme that is missing or deficient in each disease because of a mutation in its gene; for example, alpha-L iduronidase is lacking in MPS I. But in ML II and III, alpha-L-iduronidase is one of the many enzymes lacking in lysosomes, because it is not targeted correctly. This explains why I-Cell disease has some of the same clinical problems as severe MPS I and additional problems. The enzyme responsible for attaching the targeting signal is *N*-acetyl-1-phosphotransferase (GlcNAc-PT).

The enzyme deficiency within lysosomes causes an accumulation of molecules that should have been broken down. The accumulation, in turn, causes progressive damage to cells and organs.

Are there different forms of ML II and III?

Although ML II and III have the same biochemical cause, they are different in how they affect children. It is now apparent that a wide spectrum of severity exists within and between ML II and III. ML II is the severe form of the targeting enzyme deficiency, while ML III is a milder form of the same deficiency. There are some mutations in the gene that result in no enzyme activity, leading to ML II. In ML III a small amount of enzyme is produced which explains the later onset on symptoms and slower disease progression.

4 ML II starts to affect babies in the womb and there usually are obvious signs from an early age. Many children are born with dislocated hips, an early sign of the skeletal problems of the disease. In contrast, children with ML III have less severe symptoms, and their condition may not be recognized for a year or more. The two diseases are not distinguished from each other by biochemical tests, but recent molecular studies have identified mutations in ML II and III that correlate with the disease symptoms. Clinical examination by a geneticist also can aid in determining the severity of the disease.



JENNY (ML III)

There is a form of the disease that is intermediate in severity between ML II and III, called intermediate ML II/III. These individuals have early onset of growth delay with severe joint limitations but better cognitive skills. It is important, however, to remember that regardless of the label given to your child's condition, the disease is extremely varied in its effects. A wide range of possible symptoms is outlined in this booklet but your child may not experience them all.

How common are ML II and III?

These diseases are very rare and sometimes misdiagnosed, so it is difficult to give accurate figures on frequency. Reports from Australia and the Netherlands indicate that two or three in one million births have ML II and III. There may be parts of the world where the disease occurs more often. Although ML II or III is individually rare, the larger family of lysosomal storage diseases collectively occur in about 1 in every 5,000 to 7,000 births.

How are ML II and III inherited?

ML II and III are genetic diseases. 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. ML II and III are that type of genetic disease. Most families who have a child with ML II or III do not have a family history of genetic problems. ML II and III seem 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.

Regardless of the label given to your child's condition, ML diseases are extremely varied in their effects. A wide range of possible symptoms is outlined in this booklet, but your child may not experience them all.

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 ML II or III. 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 ML II or III.

This is why ML II and III are genetic recessive diseases. 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.

6 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

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 ML diseases.

of inheriting the defective gene from both the mother and from the father and thus being affected with ML II or III. There is a two in three (67 percent) chance that unaffected brothers and sisters of individuals with ML II or III will be carriers of the defective gene that causes ML II or III. 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.

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 ML diseases.

Prenatal diagnosis

If you already have a child with ML II or III, 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 that they will have or be carriers for ML II or III.

Clinical problems in ML II and III

Growth

Growth in height is usually significantly less than normal but varies according to the severity of the disease. Children with ML II will be severely restricted in growth. Usually they have stopped

growing by the age of 3 and are unlikely to be taller than about 3 feet, with the appearance of a 2 to 3-year-old child. Those who have ML III may grow taller, to between 4 feet 6 inches and 5 feet.

Intelligence

There is a wide variation in both diseases regarding intelligence. Many children with ML III have normal intelligence, but some may have learning disabilities. Some individuals with ML III suffer from obsessive compulsive disorder, and short-term memory loss later in life has been reported.

Children with ML II experience progressive storage of mucopolids and glycosaminoglycans in the brain leading to the slowing of development by ages 6 months to 2 years, followed by a progressive regression in skills until death. There is a great variation in the severity of the condition. Those affected by ML II are likely to be restricted in what they learn, but there are reports of children who have learned to talk, sing and do simple math. Parents emphasize that it is important to help babies with ML II 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 find enjoyment in life even if they lose the ability to speak.



ANDRE (ML II)

Individuals with ML II and III commonly have other medical problems that will hamper their learning and performance, including chronic ear infections, poor vision, poor hearing, osteopenia and osteoporosis, and sleep apnea. Adequate treatment of these complications can improve the function of individuals with ML II and III, so they should be evaluated early.

Physical appearance

Birth weight and length are often below normal in individuals with ML II and III, and the clinical features of the disease may be present at birth or in the first few months of life. Multiple contractures of the skeleton may be apparent at birth in addition

8 to square foreheads, enlarged hands, and kyphosis or scoliosis. In children with ML II, the neck is short, cheeks are often rosy, and the nose may be broad with a flattened bridge and upturned nostrils. The mouth may be wide, and children with I-Cell can have very prominent gums. Eyebrows may be bushy and meet in the middle, and the eye sockets are usually shallow making the eyes appear prominent. The head shape of children with ML II may change with the early closing of the soft part of the baby's skull. Some children with ML II may have fair skin, blonde hair and blue eyes, despite the coloring of their parents.

Children with ML III do not develop facial characteristics, prominent forehead, eyebrow features and broadening of the nose, until later in childhood.

Nose, throat, chest and ear problems in ML II

The problems described in this section are common to children with ML II, and to a lesser degree individuals with ML III. Children with ML II are prone to frequent chest and ear infections, and tend to have runny noses.

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 ML II can have chronic discharge of thick clear mucus from the nose (rhinorrhea), and chronic ear and sinus infections.

Throat

The tonsils and adenoids often become enlarged and can partly block the airway. The neck is usually short, which 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.

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 if the liver and spleen are enlarged, further reducing the space for the lungs. When the lungs are not fully cleared, there is an increased risk of infection (pneumonia).



ANDREA

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 happening, the child's oxygen level may be low when sleeping which can cause problems with the heart. 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 individuals by removing the tonsils and adenoids, opening up the airway with nighttime continuous positive airway pressure (CPAP), bi-level positive airway pressure treatment (BiPAP), or tracheotomy, as discussed in the following paragraphs. There are reports of tonsils and adenoids growing back and continuing to cause airway problems.

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, doctors can assess how much blockage to breathing is present and how much

10 trouble your child is having moving air into the lungs during sleep, and how much effect this has on his body.

Nighttime 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 people 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 in 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 ML II 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. The physical therapist can advise parents about this procedure.

Treatment of respiratory infections

Drugs may affect people with ML 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 people with ML II and III. Cough suppressants or drugs that are too sedating may cause more problems with sleep apnea by depressing muscle tone and respiration.

Although most children with colds do not require antibiotics, individuals with ML almost always end up with secondary bacterial infections of the sinuses or middle ear. These infections should be treated with antibiotics. Poor drainage of the sinuses and middle ear makes 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 can 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 ML diseases to determine which type of tube is best.

Many people with ML become allergic to antibiotics or may acquire resistant infections. Your doctor can prescribe other antibiotics to help manage this problem. While overusing antibiotics is not advised, most people with ML 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

Children with ML II generally have overgrown and swollen gums, which are characteristic of the disease. Their teeth may be late and troublesome in breaking through the gum. Teeth may appear just above or below the edge of the gum and are often widely spaced and poorly formed with fragile enamel. Sometimes the tongue may be enlarged, and the roof of the mouth may have a high arch. The mouths of children with ML III, on the other hand, are generally normal.

Teeth should be cleaned regularly, and if the water in your area has not been treated with fluoride the child should have 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.

It is important that the teeth are well cared for, as tooth decay can be a cause of pain. Teeth should be cleaned regularly, and if the water in your area has not been treated with fluoride the child should have 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.

Since individuals with ML generally have a heart problem, it is advised that 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

Children with ML II or III may develop heart disease, but to a very different degree. Those who have ML III may not experience problems until much later in life. In general, the heart will be much more severely affected in children with ML II.

During examinations, your doctor may hear an unusual sound in your child's heart, called a heart murmur, if heart valves have been damaged. A simple and painless test called an echocardiogram (similar to ultrasound screening of babies in the womb) is used to identify the problem. Heart valves are designed to close tightly to prevent blood from flowing in the wrong direction as blood passes from one chamber of the heart to another. If a valve becomes weakened or hardened, it may not shut firmly enough and a small amount of blood may leak through the valve. It is

possible to have heart valve problems for years without any ill effects. If problems do occur, it may be possible to treat them with surgery.

Children with ML II also can develop the more serious problems of thickening and weakness of the heart muscle (cardiomyopathy), often as a result of the damaged heart

valves. In some cases, medication may be prescribed to try to help the problem. Because of the unusual special problems that can occur in these diseases, you should select a cardiologist with some knowledge of ML. At a minimum, you should inform the doctor about the problems experienced by individuals with ML diseases.



JOEY (ML III) AND MATTHEW (ML III)

Abdomen and hernias

A child with ML II is likely to have a protruding abdomen due to posture, weakness of the muscles, and enlarged liver and spleen. The large liver is less of a problem in individuals with ML III. It does not usually cause liver problems, but it can interfere with eating and breathing and the proper fitting of clothes.

Frequently, part of the abdominal contents will push out behind a weak spot in the wall of the abdomen. This is called a hernia. The hernia can come from behind the navel (umbilical hernia) or in the groin (inguinal hernia). Inguinal hernias should be repaired by an operation, but hernias 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 reoccurrence of an umbilical hernia after a repair has been made. Individuals with ML III are less likely to have hernias.

Bowel problems

Many individuals with ML II and III suffer periodically from loose stools and diarrhea. The cause of this is not fully understood. Occasionally, the problem is caused by severe constipation and leakage of loose stools from behind the solid mass of feces. More often, however, parents describe it as “coming straight through.” It is thought that 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 the 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. The episodic diarrhea in some individuals with ML appears to be affected by the diet; elimination of some foods can be helpful.

If antibiotics have caused the diarrhea, 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

14 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

There is a wide variation in the severity of problems that affect bones and joints, even between affected brothers and sisters. Those with ML II are more severely affected and skeletal problems may even be evident at birth. Later onset of bone and joint issues occurs in ML III, the progression of which should be monitored by radiological studies.

Some individuals with ML II and III have decreased bone density leading to osteopenia and osteoporosis, also called secondary metabolic bone disease. Because of the brittle bones, there may be fracturing around the joints. IV treatment with bisphosphonates has shown success in reducing pain, maintaining mobility and improving quality of life. Your orthopedist or endocrinologist can provide additional information about this treatment.

Spine

The bones of the spine (vertebrae) normally line up from the neck to the buttocks.

Individuals with ML II 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 it usually does not need treatment, unless severe.

Neck

The bones that stabilize the connection between head and neck may be malformed (odontoid dysplasia) in individuals with ML II and III. If this occurs, fusion surgery may be required to connect all bones to each other so they do not slip further.

Parents of children with ML II and III should be cautious about how the area of the spine around the neck is handled. It is recommended that children with ML II and III 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, and hardware-like rods may not be well tolerated. In any case, the soft bone makes the surgery and recovery difficult. Some individuals need multiple procedures.

Joints

Joint stiffness is common in both ML II and III and the maximum range of movement of all joints may become limited.

Later in the individual's life this may cause pain, which may be relieved by heat and ordinary painkillers. The 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.



ROBIN (ML II)

Legs and feet

Many individuals with ML II and III stand and walk with their knees and hips flexed. This, combined with a tight Achilles tendon, may cause them to walk on their toes.

The hips are sometimes dislocated, and the knees may become “knocked” (genu valgum). The breastbone (sternum) may be curved outward (pigeon chest). The bones of the feet are sometimes deformed.

Those who have ML III may have very stiff hips, as the supporting socket is not formed properly, and they may have pain in the joints if they are very active. Surgery on the hips may be used as a last resort if pain becomes a real problem. Hip surgery may not

16 be successful until after puberty. Total hip replacement has been effective in individuals with ML III, if done after puberty.

The lack of flexibility in the hips and legs often prevents individuals from tailor sitting (the seating position of choice for most kindergarten teachers) or putting on their own socks and shoes.

Hands

The shape of the hands is very noticeable in ML II; the hands are short and broad with stubby fingers. The fingers stiffen and gradually become curved due to limited joint movement. The tips of the fingers can become permanently bent over.

Skin

Individuals with ML II and III tend to have thickened and tough skin, making it difficult to draw blood or place intravenous catheters. Excess hair on the face and back occasionally occurs. Sweating and cold hands and feet also are occasional 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. Skin sensitivity and increased sweating may cause decreased tolerance of heavy clothing or specific fabrics. Irritated areas or rashes should be monitored.

Neurological problems: brain, senses and nerves

The decline in developmental function in individuals with severe ML II may be related to storage in the neurons in the brain. Other aspects of ML II 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 ML II, the 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) 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 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 ML II.

Eyes

Children with ML II and III may be affected by mild corneal clouding. The circular window at the front of the eye (cornea) becomes cloudy which disrupts the clear layers of the cornea. If corneal clouding is severe, it may reduce sight, especially in dim light. Some people with ML II and III cannot tolerate bright lights as the clouding causes uneven refraction of the light. Wearing caps with visors or sunglasses can help. For individuals with severe corneal clouding causing severely limited vision, a corneal transplant may be recommended. The transplant may, however, need to be repeated over time.

There may be problems with vision caused by changes to the retina or glaucoma (increased pressure) that should be checked during an eye examination. 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

18 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 is common in both ML II and III. It may be conductive or nerve deafness or both (mixed deafness) and may be made worse by frequent ear infections. It is important that individuals with ML II and III 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 lining of the middle ear will build up and eventually become thick like glue. This is called middle ear effusion.



SERGIO (ML II/III)

If it is possible for the child to have a light general anesthetic, a small incision through the eardrum can be made (myringotomy) to remove the fluid by suction. A small ventilation tube may then be inserted to keep the hole open

and allow air to enter from the outer ear canal until the Eustachian tube starts to work properly again. The tubes placed in the eardrum may quickly fall out. If this happens, the surgeon may decide to use T-tubes, which usually stay in place much longer. It is expected that once the ventilation tube is in place, fluid should drain out and hearing should improve.

In most cases, the cause of nerve deafness is due to 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 ML II and III.

Carpal tunnel syndrome and other nerve entrapments or compression

Individuals with ML II and III 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, and 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 hard 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. 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 ML II and III may 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 or the sensation of pins and needles 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 people with ML II and III, and symptoms such as diarrhea tend to come and go naturally. Some parents, however, find that a change in their child's diet can ease problems such as excessive mucus, diarrhea or hyperactivity. Reducing the 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 seems to increase the child's symptoms.

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

Some children with ML II are not tolerant of whole foods, preferring soft foods. This may be the result of the tongue thickening or

swallowing complications. If this occurs, an evaluation by a pediatric nutritionist is recommended to ensure the child is receiving adequate nutrition.

Physical therapy

Joint stiffness is a common feature of ML II and III. 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

It makes common sense for individuals to be as active as possible to maintain their 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.

be started early. Passive hydrotherapy is beneficial for the joints while minimizing painful impact. 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 ML II and III 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.

Anesthetics

Giving an anesthetic to a ML II or ML III individual requires skill and should always be undertaken by an experienced anesthetist. Inform your child's school or any other caregivers of this in case you cannot be contacted in the event of an emergency. If you have to go to a different hospital in an emergency, 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.



TRISTIN, AUSTIN (ML II/III) AND ZACHIE (ML II/III)

It is important to advise physicians of the critical nature of these problems, and that many problems have occurred during anesthesia of individuals with ML II and III. For any elective surgery, it is important to choose a pediatric anesthesiologist who has experience with difficult airways. This may require the surgery

22 be performed at a regional medical center, not at a local hospital. See additional information on anesthesia in the booklet titled *Is Your Child Having an Anesthetic?* published by the National MPS Society.

Living with a child with ML II

Children with ML II 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 ML II 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. The IEP should emphasize the child's mobility limitations, adaptive physical education, and attention to fine motor modifications. For more information on education, see the booklet titled *A Guide for Parents: Education Strategies and Resources* published by the National MPS Society.

Home adaptations

Children with ML II 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 their affected child. Many parents use some form of respite care or have someone come in regularly to help at busy times.

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.



KELLEY (ML III)

Life expectancy

Life expectancy in ML II is varied. Individuals with ML III 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.

Living with a child or adult with ML III

Education

The majority of children with ML III will attend mainstream school and achieve academically. For the child to reach full academic potential, it is important to ensure the school and school personnel are aware of the resources required. This may include a one-to-one classroom assistant, appropriate classroom furniture and access to an individual computer.

Independence

Individuals with ML III should be encouraged to be as independent as possible to lead full and enjoyable lives. Contact with teenagers and adults with ML III can provide mutual support and helpful information for living an independent life. Palliative care in the adult years can ease the problems associated with disease progression.

Employment

The physical disabilities of those suffering from ML III should not prevent people from accessing meaningful employment. The Americans with Disabilities Act protects against discrimination to Americans with disabilities. Vocational Rehabilitation is a state program to help people with disabilities make career plans, learn job skills and live independently.

Home adaptations

Appropriately adapted living accommodations will greatly enhance the ability of an individual with ML III to develop independent living skills. Where mobility is restricted, a wheelchair may be helpful. Grants may be available through community or state agencies to cover the cost of home adaptations.

Puberty and marriage

Teenagers with ML III will go through the normal stages of puberty, although the stages may be delayed. Some women with ML III may not have onset of menses, irregular periods, or premature stopping of her menstrual cycles. A woman with

ML III could bear children, but her doctor may advise against it due to the physical challenges it would present. Due to the physical effects of the disease, expectant mothers with ML must be closely monitored and will likely deliver using Caesarean section.

Remember that affected individuals are automatically carriers of the recessive genes that cause ML II and III. Children born to a parent with ML can only be affected with the disease if the other parent is a carrier.

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.

Specific treatment of ML II and III

It was shown by Dr. Elizabeth Neufeld that small amounts of lysosomal enzymes, although they are intracellular in nature, could be secreted from normal cells. The secreted enzymes could then be taken up by adjacent cells and directed to the lysosome where they functioned normally. It was then shown that the biochemical defect in a cell that is deficient in a lysosomal enzyme could be corrected by taking up the small amount of enzyme secreted from an adjacent normal cell. This phenomenon, referred to as “cross section,” forms the basis of all of the therapeutic strategies being developed.



JONALIN (ML II)


At present there is no cure for the diseases, although symptoms may be managed to create a better life for children. Natural history studies are providing information about the course of the disease that can shape the development of future treatments.

The biochemical cause of ML II and III, a lack of the targeting enzyme, suggests that treatments being developed for mucopolysaccharide diseases, such as enzyme replacement therapy, would likely not work well in ML II and III. Some children have had hematopoietic stem cell transplant (HSCT). 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. Results of this procedure in children with ML II and III have varied, so it is not considered standard of care.

The National MPS Society can put you in touch with physicians and families so you can become better informed before reaching a decision.

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 into the nature of this disease, as well as to help families understand more about what is happening to those with ML II and III and what they can do to manage it. In 2009, this booklet was updated by the National MPS Society with help from experts in the field and ML parents to provide families with the latest information.



This booklet is not intended to replace medical advice or care. The contents of and opinions expressed in A Guide to Understanding Mucopolysaccharidoses (ML) II and III (I-Cell Disease and Pseudo-Hurler Polydystrophy do not necessarily reflect the views of the National MPS Society or its membership. This booklet may be reproduced or copies can be made available upon request for a nominal fee from the National MPS Society.

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.



For more information or to join the National MPS Society:

Visit www.mpsociety.org

Contact us at 877.MPS.1001

Or email us at info@mpsociety.org