A Guide to Understanding

Sanfilippo syndrome

(mucopolysaccharidosis type III; MPS III)

Introduction

This information sheet has been developed by the Mucopolysaccharide & Related Diseases Society of Australia (the MPS Society) to provide information about mucopolysaccharidosis type III (MPS III), its clinical presentation and medical management.

The content of the information sheet draws on the experiences of parents and doctors with reference to the medical literature. It is not intended to replace medical advice or care.

For reference purposes, it may be useful to provide a copy of this information sheet to your GP and others who are involved in providing medical or supportive care.

What is MPS III?

MPS III is an inherited disorder that encompasses a wide spectrum of severity. The brain is the primary site of disease and its function declines with time; physical symptoms may also develop with time, and may include hearing and breathing difficulties. The age of onset of symptoms and rate of disease progression vary considerably, even in affected siblings: in some, disease progress may be rapid with diagnosis in the first few years of life; in others it may be relatively slow and diagnosis may not occur until the third or fourth decade. Generally, if clinical symptoms are apparent early in life, it is more likely that disease progress will be rapid.

There are four types of MPS III, known as types A, B, C and D. Recently, type E was described in a mouse but is yet to be reported in humans. MPS III is also referred to Sanfilippo syndrome, so named after the doctor who first described the condition.

What causes MPS III?

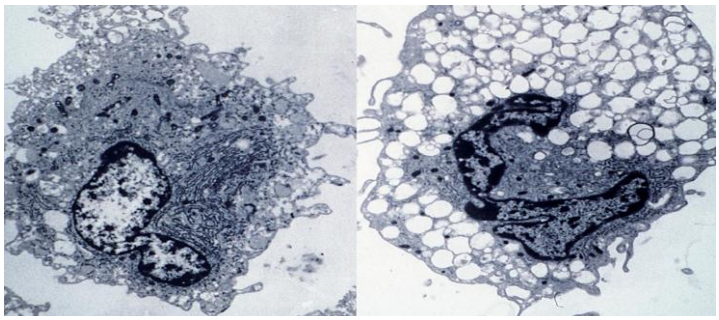
In common with the other MPS disorders, the characteristic of MPS III is the build up (or 'storage') of long chains of sugar molecules called *mucopolysaccharides* in the body's cells. '*Muco*' refers to the thick jelly-like consistency of the molecules, '*poly*' means many, and '*saccharide*' is a general term for the sugar part of the molecule. Mucopolysaccharides are also referred to as *glycosaminoglycans* (or GAGs for short) but for the purpose of this information sheet, the term mucopolysaccharide will be used.

Mucopolysaccharides are used by the cells to build connective tissues in the body, such as skin, muscle, cartilage and bone. They also help with many other cellular functions, including growth control, organ development and signalling between cells.

The human body is made up of billions of cells. Each cell contains various structures that carry out many functions important to life. One such structure is known as the lysosome [pronounced *lie-so-soam]*. Mucopolysaccharides carry out their tasks outside the cell. Once their job is complete they are transported

to the lysosomes to be broken down (or degraded) into their basic building blocks. Degradation requires the action of enzymes that are found inside the lysosomes. Once the mucopolysaccharides have been broken down by these enzymes, they are transported out of the lysosomes to be reassembled and re-used to build tissue, etc. Mucopolysaccharides are therefore in a continuous process of being recycled.

In people with an MPS disorder one of the lysosomal enzymes that is needed to degrade mucopolysaccharides is either missing or is present at levels that do not allow the recycling process to work properly. This means that the mucopolysaccharides cannot be completely degraded and removed from the lysosomes in the usual way. As a result, partially broken down mucopolysaccharides remain 'stored' in the lysosomes: with time, lysosomes increase in size as the amount of storage increases. This interferes with normal cell functioning and causes progressive clinical problems in affected people.



These pictures show a normal cell (left)
and a cell that is filled with stored mucopolysaccharides in the lysosomes (right).

People with MPS III are deficient in *one* of the four lysosomal enzymes shown below:

Disorder	Enzyme Deficiency
MPS type IIIA	Sulphamidase
MPS type IIIB	N-Acetylglucosaminidase
MPS type IIIC	Acetyl-CoA:alpha-glucosaminide-acetyltransferase
MPS type IIID	N-acetylglucosamine 6-sulphatase

Each of these enzymes is essential in breaking down a mucopolysaccharide called *heparan sulphate*. In all four forms of MPS III, heparan sulphate storage occurs in the brain, leading to its progressive deterioration; the amount of heparan sulphate storage in other tissues influences the extent of physical symptoms.

How common is MPS III?

The estimated incidence of MPS III (all four types combined) is 1 in 70,000 births.

The incidence of all MPS disorders combined (of which 11 are currently recognised) is estimated to be 1 in 25,000 births.

The MPS group of disorders belong to a larger group of about 50 inherited disorders collectively known as *lysosomal storage disorders*, so named because storage of materials that are unable to be properly degraded (mucopolysaccharides in the case of the MPS disorders) occurs in the lysosome. It is estimated that lysosomal storage disorders occur in about 1 in every 5,000 to 7,000 births.

How is MPS III inherited?

All four forms of MPS III are inherited in what is known as an *autosomal recessive* manner. In this form of inheritance both parents must carry a copy of the defective gene and each pass that defective gene to their child. In the case of MPS III, the defect relates specifically to the faulty production of one of the four enzymes shown in the table above.

In autosomal recessive inheritance, in *each* pregnancy of a carrier couple, there is a:

- 25% (1 in 4) chance of having an affected child;
- 50% (1 in 2) chance of a child receiving only one copy of the defective gene and therefore being a carrier. A carrier will not be affected but can pass the defective gene to his/her offspring; and a
- 25% (1 in 4) chance that a child will be neither affected nor a carrier.

The child of an affected person will not have MPS III but they will be a healthy carrier of the defective gene. Only in the rare case that the affected person's partner is also a carrier is there a chance (50%; 1 in 2) that the child will be affected.

The MPS Society has produced a specialist booklet (*The Pattern of Inheritance*) that is available.

Genetic Counselling

Because MPS III is inherited it is important to seek genetic counselling as there may be implications for other children in the family, future pregnancies and extended family members. Geneticists and/or genetic counsellors will explain the inheritance pattern and help determine who should be tested.

Diagnosis

At present, there is no routine newborn screening procedure to diagnose a baby with MPS III. If there is a family history of the disorder, however, prenatal testing can be arranged during the early stages of pregnancy (see below) or soon after birth. MPS III is not well known in the community. As the initial symptoms are variable it is often not easily recognised by doctors, hence (in the absence of a family history) diagnosis is often made after obvious problems have developed.

To diagnose MPS III, mucopolysaccharides are usually first measured in urine, followed by measurement of enzyme activity in blood. Increased heparan sulphate in urine, and a decrease in the activity of any *one* of the four enzymes (shown in the table above) in blood is usually consistent with a diagnosis of MPS III and will identify the specific form of the disorder (A, B, C or D). To confirm the urine and blood results it is useful to measure enzyme activity in a small piece of skin. Whilst all four forms of MPS III appear clinically similar, it is important to identify the correct form of the disorder to assist with future testing and application of treatments as they are developed.

Diagnosis by mutation testing may also be possible. Mutations are mistakes in the genetic information (DNA) that is inherited by an affected child from their parents. In MPS III, the mutations are present in the gene that codes for any one of the four enzymes shown in the table above, and lead to a defect in its production. If the disease-causing mutations are found (which is not always possible to achieve) testing future pregnancies or other family members may be simplified. Mutation testing can be done using either blood or skin.

It is generally agreed that a comprehensive medical and supportive care plan should be started as early as possible after diagnosis to promote the best quality of life.

Can you test for MPS III in pregnancy?

Testing a fetus for an inherited condition whilst it is still in the womb is called prenatal testing and can be performed if there is a family history of the condition.

Prenatal testing is usually done within the first three months of pregnancy. If the parents of an affected child wish to consider prenatal testing, it is important to discuss it with your doctor, a geneticist or genetic counsellor prior to or during the very early stages of pregnancy.

Prenatal testing for carriers of MPS III in the family is not done routinely unless their partner is known to be a carrier. If a partner's carrier status is not known, it is highly recommended that the advice of a geneticist or genetic counsellor is sought prior to pregnancy.

Disease Progression

In common with other MPS disorders, all four forms of MPS III are progressive, meaning that the symptoms worsen with time.

The biological processes that determine the age at which symptoms appear and the rate at which they progress are complex and not all are clearly understood. Storage of mucopolysaccharides begins as a result of mistakes (mutations) in the genetic information (DNA) that code for the production of a specific enzyme that is responsible for breaking down specific mucopolysaccharides. These mutations determine how much active enzyme can be made, which will affect how much mucopolysaccharide can be broken down in the lysosome. As a general rule, if a mutation allows more active enzyme to be made, the mucopolysaccharide can be broken down more efficiently so disease progress is likely to be slower, with less storage occurring; if a mutation allows little or no active enzyme to be made, mucopolysaccharide break down will be much less efficient and more will remain stored, so disease progress is likely to be more rapid.

Whilst mucopolysaccharide storage is a significant cause of symptoms, it is important to understand that it is one part of a complex 'cascade' of changes that occur as a result of the reduction in enzyme activity: the mucopolysaccharides cannot be properly broken down in the lysosomes at the correct time and recycled; in turn, this causes abnormal changes to their function as well as to other functions of the cell. The flow-on effects of these changes significantly contribute to clinical outcome and disease progression in addition to the storage itself. Research is continuing to understand this 'cascade' of changes to improve diagnosis, predicting the rate of disease progression (prognosis) and treatment options.

Life Expectancy

It is difficult to be precise about life expectancy because of variation in severity and age of onset. Some individuals have lived into adulthood but this is usually accompanied by a decline in their quality of life as brain function deteriorates.

Fertility

MPS III does not affect fertility. Teenagers will go through puberty, although it may be delayed.

Clinical Presentation

This information sheet addresses a wide range of possible symptoms and presentations of MPS III. However, an affected person may not experience them all or to the degree described here.

Physical and mental development may be normal at first. The rate at which mental decline will occur may be difficult to predict early on. Declining brain function and associated problems with behaviour and communication may make medical examinations difficult. It is important that simple and treatable problems such as ear infections and toothaches are not overlooked as a cause of pain or distress. These children may have an increased tolerance of pain or may find it difficult to communicate that they are in pain. Do not hesitate to consult a doctor if you think your child might be in pain.

Growth

People with MPS III grow to a fairly normal height.

Facial Appearance

Changes in appearance may gradually develop with time. The eyebrows may be dark and bushy and meet in the middle; the hair tends to be thick.

Intellectual Ability

Generally, intellectual development slows down by about 2 to 4 years of age, followed by a gradual loss of skills. However, the pattern is varied: some will only learn to say a few words while others may learn to talk and read a little. Emphasis should be on helping infants and children learn as much as they can before the disorder progresses.

Milder learning difficulties may be experienced by those whose disorder is less severe or later-onset. However, as brain function declines intellectual ability is likely to worsen.

However, in all individuals with MPS III the ability to learn may be affected by other complications of the disorder that are not directly related to the brain. For example, deafness may make it more difficult to learn spoken language. This emphasises the importance of being aware of the various problems associated with the disorder to maximise quality of life.

Eyes

Clouding of the cornea (the outer clear layer of the eye) does not usually develop.

Vision may be affected by changes to the retina, or glaucoma (increased fluid pressure inside the eye). Mucopolysaccharide storage in the retina can result in loss of peripheral vision and night blindness. Night blindness may make a person not want to walk in a dark area, or wake up at night and be afraid; the use of a night-light or lamp may help. If vision is a concern, examination by an eye doctor (ophthalmologist) is recommended.

Head

Although not common, a condition known as hydrocephalus may develop. This is caused by a build-up of the fluid that surrounds the brain (the cerebrospinal fluid, or CSF). Thickening of tissues around the brain may obstruct the circulation and absorption of this fluid and cause pressure on the brain. Symptoms may include an increase in the size of the head, vomiting or drowsiness. Hydrocephalus needs to be monitored closely and can be treated surgically, if necessary, usually by the insertion of a shunt (a tube placed inside the skull that helps drain the excess fluid, usually into the abdomen).

Nose

The bridge of the nose may be flattened, and the passage behind the nose may be smaller than usual due to poor growth of the bones in the mid-face and thickened soft tissue in the nose and throat, and lead to narrowing of the airway. Chronic drainage of clear mucus from the nose (rhinorrhea) may occur, which is due to the abnormal drainage of normal secretions and chronic ear and sinus infections.

Throat

The tonsils and adenoids may become enlarged and may narrow the airway. If required, the adenoids can be surgically removed.

Breathing Problems

Sleep apnoea (not breathing for short periods whilst asleep) is not common but a person may sometimes stop breathing for short periods. It may be a sign that the oxygen level is low during sleep, which can damage the heart over time. (Note: pauses of up to 10-15 seconds may be normal.) The stop-start breathing can be very frightening for parents. If significant choking or episodes of interrupted breathing

whilst asleep are being experienced, evaluation by a sleep specialist is recommended. It is important to know that many individuals may breathe like this for years.

Management of airways and breathing problems

Sleep studies measure the blood oxygen level, breathing effort, brain waves during sleep and other monitors of the body's function. A sleep study is likely to require an overnight stay in hospital.

If sleep apnoea is a problem, treatment with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) may be needed during sleep. This involves placing a mask on the face each night and having air pumped into the airway to keep it open. This may seem extreme but is usually well tolerated because it can improve sleep quality as well as help prevent or reduce the risk of heart failure caused by low oxygen.

Chest postural drainage can also be helpful in clearing secretions from the lungs to improve breathing. A physiotherapist will be able to teach parents and caregivers how to do this.

Respiratory Infections

Frequent coughs and colds are common.

Medication can affect individuals differently, so it is advisable to consult your doctor before using over-the-counter medicines. Drugs to control mucus production may not help: antihistamines, for example, 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 in MPS III. Cough suppressants or drugs that are too sedating may cause problems with sleep apnoea by depressing muscle tone and respiration.

Secondary bacterial infections of the sinuses or middle ear may occur and require treatment, usually with antibiotics. Poor drainage of the sinuses and middle ear can make overcoming infections difficult: infections may improve whilst taking medication but promptly recur after it is stopped. Chronic antibiotic therapy may help with recurrent ear infections. Ventilation tubes can be used to improve drainage from the ear and speed resolution of infections: an ear, nose and throat (ENT) specialist will advise on which tube is best.

Infections that do not respond to antibiotic treatment may develop. Other medications can be prescribed to help manage this problem if it occurs. While over-using antibiotics is not advised, most individuals will require some type of treatment for most infections.

Ears

Deafness is common: it may be *conductive* or *nerve deafness* or both (*mixed deafness*) and may be made worse by frequent ear infections. It is important that hearing is monitored regularly so problems can be treated early to maximise the ability to learn and communicate.

Conductive deafness is due to impaired transmission of sound waves through the ear canal, the ear drum and the middle ear. Correct functioning of the middle ear depends on the pressure behind the ear drum being the same as that in the outer ear canal and the atmosphere. This pressure is equalised by a tube in the ear called the Eustachian tube, which runs from the middle ear to the back of the nose. If the tube is blocked, the pressure behind the ear drum will drop and the drum will be drawn in. The transmission of sound waves will then be impaired. If this negative pressure persists, fluid from the lining of the middle ear will build up and in time become thick, like glue, hence the condition being known as 'glue ear'.

Under general anaesthetic a small incision can be made in the ear drum (myringotomy) and the fluid sucked out. A small ventilation tube called a 'grommet' 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. Grommets will eventually fall out. If the conductive deafness recurs, T-tubes (a type of grommet which

stays in place longer) may be used. Due to the anaesthetic risks in MPS III (see *Anaesthetic*, below) the surgeon may decide to use T-tubes on the first occasion.

Sensorineural (nerve) deafness: in most cases nerve deafness is caused by 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 deafness is managed by the fitting of hearing aids. Some individuals may keep pulling out their hearing aids at first but it is important to persevere at wearing them to maintain communication.

Mouth and Teeth

The tongue may become enlarged; gum ridges can be broad, and the teeth widely spaced and poorly formed with fragile enamel. It is important to look after the teeth as tooth decay can be a cause of pain. Teeth should be cleaned regularly, and if the water in your area is not treated with fluoride it is advisable to give fluoride tablets or drops daily. Cleaning inside the mouth with a small sponge on a stick soaked in mouthwash will help keep the mouth fresh. 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.

If an individual has a heart problem, it may be advisable to give antibiotics before and after any dental treatment. This is because certain bacteria in the mouth may get into the bloodstream and cause an infection in an abnormal heart valve, potentially damaging it further.

If teeth need to be removed while under an anaesthetic, it should be done in the hospital under the care of both an experienced anaesthetist and dentist – never in the dentist's office.

Heart

Serious heart problems rarely occur in MPS III. If heart problems do develop, however, they may not cause any real problems until later in life.

Heart murmurs (sounds caused by turbulence in blood flow in the heart) may develop if the valves become damaged as the disorder progresses. Heart valves close tightly as blood passes from one chamber of the heart to another to stop blood 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. The opening of the valves may also become narrowed and make it more difficult for the heart to pump the blood properly. Some degree of heart valve leakage or blockage is common, but it is usually mild and surgery is rarely needed.

Slowly progressive valvular heart disease may be present for years without any apparent clinical effects. If the condition worsens, however, medications can be used to lessen the effect on the heart. Sometimes, an operation may be required to replace the damaged valves.

Your doctor may recommend a test known as an echocardiogram as often as necessary to monitor the heart. The test is painless and similar to ultrasound screening of babies in the womb.

Liver and spleen

The liver and spleen may become enlarged (hepatosplenomegaly). This does not usually lead to liver failure but it may interfere with eating and breathing and the proper fitting of clothes.

Abdomen and hernias

The abdomen may bulge out due to posture or weakness of the muscles. Part of the abdominal contents may push out from behind a weak spot in the wall of the abdomen: this is called a hernia. Hernias can come from behind the navel (umbilical hernia) or in the groin (inguinal hernia). Inguinal hernias can be

surgically repaired but will sometimes recur. Umbilical hernias are not usually treated unless they are causing problems: it is common for an umbilical hernia to recur after a repair has been made.

Bowel problems

Loose stools and diarrhoea are common. The cause of this is not fully understood. Occasionally, it results from severe constipation and leakage of loose stools from behind the solid mass of faeces. More often, however, parents describe it as "coming straight through". A medical examination may establish the cause. It may disappear with time but it can be made worse by antibiotics prescribed for other problems.

The episodic diarrhoea may be affected by diet; elimination of some foods may help. If antibiotics are the cause, eating plain live-culture yoghurt can provide a source of 'good bacteria' to help prevent the growth of harmful bacteria within the bowel: a diet low in roughage may also be helpful.

If constipation is a problem, an increase in roughage in the diet may assist. If this does not help or is not possible, laxatives or a disposable enema may be needed.

Skin

The skin is generally soft and has greater elasticity than in the other MPS disorders. However, thickening of the skin can occur as the disorder progresses. Excess hair on the face and back may also occur: this is called hirsuitism.

Bones and Joints

Problems with bone formation and growth are usually minimal. Features of osteoporosis can, however, develop as early as the teen years. As the bones become fragile and brittle there is an increased risk of fractures, and the decrease in overall stability increases the risk of falling. Prolonged use of anti-seizure drugs combined with decreased mobility can lead to brittle bones. Recent research has shown that high-dose vitamin D therapy can improve bone mineral density. Sensible exposure to sunlight will help maintain vitamin D levels.

Joint problems are also minimal but later in life joint stiffness may cause pain, which can be relieved by warmth and the prescribing of analgesics (pain relievers). Limited movement in the shoulders and arms may make dressing, toileting and self-care (e.g. brushing hair) difficult. Anti-inflammatory drugs, such as ibuprofen, can help with joint pain but they should be taken with or after food and monitored closely to prevent stomach irritation and ulcers.

Hips

The hips may become dislocated, usually due to muscle spasms and after the ability to walk is lost. Often, this does not cause problems and treatment may be unnecessary unless it is causing pain or other disability.

Cervical Spine

The *cervical spine* refers to the bones that support the neck. Whilst bone problems are not common in MPS III, the spinal cord may be gradually compressed by surrounding tissues, which are thickened, partly as a result of mucopolysaccharide storage or, more rarely, by structural defects in the upper vertebrae (bones) of the spine that results in instability. This can lead to weakness in the limbs and even paralysis. Both problems can be treated surgically if necessary.

Legs and feet

Over time, a tendency to stand and walk with the knees and hips flexed may develop. This, combined with a tight Achilles tendon, may cause a person to walk on their toes. Knock-knees can sometimes be a problem; this is unlikely to need treatment but, if severe, surgery may be required.

Hands
The fingers may contract and bend at the joints, and fully extending the arms may become difficult as the disorder progresses.

Cold hands and feet
As the disorder progresses, the part of the brain that regulates temperature may become damaged and result in cold hands and feet. It may not cause discomfort, but if it does the obvious remedies of heavy socks and warm gloves may be useful. In the later stages, sweating may become a problem at night, as well as cold hands and feet by day. Body temperature may sometimes drop (hypothermia): if this happens, they should be kept warm and medical advice sought on the best ways of managing the problem.

Movement disorders
A variety of movement problems have been reported in teenagers, beginning with eye fluttering, fast breathing and extreme restlessness. This can lead to sweating, arm and leg jerking and kicking and, in some cases, spasms with rigid arms and legs. These may or may not be linked to seizures and can be difficult to treat. Some individuals may appear to be in pain, while others may not. Therapies such as physical therapy, massage and water therapy have been tried, with varied success. Medical advice should be sought on the best ways of managing the problems.

General Management

MPS III children may be overactive, strong, usually cheerful and affectionate but hard work to look after. They usually have limited powers of concentration and less understanding than you would expect for their age and physical development. They could, for example, lock the bathroom door but be unable to understand how to get out again, even when told. They enjoy rough and tumble play, making a lot of noise and throwing toys rather than playing with them. They may be unaware of danger, stubborn, and unresponsive to discipline as they cannot understand what is required. Some may have outbursts of aggressive behaviour. As the disorder progresses, they become hyperactive, restless and their behaviour is often very difficult to manage. Toilet training may be achieved briefly but most will remain in nappies.

Initially, they may be able to learn although it will be more difficult for them than children without similar problems. Their rate of learning will slow: this may be apparent by 2-3 years of age or it may occur significantly later – the pattern is varied. Their ability to talk and communicate will also gradually be lost (talking may initially be delayed due to deafness). They will become more unsteady on their feet, and tend to fall frequently as they walk or run; eventually the ability to walk will be lost.

This gradual decline is very upsetting to family and friends but it is important to know that even when the child starts to lose skills they have learned there may be some surprising abilities left. Children will continue to find enjoyment in life even if they lose the ability to speak.

Behavioural problems
The difficult behaviour is generally not altered by behavioural therapy. Medications can sometimes help but will usually require regular medical review to help maintain effectiveness. Some parents have tried to modify behaviour with the support of a psychologist and a few have reported some limited success. However, behaviour will continue to change as the disorder progresses, and the usefulness of a particular behaviour modification technique may be short-lived.

It may be helpful for the child to join a play group or attend a school or after-school program where a variety of activities can occupy them. Ideally, there should be space to run around in and keep fit for as long as possible. Many children are calmed by the movement of a car and will travel well.

Diet

A balanced diet is important for health and well-being. There is no scientific evidence that a particular diet has any helpful effect in MPS III, and problems such as diarrhoea tend to come and go naturally. A change in diet may ease problems such as production of excessive mucus, diarrhoea or hyperactivity; reducing intake of milk, dairy products and sugar, as well as avoiding foods with too many additives and colouring have sometimes helped. It is advisable to consult your doctor or a dietician if major dietary changes are planned to ensure that essential nutrients are not left out. If the problems are eased, foods can be reintroduced one at a time to test whether any particular item seems to increase symptoms.

It is important to note that no diet can prevent the storage of mucopolysaccharides because they are made by the body. Reducing sugar intake or other dietary components does not reduce this storage.

Feeding and Swallowing

In the early stages of the disorder, feeding usually causes few problems. As it progresses, however, the ability to chew food and swallow is gradually lost. Foods may need to be mashed or pureed to an appropriate consistency; it is advisable to avoid mixing 'lumpy' foods with food of a smooth texture; meat may be tolerated more easily if it is made by slow cooking rather than just chopped into small pieces. Many become quite picky and may reject foods for no clear reason.

As the rhythm of swallowing is lost, spluttering and coughing whilst eating may become a problem. Moving your hand gently backward under their chin and slowly down the throat can help move the tongue and encourage swallowing. As the ability to swallow worsens, food or liquids may enter the lungs, which can result in recurrent pneumonia. During this time they may lose weight and require more time to be fed.

It is often difficult for a family to consider alternate means of feeding, such as through a naso-gastric (N/G) tube or a gastrostomy (G) tube. Talking with your doctor can help with your decision making.

Choking

When a person cannot chew and has difficulty swallowing, there is a risk of choking. Choking is frightening and reassurance can be provided by rubbing their back and holding their hands. If choking occurs, they should quickly be turned upside down or placed head-down over your knee, followed by three or four sharp pounds between the shoulders. If necessary, you may need to put your finger down their throat to try to dislodge the food item. Pounding on the back while they are sitting upright can make things worse because they might breathe in the food rather than coughing it out.

Choking can also occur with liquids, including secretions made by the body such as saliva. As swallowing becomes more difficult, drooling may become a problem and may require suctioning. Medication may sometimes be used to reduce the production of saliva and should be discussed with your doctor. If fever develops within a day or so of a choking episode, consult your doctor. It is possible that some food particles have entered the lungs and pneumonia may have developed.

Sleeping difficulties

Restlessness at night is common and many children do not sleep for more than a couple of hours at a time. The reason for this is not known. Medications may sometimes help but it may take a period of trial and error to establish which drug works best. Drugs often lose their effect after a while. Some parents choose to ration the use of medications to a few nights a week or accept that after a few weeks it may have to be discontinued for a while.

The thought of the child getting up in the middle of the night and having an accident while the rest of the household is asleep worries many parents. Some find it helpful to put a lock on the outside of the child's bedroom door, to replace the bedroom door with a Dutch door and lock the bottom section, to fit a stair gate in the doorway, or to place special pads under the carpet by the door which cause a bell to ring if the child leaves their room. Removing furniture and placing only a mattress on the floor helps prevent falls or injury in the night. Some parents find that special beds that help contain the child may be effective.

It is vital for parents to get sleep if they are to cope during the day. Some parents find they can achieve a longer period of unbroken sleep by putting the child to bed later and following a regular routine.

Seizures

In its later stage, frequent, minor seizures (known as *petit mal*) may occur, during which the ability to focus and concentrate is momentarily lost. More generalised seizures (known as *grand mal*) may also occur. During a seizure they should be placed on their side to prevent the inhalation of vomit and left in that position until the seizure is over. The airway should be checked to make sure it is clear; nothing should be put in their mouth. Seizures can usually be managed with conventional anti-seizure medications: it is not unusual to try several before finding what works best. It may be necessary to consider a helmet or other protective head-wear to prevent head injury if seizures are frequent or difficult to control.

Physical therapy

When the child is young and mobile, physical therapy may not be needed. Chest physiotherapy may be needed later to help clear infection.

As the child becomes older, the joints of the feet and ankles may become tight and less flexible. Hydrotherapy may help to keep the joints mobile. Some range-of-motion physical therapy may be useful but need not be intensive. Exercises that cause pain should be avoided. Even when immobile, it is important that proper support is provided whilst sitting to avoid uneven pressure on particular joints. Special braces may help if a problem at the ankle joint develops and makes walking difficult.

Anaesthetic

Generally, anaesthesia causes fewer problems in MPS III than in other MPS disorders.

However, because the airway may be narrower than usual, insertion of a very small breathing tube may be required for surgery. Placing the tube (intubation) may prove difficult. In addition, the neck may be somewhat lax and repositioning it during anaesthesia or intubation could injure the spinal cord. In some cases it may be difficult to remove the breathing tube after surgery due to swelling that may have occurred and it may need to be left in place.

In view of the anaesthetic risks it is recommended that all surgery (including elective surgery) is performed at a specialist medical centre rather than a local hospital, with anaesthetists who are experienced in managing difficult airways.

It is highly recommended that teachers and caregivers are informed of the anaesthetic risks in case of emergency.

There is a more detailed explanation of this subject in the specialist anaesthetic booklet published by the MPS Society.

Chewing

As they become more out of touch with their environment, behaviours such as chewing fingers, clothes or other items may develop. Because there is little one can do to stop this, it is best to provide a wide range of safe items on which to chew, such as rubber toys, teething rings or soft cloths. If the problem is severe and they start to injure their fingers, the elbows may need to be splinted for periods of the day so the hands cannot reach the mouth.

Education

Some children may benefit from attending a mainstream school in their primary school years and enjoying the social interaction with peers; a majority will equally benefit from a Special Educational Needs placement with small class sizes and a range of communication systems in place. Many will need the help of a classroom assistant. Behaviour problems may, however, limit or prevent school attendance.

Adapting the house

Mobility is likely to become progressively worse and dependence on parents and carers to meet everyday needs will likely increase in areas of incontinence, personal hygiene and nutrition. It is important to give early thought to how this can be managed when weight bearing and walking or climbing the stairs is no longer possible.

Parents have found it helpful to designate a room or part of a room for their affected child. If possible, the area should be within hearing and visual distance and be made safe for the child to play without constant supervision, so the parent can interact with other children or deal with household tasks.

The Quieter Stage

The change from the hyperactive, noisy period to a quieter period is likely to be gradual. Families will realise that their child no longer runs everywhere and is happier sitting than standing; many will be easily pleased, perhaps by looking through the same little book of photographs, having stories read or watching the same video many times over; frequent dozing is not uncommon.

Weight will be lost gradually as muscles weaken and chest infections may become more frequent. Many die peacefully after an infection or from the heart's gradual failure. Family and friends may find it helpful to prepare for the time of death. It is not possible to say how long this 'quiet' period will last.

Taking a break

Caring for someone with progressive disability is physically and emotionally tiring. Parents will need regular breaks so they can continue providing care without becoming exhausted; brothers and sisters also need to have their share of attention and to be taken on outings that may not be feasible with an affected child.

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 and that of their family. This may include respite care, symptom management and bereavement support and may extend over a period of time. It is important to talk with your medical team to ensure you are aware of and have access to the various services and support networks that are available.

Enjoying your child

A child with MPS III will have a life that is different from the majority of others but they have delightful personalities and are extremely lovable. They will give you love that is totally unconditional. They will make you laugh when you think you may never laugh again. Their love is infectious to everyone around them.

They communicate with you even when they lose their verbal skills. Their eyes will beguile you, their smiles will entice you and their spirit will raise yours when you think nothing else can.

The majority of people with MPS III are likely to develop rapidly progressive symptoms. Whist brain function will be affected in all people with MPS III, in some cases symptoms may develop more slowly or later in life. The following information may therefore be relevant in those cases.

Psychosocial Issues

At the present time there has been no research carried out that explores the psychosocial development of people who have more slowly progressive or later-onset MPS III.

However, it is important to consider how the additional challenges in life may be experienced. People with later-onset or less severe MPS III can adapt socially and emotionally in different ways to new challenges or problems. The adolescent and teenage years may be more difficult because of all the physical and psychological changes that occur, whilst also having to cope with the problems caused by the disorder itself**.** Mental health is an important issue and it is therefore vital that steps are taken for an appropriate psychology referral as part of a comprehensive, on-going package of support.

Siblings also need to be considered. No formal studies have been carried out to assess the psychosocial effects of MPS III in siblings. It is not uncommon for unaffected siblings to feel somewhat neglected or less important in the family unit as the greater share of attention is placed on the needs of the affected person. Parents may need to monitor the broader impact of the disorder on siblings and seek medical or psychological help if necessary.

Education

Academic achievement is possible. To reach their full academic potential it is important that the education authority and school are aware of resources that may be required: this may include a one-to-one classroom assistant, appropriate classroom furniture and access to an individual computer, hearing or visual aids and extra time to complete tasks that may not seem difficult but which may require more effort to complete due to the intellectual and physical problems associated with the disorder.

Independence

Developing the necessary skills to lead an independent adult life can be very difficult and is uncommon in MPS III. However, if independence is possible it should be encouraged but with provision for appropriate support as the condition progresses.

Employment

The disabilities caused by the disorder should not prevent access to meaningful employment. There is considerable responsibility on the part of employers under the Disability Discrimination Act to meet the needs of employees with a disability.

Treatment

Overview

Currently, there is no effective treatment or cure for MPS III and treatment options are generally aimed at symptom management and supportive or palliative care.

The involvement of the brain in MPS III presents a special challenge in devising effective therapies. This is primarily because the brain is protected from the rest of the body by a barrier (the *blood-brain barrier*) that carefully controls what can and cannot enter the brain. This creates problems for treatments that are given via the bloodstream, such as enzyme replacement, for example (see below): the enzyme circulates throughout the body to treat the physical symptoms of the disorder but it does not readily enter the brain to stop the progressive decline in brain function. Researchers are therefore devising different methods by which to deliver enzyme to the brain, and progress is being made.

Several forms of treatment for MPS III have been tried or are in clinical trial. These include:

Haematopoietic Stem Cell Transplant (HSCT)

Bone marrow transplant and umbilical cord blood transplants are both forms of HSCT. The principle of HSCT is that cells taken from a healthy, unaffected donor (either bone marrow or cord blood) are transplanted into an affected person to produce normal amounts of the enzyme that is otherwise defective and thereby treat the disorder. The donor enzyme is not only produced within the transplanted cells but is also released by those cells into the circulation where it can be taken up by other cells in the body, including the brain.

HSCT has been used in children with MPS III but there is no evidence that it stops the decline in brain function and is therefore not recommended as a treatment. The reason(s) why it does not work in MPS III is not yet known.

Enzyme replacement therapy (ERT)

This form of therapy is based on the same principle as HSCT except that the missing enzyme (one of the four listed in *What causes MPS III?*) is replaced with a pharmaceutical-grade enzyme prepared commercially and given by infusion into the bloodstream rather than being produced inside the body by transplanted cells.

At the present time, ERT is not generally available for MPS III. However, a clinical trial is currently being conducted in patients with MPS III type A. Patients enrolled in this trial are receiving enzyme (in this case, sulphamidase) via injection directly into the cerebrospinal fluid (the fluid that surrounds the brain and spinal cord). To find out more about this trial visit *www.clinicaltrials.gov [ID: NCT 01299727]*

Gene Therapy

Gene therapy aims to replace the defective gene with a functional one. The principle is that the functional gene will code for the normal production of enzyme, reproduce within the cells of the body (and brain) and produce sufficient amounts of enzyme to remove stored mucopolysaccharide and prevent further storage. Unlike ERT, which requires repeated administration, it is hoped that gene therapy will be a once-off treatment. A clinical trial of gene therapy in patients with MPS III type A commenced in 2011. For further information about the trial, visit *www.sanfilippo-syndrome.org/news/*.

It is important to note that ERT and gene therapy specific for one form of MPS III will not work for the other three. This is because they are all caused by different enzyme deficiencies. Therefore, these forms of treatment will need to be developed independently for each of the four MPS III disorders.

Substrate Deprivation/Reduction Therapy

This aims to reduce the amount of mucopolysaccharide that is being made by the body, leading to a reduction in the amount being stored. Two clinical trials of this form of therapy have been trialled in MPS III patients. The first used a compound called *Miglustat*, which did not improve clinical symptoms and has not been recommended for use as a treatment for MPS III. The second compound tested is called *genistein*; the results have been inconclusive and further studies are needed. Further information on these trials can be obtained by visiting *www.sanfilippo-syndrome.org/news/*.

As a general rule, substrate deprivation/reduction therapy will only work in those individuals whose mutations allow some active enzyme to be made by the body.

The Future

In common with all of the MPS disorders, treatment and management for MPS III continue to evolve so the information presented here will change with time. It is important to keep up a regular dialogue with your medical team. Regular monitoring is an important way of managing problems before they become potentially serious, and to maximise quality of life. Living with a progressive disorder such as MPS III is difficult and challenging and this monitoring can also be a way to share some of that difficulty. As knowledge is built up and shared new treatments can be developed and quality of life improved for all.