What is ML III?
Mucolipidosis Type III (ML III) is one of the lysosomal storage disorders known collectively as Mucolipidoses and is closely related to Mucopolysaccharidoses.

ML III is sometimes referred to as Pseudo-Hurler Polydystrophy as it resembled a less severe form of Hurler Disease (MPS I). Polydystrophy means that many organs are abnormal.

ML III was first described in 1966 by Dr Maroteaux and Dr Lamy from France.

Whilst there is no cure for individuals affected by ML III, this fact sheet explores the disease’s presentation and clinical management. This fact sheet is produced by the Society for Mucopolysaccharide Diseases (MPS Society) drawing on the experiences of parents and doctors with reference to medical literature.

What Causes ML III?
In the course of normal life there is a continuous recycling process of building new materials and breaking down old ones ready for disposal. This activity takes place in a special part of the body’s cells called the lysosome. This process requires a series of biochemical tools called enzymes which can only reach the lysosomes after a special signal has been attached to them. In individuals with ML III this signal is not attached so the enzymes are unable to get to the right place and are therefore lost outside the cell.

Babies may show little sign of the disease but symptoms start to appear as more and more cells become damaged by the accumulation of unwanted deposits.

Does ML III Affect Individuals Differently?
Mucolipidoses are a group of storage disorders displaying a spectrum of clinical symptoms. At the severe end, these are labeled ML II. Less severely affected individuals are considered to have ML III.

How Common is ML III?
The MPS Society, which co-ordinates the Registry for Mucopolysaccharide and related diseases has shown that ML III is a rare condition. For example, between 1989 and 1999, 5 babies were born with ML III in the UK.

How is ML III Inherited?
ML III is an autosomal recessive disease whereby both parents must carry the same defective gene and each pass this same defective gene to their child. Where both parents are carriers of the ML III gene there is a 25% (1:4) chance of having an affected child with each pregnancy. There is a 50% (1:2) 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. The remaining 25% (1:4) will be neither affected nor a carrier.

There is a more detailed explanation of this complex subject in the booklet on inheritance available from the MPS Society.
Conductive Deafness (Glue Ear)
Under general anaesthetic a small incision behind the eardrum can be made (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 Conductive Deafness recurs T-tubes (a type of grommet which stays in place longer) may be used. Due to the anaesthetic risks for individuals with ML III, the surgeon may decide to use T-tubes on the first occasion.

Can You Test for ML III in Pregnancy?
For each pregnancy the chances of a baby inheriting ML III are totally independent of whether a previous child was affected by the disease. Prenatal tests can be arranged early on during a pregnancy for those families who already have had a child with ML III. Both Amniocentesis and Chorionic Villus Sampling (CVS) can be used to diagnose the disease in utero. Most laboratories do prenatal tests on cultured cells. It may take three to four weeks for a result.

Genetic Counselling
All parents of children with a lysosomal storage disease should consider asking for genetic counselling before having another child. The counsellor will be able to advise on the risk to close relatives and to suggest whether the wider family should be informed.

Clinical Presentation of ML III
Growth
Individuals with ML III may grow between four foot and five feet six inches.

Physical Appearance
The facial appearance of most individuals with ML III may be little changed by the disease. Others may be affected in the same way as those with ML II. In this instance 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 have very prominent gums. Eyebrows may be bushy and meet in the middle and the eye sockets are shallow which makes the eyes appear prominent.

The hair on the head often has a lighter colour than that of brothers or sisters and can gradually turn white. The head shape of children with ML III may be changed by the early closing of the soft part of the baby’s skull.

Intellectual Ability
Many individuals with ML III will be of normal intelligence but some may have a learning disability which, in the majority of cases, is mild to moderate.

Eyes
Clouding of the cornea caused by storage of waste products may be seen in individuals with ML III. However, this rarely interferes with vision and is not particularly noticeable.

Mouth & Teeth
The gums are often overgrown and swollen and teeth may be late and troublesome coming through. Teeth may not come down much below the edge of the gum and are often widely spaced and poorly formed with fragile enamel.

It is important that teeth are well cared for as tooth decay could be a cause of pain. The tongue may be enlarged and the roof of the mouth has a high arch.

Dental Hygiene
Teeth must be well cared for to avoid the need for extractions. If the water in your area has not been treated with fluoride, fluoride tablets or drops daily should be considered. If your child is severely affected it may be safer for any treatment to be carried out in hospital.

The dentist should be informed if your child has a heart problem. You will probably be advised that s/he should be given antibiotics before and after any dental treatment because certain bacteria in the mouth may get into the blood stream and cause an infection of the heart valves.

If teeth need to be removed under anaesthetic, this should be carried out in hospital under the care of an experienced anaesthetist and never in the dental surgery.

Ears
Some degree of deafness is common in individuals suffering from ML III. It may be Conductive Deafness, Nerve Deafness or both (Mixed Deafness) and can be made worse by frequent ear infections.

It is important that individuals with ML III have their hearing checked regularly and for problems to be treated early to improve or maintain the ability to communicate and learn.

Conductive Deafness is concerned with 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 the Eustachian Tube which runs from the middle ear to the back of the nose. If this tube is blocked the pressure behind the eardrum will drop, the drum will be drawn in and the transmission of sound waves will 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 is known as ‘glue ear’.

Conductive Deafness (Glue Ear)
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Grommets will eventually fall out. If Conductive Deafness recurs T-tubes (a type of grommet which stays in place longer) may be used. Due to the anaesthetic risks for individuals with ML III, the surgeon may decide to use T-tubes on the first occasion.
Skin
The skin is often thickened and lacking elasticity. Occasionally there may be more body hair than normal. This is called hirsutism.

Respiratory Infections
Medication may affect individuals with ML III differently so it is essential to consult your doctor rather than using over-the-counter medication. Medication for controlling mucus production may not help, for example; 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 children with ML III. Cough medicines that have a sedating effect may cause more problems with sleep apnea by depressing muscle tone and respiration. Children with ML III commonly end up with secondary bacterial infections which should be treated with antibiotics.

Heart
Some individuals may develop problems with one of the heart valves. ‘Heart murmurs’ will occur if the valves become damaged by the storage of Mucopolysaccharides.

In order to stop blood flowing back in the wrong direction, the heart valves are designed to close tightly as blood passes from one chamber of the heart to another. If a valve is weakened or changed in shape it may not shut firmly enough and a small amount of blood may leak back. This may, in time put a strain on the heart. This condition can be treated.

Individuals with ML III may develop the more serious problem of thickening and weakening of the heart muscles (known as cardiomyopathy) often as a result of the damaged heart valves. In some cases drugs may be prescribed to try and help the problem.

Infections
Children with ML III are prone to frequent chest and ear infections and tend to have runny noses. The shape of the chest is abnormal and it cannot move freely in order to allow the lungs to take in a large volume of air. The tissue of the lungs becomes thickened by storage material and stiffer than usual. The lungs become like a balloon which has never been blown up before and will, therefore need greater force to cause expansion.

There is an increase in secretions which are harder to clear as the restricted lungs make it difficult for sufferers to take a deep enough breath to cough properly.

When the lungs are not fully cleared there is an increased risk of infection which can lead to scarring of the airways causing further obstruction.

Liver, Spleen & Abdomen
The liver and spleen are not usually enlarged in individuals with ML III. The abdomen, however, may protrude due to weakness of the muscles and to the limited space available to internal organs.

There is a possibility that part of the abdominal contents may push out behind a weak spot in the wall of the abdomen. This is called a hernia.

Hernias
A hernia can come from behind the navel (umbilical hernia) or from the groin (inguinal hernia). Inguinal hernias should be repaired by an operation but hernias will sometimes recur. Umbilical hernias are not usually treated unless they are small and cause entrapment of the intestine, or are very large and problematic. Recurrence of an umbilical hernia is common even after a repair.

Bones & Joints
There is a wide variation in the severity of problems, even between affected brothers and sisters.

Skeletal problems may develop later in life. Some individuals may have stiff hips as the supporting socket is not formed properly. They may also have pain in their joints if they are very active.

Surgery on the hips may be used as a last resort if pain becomes a real problem. Pain may also be relieved by warmth and the prescribing of analgesics. The limited movement in the shoulders and arms make dressing difficult.

Sensorineural Deafness (Nerve Deafness)
In most cases the cause of Nerve Deafness is damage to the tiny hair cells in the inner ear. It may accompany Conductive Deafness, in which case it is referred to as Mixed Deafness.

Nerve Deafness is managed by the fitting of hearing aids. More severely affected children may keep pulling out their hearing aids at first but it is important to persevere at wearing them so that communication can be maintained.

Heart Problems
Some individuals with ML III may develop problems with the aortic or mitral valve having slowly progressive valvular heart disease for years without any apparent clinical effects. An ECG (electrocardiogram) should be carried out annually or as often as your doctor thinks necessary in order to show whether any problems are starting. The test is painless and similar to the ultra sound screening of babies in the womb. It can identify problems with the heart muscle, function and valves.

Spine
Sometimes the second vertebra in the neck does not develop properly but this is very unlikely to cause problems.

This situation can be kept under review by MRI scans and, if there are clinical signs or other evidence of compression of the spinal cord, an operation could be performed to correct the defect.
Hands
The shape of the hands is very noticeable in individuals with an MPS or related disease and has been used as the symbol of the MPS Society. The hands are short and broad with stubby fingers which gradually become curved over or ‘clawed’. Many individuals with ML III develop Carpal Tunnel Syndrome.

Carpal Tunnel Syndrome
Although a child or adult with ML III may not complain of pain, they may already have Carpal Tunnel Syndrome. Doctors may advise that this is monitored with a nerve conduction study which will show whether the syndrome is present. This test would also be carried out if there is any weakness or numbness in the hand or decreased muscle mass at the base of the thumb. This disorder can be treated by a minor operation.

General Management of ML III
Diet
There is no scientific evidence that a particular diet has any beneficial effect. Symptoms such as diarrhoea tend to come and go naturally. Some parents find that a change in their child’s diet can ease problems such as diarrhoea. Cutting down on milk, dairy products and sugar as well as the avoidance of foods with too many additives and colourings have all been said to help individual children. It would be advisable to consult your doctor or a dietician if you plan major changes to ensure that the proposed diet does not leave out any essential nutrients. If your child’s problems are eased you could try re-introducing foods one at a time to test whether anything in particular appears to increase your child’s symptoms.

Physiotherapy & Hydrotherapy
Individuals should be as active as possible to improve their general health and a physiotherapist may be able to suggest ways of achieving this. For children the best forms of physiotherapy are exercises that are introduced through play and that don’t involve stretching or the rotating of joints.

Drugs
Individuals with ML III may be affected differently by drugs so it is essential to consult your doctor rather than purchase over-the-counter medication. Drugs may be tried for controlling mucus production but some may make the mucus thicker and harder to dislodge. This may also make your child more irritable. The use of sedatives can increase the problem of sleep apnea by depressing respiration.

It is now recognised that frequent use of antibiotics may make them less effective when really needed and that repeated use can also cause thrush (a fungal infection which commonly affects the mouth or vagina and produces a white curd-like deposit). Thrush causes irritation and discomfort and will need to be treated.

Your doctor may therefore wish to limit the number of times antibiotics are prescribed for coughs and colds.

Anaesthetic
Giving an anaesthetic to an individual with ML III requires skill and should always be undertaken by an experienced anaesthetist or paediatric anaesthetist in the case of children. In some cases it is difficult to remove the breathing tube after surgery is completed.

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

Life Expectancy
Individuals with ML III live well into adult life, however, it is hard to be precise about life expectancy as the condition has only been recognised for approximately 30 years; therefore there may be even older adults who have never been given the diagnosis of ML III.

Living with a Child or Adult with ML III
Psychosocial Issues
At the present time there has been no research carried out that explores the psychosocial development of individuals affected by ML III so it is not possible to make definitive statements about this subject. However, as a parent of a child or young person with ML III, it is important to consider how their disability may cause them to experience additional challenges in life.

Children and adults with ML III adapt socially and emotionally in different ways and some may not differ greatly from their healthy peers in terms of mental health problems or achievements in developmental milestones. Other children and young adults, as they grow older, adapt to the challenges posed by their disability in other ways. This can be manifested as social inhibition and a tendency to internalise problems. Adolescence may be more of a challenge for young people with ML III as they have to experience all the physiological and psychological changes as well as any illness-related changes or limitations. Developing the necessary skills to lead independent adult lives can be very difficult and some young people with ML III may experience difficulty in establishing independence from their family, an important step in achieving social maturity.

Mental health problems such as depression and lack of motivation are seen in teenagers and young adults with ML III so it is vital that, as part of a comprehensive, on-going package of support, steps are taken for an appropriate psychology referral.
Independence

Individuals with ML III should be encouraged to be as independent as possible to lead full and enjoyable lives. The teenage years may be difficult; if ordinary adolescents worry about a pimple on the chin, think how much more teenagers with ML III must worry about their appearance and the restrictions imposed by their condition. Individuals may be helped by meeting or being put in touch with other teenagers and adults with the same condition. Ask the MPS Society to put you in touch through the MPS Befriending Scheme. Adults with ML III have the potential to live independently, claiming appropriate financial support to purchase the services required.

Education

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

Employment

The physical disabilities of those suffering from ML III should not, in themselves, prevent people from accessing 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.

Home Adaptations

Appropriately adapted living accommodation will greatly enhance the ability of an individual with ML III to develop independent living skills. Where mobility is restricted, a wheelchair may be required for mobility outdoors whilst mobility indoors could be reduced to only a few metres due to the pain and joint constrictures resulting from the disease.

Furthermore, this pain may impact on the individual’s ability to undertake personal care and daily living tasks. A carer may be required to assist.

If mobility is restricted to such an extent that a wheelchair is used, plans for any home adaptations will need to allow adequate space to accommodate this. This may also be an important consideration for the future even if a wheelchair is not required at the time.

Appropriately adapted living accommodation will therefore greatly enhance independence. The process of achieving a home adaptation is means-tested and is a lengthy process. It is prudent to plan ahead whenever possible.

The Future

Teenagers with ML III will go through the normal stages of puberty although it may be delayed. There is a report of one affected male who has four children.

A woman with ML III would almost certainly be fertile. Individuals with ML III are automatically carriers but would not pass the disease to their children unless they happened to have a partner who was a carrier.

Treatment of ML III

At present there is treatment for symptoms as they arise, but no cure for the underlying disease. Bone Marrow Transplant (BMT) is not recommended for individuals with ML III. Research into Bisphosphonate Therapy, a treatment commonly used to reduce bone loss and weakness, is being carried out to investigate the effect of the drugs on skeletal problems. Advice on this should be discussed with your, or your child’s consultant.

About the MPS Society

The Society for Mucopolysaccharide Diseases (MPS Society) was founded in 1982 and represents children and adults suffering from MPS and related diseases, their families, carers and professionals throughout the UK.

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