What is Beta Mannosidosis?
Beta Mannosidosis is a rare lysosomal storage disorder of glycoprotein catabolism caused by a deficiency of lysosomal beta Mannosidase activity.

Beta Mannosidosis was first described by Jones and Dawson in 1981.

Beta Mannosidosis is an enzyme deficiency disorder which results in defective mannosidase activity (the accumulation of mannose-rich Oligosaccharide chains). This accumulation is responsible for many problems that affect individuals with Beta Mannosidosis.

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

What Causes Beta Mannosidosis?
Oligosaccharides are long chains of sugar molecules used in the building of bones, cartilage, skin, tendons and many other tissues in the body.

“Oligo” means a small number and “saccharide” is a general term for a sugar molecule.

In the course of normal life there is a continuous recycling process of building new Oligosaccharides and breaking down old ones. This process requires a series of special biochemical tools called enzymes. Children and adults affected with Beta Mannosidosis have a malfunctioning or missing enzyme called Beta Mannosidase.

Partially broken down mannose-containing chemicals remain stored in the body and over time begin to build up. This causes progressive damage to the cells.

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

How Common is Beta Mannosidosis?
The MPS Society, which co-ordinates the MPS Registry for MPS and related diseases, knows of 3 affected individuals in the UK. There are probably many more patients that have not been diagnosed or reported.

Does Beta Mannosidosis Affect Individuals Differently?
Beta Mannosidosis, like most MPS and related disorders is very variable. Some individuals with Beta Mannosidosis will have mild to moderate learning difficulties which may develop in childhood or adolescence.

It is important to remember that Beta Mannosidosis is extremely varied in its effects. A whole range of possible symptoms are outlined in this fact sheet, however affected individuals may not experience all of them.

How is Beta Mannosidosis Inherited?
Genes are inherited from our parents and control how tall we are as well as the colour of our eyes and skin. Some genes we inherit are “recessive” which means we carry that gene but it does not have any effect on our development.

Beta Mannosidosis is caused by a recessive gene. If an adult carrying the abnormal gene has a partner who is also a carrier, there will be a 25% chance with every pregnancy that the foetus will inherit the defective gene from each parent and will suffer from the disease. There is a two out of three chance that unaffected brothers and sisters of those affected by Beta Mannosidosis will be carriers. They can be reassured, however that as the disease is so rare, that the chance of having a partner who is another carrier is very slight, unless the individuals are from the same family.
**Can You Test for Beta Mannosidosis in Pregnancy?**

If you have a child with Beta Mannosidosis it is possible to have tests during any subsequent pregnancy to find out whether the foetus is affected. It is important to contact your doctor as soon as you suspect that you may be pregnant if you wish for tests to be arranged.

Both amniocentesis and chorionic villus sampling can be used to diagnose Beta Mannosidosis in utero.

**Genetic Counselling**

All parents of children with a lysosomal storage disease should consider asking for Genetic Counselling before having other children. The counsellor should be able to provide non-directive advice on the risk to close relatives, the reproductive choices available and to suggest whether the wider family should be informed.

**Clinical Presentation of Beta Mannosidosis**

**Growth**

Babies with Beta Mannosidosis may be larger than average at birth and may grow faster than normal during the first few years of life. However, as they get older individuals with Beta Mannosidosis will be restricted in their growth.

**Physical Appearance**

Unlike other storage disorders, the facial appearance of children with Beta Mannosidosis can be normal. Others, however will resemble each other very closely. Their faces may be chubby and their heads rather large with a prominent forehead. The neck may be short and the nose broad with a flattened bridge. The lips are often thickened and the hair tends to be coarse. The ears are often large and low-set.

**Intellectual Ability**

Individuals with Beta Mannosidosis at the severe end of the spectrum usually experience progressive storage of Oligosaccharides in the brain. This is primarily responsible for the learning difficulties seen in affected children and adults however, the pattern is very varied.

Individuals at the less severe end of the spectrum may have mild to moderate learning difficulties.

**Behaviour**

Some individuals may be very introverted, prone to depression and other behavioural problems such as hyperactivity, impulsivity or aggression.

**Brain**

The brain and the spinal cord are protected from jolting by the cerebrospinal fluid that circulates around them. In some individuals with Beta Mannosidosis the circulation of the fluid may become blocked over time.

The blockage (known as communicating hydrocephalus) causes increased pressure in the head which can press on the brain and cause headaches, vomiting and problems with vision. If left untreated development can be delayed.

**Hydrocephalus**

Hydrocephalus can be confirmed using a CT or MRI scan. A lumbar puncture with a pressure measurement is another way to assess if Hydrocephalus exists. If Hydrocephalus is confirmed it can be treated by the insertion of a thin tube (called a shunt) which drains fluid from the brain. This shunt has a pressure sensitive valve which allows spinal fluid to be drained when the pressure around the brain becomes too high. A lack of swelling around the optic disc does not rule out Hydrocephalus in an individual suffering from Beta Mannosidosis.

**Eyes**

Individuals with Beta Mannosidosis may have minor abnormalities that are not usually associated with severe visual impairment.

**Seizures**

Almost half of those affected by Beta Mannosidosis are likely to have seizures or fits. This may take different forms, for example absence episodes or more generalised tonic-clonic seizures. Fortunately, most individuals will respond favourably to anticonvulsant medication.

**Ears**

Some individuals suffering from Beta Mannosidosis may have a degree of hearing loss. 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 Beta Mannosidosis have their hearing checked regularly and for problems to be treated early to improve or maintain the ability to communicate.

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 equalised by the Eustachian Tube which runs from the middle ear to the back of the nose. If the tube is blocked, the pressure behind the eardrum will drop and the drum will be drawn in.

If this negative pressure persists, fluid from the lining of the middle ear will build up and in time become thick like glue, hence the condition being known as “glue ear”.

**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 the surgeon may decide to use T-tubes, a type of grommet which stays in place much longer. In view of the anaesthetic risks for individuals with Beta Mannosidosis, the surgeon may decide to use T-tubes on the first occasion.
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 which is referred to as Mixed Deafness. Nerve Deafness is managed by the fitting of hearing aids in most individuals with Beta Mannosidosis. 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. Other children with Beta Mannosidosis have found radio aids and the loop system helpful at school and at home.

Nose & Throat
Frequent coughs, colds and throat infections are common problems for those suffering from Beta Mannosidosis. The tonsils and adenoids often become enlarged and can partly block the airway. For this reason they may be removed. The neck may be short, which may contribute to the problems in breathing. The windpipe (trachea) becomes narrowed by storage material and is often more floppy, or softer than usual due to abnormal cartilage rings in the trachea. Nodules or excess hardening of tissue can further block the airway.

Typically the bridge of the nose is flattened and the passage behind the nose is smaller than usual due to poor growth of the bones in the mid-face and thickening of the mucosal lining.

Mouth & Teeth
Individuals with Beta Mannosidosis may have an enlarged tongue.

Dental Hygiene
It is important that the teeth are well cared for to avoid the need for extractions. If the water in your area has not been treated with fluoride, individuals with Beta Mannosidosis should have fluoride tablets or drops daily.

Cleaning around the mouth with a small sponge or a stick soaked in mouthwash will help keep the mouth fresh and avoid bad breath. Dribbling is a common problem and a plastic-backed bib under the clothes may prevent soreness.

Regular checks at the dentist are important as tooth decay could be a source of pain. If your child is severely affected it may be safer for treatment to be carried out at a hospital. It is important that you inform the dentist if your child has a heart problem as you will probably be advised that s/he should be given antibiotics before and after any dental treatment. This is 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 a hospital under the care of an experienced anaesthetist and never in the dental surgery. It may be possible for the hospital to carry out other treatment or investigations under the same anaesthetic.

Chest
The shape of the chest may be 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 unable to move freely to allow the lungs to take in a large volume of air. The muscles at the base of the chest (diaphragm) may be pushed upwards by an enlarged liver and spleen, further reducing the space for the lungs. When the lungs are not fully cleared, there is an increased risk of infection.

Respiratory Infections
Individuals with Beta Mannosidosis commonly suffer from recurrent respiratory infections, particularly within the first year. These infections should be treated with antibiotics. Medication may affect individuals with Beta Mannosidosis differently, so it is essential to consult your doctor rather than using “over-the-counter” medication.

Medication for controlling mucus production may not help. Medicines 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. Cough medicines that have a sedating effect may cause more problems by depressing muscle tone and respiration.

Immune System
Frequent coughs, colds and throat infections are common problems for many individuals with Beta Mannosidosis. The white blood cells that are important for fighting off infection do not work very well in those with Beta Mannosidosis. This means that infected individuals are at risk from infection, especially within the respiratory system and middle ears. Antibiotics should be prescribed early to affected patients and should be given continuously to prevent infection in those patients who suffer from recurrent or repeated infections.

Liver & Spleen
In most individuals with Beta Mannosidosis the liver and spleen become enlarged by storage of Oligosaccharides (known as hepatosplenomegaly). The enlarged organs do not usually cause problems, but they can interfere with eating and breathing.

Bones & Joints
Individuals with Beta Mannosidosis tend to have problems with bone formation and growth. This may lead to both bone and neurological problems if nerves are compressed by bone. Over time, bone changes in Beta Mannosidosis tend to be progressive and arthritis may occur from a young age. Beta Mannosidosis sufferers tend to have shallow hip sockets that are deformed.

The heads of the Femur (the highest part of the thigh bones) are porous and the shaft of the long bones are sometimes widened. Joint stiffness is a common feature of Beta Mannosidosis and the maximum range of movement of all joints may become limited. Stiffness may cause pain. This may be relieved by warmth and ordinary painkillers. Anti-inflammatory drugs such as Ibuprofen can help with joint pain but they should be taken with or after food and monitored closely to make sure that irritation and ulcers of the stomach do not occur.
Spine
The bones of the spine (vertebrae) normally line up from the neck to the buttocks. Individuals with Beta Mannosidosis can have poorly formed vertebrae that may not stably interact with each other. One or two of the vertebrae in the lower back are sometimes smaller than the rest and set back in line. This mild backward slippage of the vertebrae can cause a slight angular curve to develop. This is known as kyphosis or gibbus. This is usually mild in patients with Beta Mannosidosis.

Scoliosis (when the spine is curved from side to side) is also seen in individuals with Beta Mannosidosis.

Hands
Individuals with Beta Mannosidosis often experience pain and loss of feeling in the fingertips caused by a condition called 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 wrist in the space between the carpal bones and the ligaments. Thicken of these ligaments causes pressure on the nerves which can cause irreversible nerve damage. This will cause the muscle at the base of the thumb to waste away.

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

Legs & Feet
Many individuals with Beta Mannosidosis stand and walk with their knees and hips flexed. This, combined with tight Achilles Tendon, may cause them to walk on their toes. Sometimes these individuals have knocked knees but this is very unlikely to need treatment. The feet are broad and may be stiff with the toes curved under, rather like the hands.

Skin
Individuals with Beta Mannosidosis have been seen to exhibit a skin rash of small red spots called angiokeratoma) on the bathing trunk area.

General Management of Beta Mannosidosis

Anaesthetic
Giving an anaesthetic to an individual with Beta Mannosidosis requires skill and should always be undertaken by an experienced anaesthetist. Where a child is concerned this should be a paediatric anaesthetist.

The airway can be very small and may require a very small endotracheal tube. Placing the tube may prove difficult and require the use of a flexible bronchoscope. In addition, the neck may be somewhat lax and repositioning during anaesthesia or intubation could cause injury to the spinal cord.

For some individuals, it is difficult to remove the breathing tube after surgery is completed.

There is a more detailed explanation of this complex subject in the booklet on ‘Anaesthetic Management in MPS’ available from the MPS Society.

Physiotherapy & Hydrotherapy
Physiotherapy and Hydrotherapy can be useful to help individuals with Beta Mannosidosis achieve specific and realistic goals in daily life and to drain mucus from the chest.

It is common sense for individuals to be as active as possible to improve their general health and the physiotherapist may be able to suggest ways of achieving this. For younger individuals the best forms of physiotherapy are exercises that are introduced through play.

In adults it is important to remember that passive stretching may be painful and should only be used with caution.

Life Expectancy
There is a wide range of life expectancy according to the severity of the disease.

Those who are less severely affected may have a reasonably normal life span. Survival into the fifth and sixth decades of life is well documented.

Those who are more severely affected may lose their lives in early adulthood.
Specific Treatment of Beta Mannosidosis

Haematopoietic Stem Cell Transplantation (HSCT)

Haematopoietic Stem Cell Transplantation (HSCT) involves taking cells that are normally found in the bone marrow from bone marrow umbilical cord blood or peripheral blood (after simulation of the bone marrow to produce lots of stem cells) and then transplanting them into the affected patient. Cord blood is collected from the afterbirths (placenta) of new born babies with their parent’s consent. The baby donors are not normally related to the patient although the cord blood needs to provide a suitable match. In all other aspects of the procedure, the outcomes are the same as having a bone marrow transplant.

For some years now, (HSCT) has been used to treat children with Mucopolysaccharide and related diseases. A few children with Mannosidosis have undergone HSCT, although this has not been shown to have any therapeutic benefit in preventing the damage to the brain that occurs in individuals severely affected by Mannosidosis.

Enzyme Replacement Therapy (ERT)

Enzyme Replacement Therapy (ERT) is based on the principle that the recombinant form of the enzyme that is missing or malfunctioning in individuals with an MPS or related disease is given via repeated intravenous infusion in order to reduce the symptoms and clinical manifestations associated with the disease.

Although there is reason to hope that ERT will help some of the physical problems, the blood-brain barrier may prevent this treatment from directly helping the brain. However, ERT for Beta Mannosidosis may be a possibility in the future and a clinical trial of ERT in Alpha Mannosidosis commenced in 2011.

Future Treatments

There is a great deal of research being carried out that may lead to possible treatments. Gene therapy (replacing the faulty gene with a copy of a normal gene) may be a realistic possibility in years to come. It is possible that not all those affected by Beta Mannosidosis will be able to benefit from these advances. Your paediatrician or physician may be able to give you up to date information on treatment options or you may contact the MPS Society.

About the MPS Society

The Society for Mucopolysaccharide Diseases (MPS Society) was founded in 1982 and represents from throughout the UK, over 1200 children and adults suffering from MPS and related diseases, their families, carers and professionals. It is a registered charity entirely supported by voluntary donations and fundraising and is managed by the members themselves.