

GUIDE TO UNDERSTANDING

MULTIPLE SULFATASE DEFICIENCY

What is Multiple Sulfatase Deficiency?

Multiple Sulfatase Deficiency (MSD) is a lysosomal storage disorder closely related to the mucopolysaccharidoses in which all twelve of the known sulfatase enzymes are deficient or inoperative. MSD may also be called Austin's disease.

Whilst there is no cure for individuals affected by MSD this factsheet explores the disease's presentation and clinical management. This factsheet is produced by the Society for Mucopolysaccharide Diseases drawing on the experiences of parents and doctors and with reference to medical literature.

What causes MSD?

MSD is caused by the deficiency of an enzyme, Formylglycine Generating Enzyme (FGE) that is in turn responsible for activating a group of different enzymes called sulfatases. Deficiency of this enzyme results in defective functioning of all the different sulfatases. The sulfatases are a group of lysosomal enzymes that are responsible for breaking down and thus recycling complex sulphate containing sugars from both lipids and mucopolysaccharides. The lipids that contain these sulfated sugars are critical for normal brain development and function. Individuals affected with MSD experience similar problems as children affected with leucodystrophy and mucopolysaccharidosis.

Does MSD affect individuals differently?

MSD, like most MPS and related disorders, is very variable and there is a wide spectrum of severity. A whole range of possible symptoms are outlined in this fact sheet, however affected individuals may not experience all of them.

How common is MSD?

MSD is one of the rarest forms of MPS with one child born on average every 4-5 years in the United Kingdom.

How is MSD inherited?

MSD is an autosomal recessive disease and is caused by mutations in the SUMF1 gene that encodes for the FGE enzyme; 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 MSD 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. Using information from an affected individual's DNA, it may be possible to determine whether brothers and sisters are carriers of, or affected by, MSD.

For further information on the inheritance pattern of MPS and Related Diseases contact the MPS Society for a specialist booklet on inheritance.

Can you test for MSD in pregnancy?

If you have a child with MSD 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 MSD 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, reproductive choices available and to suggest whether the wider family should be informed.

Diagnosis

The diagnosis of this disorder relies on the detection of mucopolysaccharides as well as other

sulfated complex sugars in the individual's urine; certain specific changes on brain MRI scans may also lead to the diagnosis. A definite diagnosis is made by the demonstration of a deficiency of more than a single sulfatase in either white blood cells, obtained through a blood test or cultured fibroblasts from a skin biopsy, or by genetic analysis of the SUMF1 gene.

Life expectancy

Sadly, children affected with MSD rarely live beyond their tenth birthday and some die younger. Parents often worry about their child's death, but further advice, information and support can be obtained through the MPS Society.

Clinical Presentation of MSD

There is wide variation in the manifestations of MSD; although all the features described below occur in most, the severity of each of these can vary widely between different individuals with MSD.

Growth

Growth is usually significantly restricted in individuals with MSD but this depends on the severity of the disease.

Physical Appearance

Individuals with MSD tend to bear a close resemblance to each other with many similar features. They may have rather large heads, low set ears and a flat bridge of the nose. The lips may be thickened and the tongue enlarged. As the disease progresses, the facial features become more coarse. Individuals with MSD have prominent tummies due to the storage in the liver and spleen.

Skin

In children affected by MSD the skin is often dry and scaly and this is known as ichthyosis. Commonly, it appears on the limbs, trunk and scalp. This rash is not itchy and does not cause discomfort.

Intellectual ability

Some affected children have experienced severe development delay from infancy. Children with MSD usually attain the ability to pull themselves up to a standing position and have relatively normal early language skills. However, children affected with MSD will gradually lose the skills they have learnt including being able to sit, stand and speak. Brain MRI scanning may reveal a specific pattern of findings called leucodystrophy.

It is important to remember that there is a wide spectrum of disease severity and all children with MSD should be encouraged to integrate with others and be given the opportunity to learn and enjoy life to the fullest.

Epilepsy

A number of individuals who are severely affected by MSD will develop epilepsy. This may take different forms, e.g. absence episodes or more generalised tonic-clonic seizures. Fortunately most individuals will respond favourably to anticonvulsant medication.

Eyes

Clouding of the cornea caused by storage of mucopolysaccharides may be seen in children with MSD and can lead to significant visual disability. Severe corneal clouding may reduce sight, especially in dim light.

Ears

Individuals suffering from MSD commonly 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 MSD have their hearing checked regularly and for problems to be treated early to improve or maintain the ability to communicate.

Nose and Throat

Frequent coughs, colds and throat infections are common problems for those suffering from MSD. 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 and this 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.

Respiratory infections

Individuals with MSD commonly suffer from recurrent respiratory infections, which should be treated with antibiotics. Medication may affect individuals with MPS and Related Diseases differently, so it is essential to consult your doctor rather than using "over-the-counter" medication.

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.

Mouth and Teeth

The lips may be thick, the gum ridges broad and the tongue can become enlarged. Teeth are widely spaced and poorly formed with fragile enamel. It is important that the teeth are well cared for as tooth decay could be a cause of pain.

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 MSD 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.

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 and 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 on 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.

Heart

Heart disease is common in individuals with the severe form of MSD but may not develop or cause major problems. Some individuals with the less severe form of MSD may develop problems with one of the heart valves but they may have valvular heart disease for years without any ill effects. If the condition worsens an operation may be possible to replace the damaged valves.

Liver and Spleen

In most individuals with MSD the liver and spleen become enlarged by storage of mucopolysaccharides (hepatosplenomegaly).

Stiffness

Stiffness of the limbs is common in the later stages of the condition. This may arise from either the joints as described below, or from increased limb tone. This can be painful and interfere with movement and activities such as dressing and washing. This must be assessed carefully as specific treatment measures need to be implemented depending on the cause.

Bones and joints

Individuals with MSD tend to have problems with bone formation and growth due to the storage process. The bone involvement is often mild and often may only be evident through x-ray examination. The changes that occur in the bones are referred to as mild dysostosis multiplex.

Joint stiffness can also occur. The joints become stiff and the movement of the joints may become limited. The limited movement in the shoulders and arms may make dressing difficult. Hands and toes may be affected as the joints become stiff and curled under.

Hands

Individuals with MSD may experience pain and loss of feeling in the fingertips caused by 'carpal tunnel syndrome'. The wrist, or carpus, consists of eight small bones known as the carpals which are joined by fibrous bands of protein called ligaments. Nerves have to pass through the wrist 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.

Carpal tunnel syndrome

Although a child or adolescent with MSD may not complain of pain they may already have carpal tunnel syndrome. Doctors may advise for this to be monitored with a test called a nerve conduction study which will show whether there is carpal tunnel syndrome present. This test would also be carried out if there is any weakness or numbness in the hand at all or decreased muscle mass at the base of the thumb. This disorder can be treated by a minor operation.

General management of MSD

Anaesthetic

Giving an anaesthetic to an individual with MSD 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 the neck 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 managing anaesthesia in MPS individuals available from the MPS Society.

Physiotherapy and hydrotherapy

Physiotherapy and hydrotherapy can be useful to help individuals with MSD achieve specific and realistic goals in daily life or to drain mucus from the chest. At other times it is common sense for the individuals to be as active as possible to improve their general health and the physiotherapist may be able to suggest ways of achieving this. The best forms of physiotherapy are exercises that are introduced through play in the younger individuals. In adults it is important to remember that passive stretching may be painful and should only be used with caution.

Specific treatment of MSD

At the present time, there is no cure for children affected by MSD, but there are many ways of helping children to enjoy their lives and to manage the problems they will face. It may be that treatment will be available in the future.

About the MPS Society

The Society for Mucopolysaccharide Diseases is a voluntary support group, founded in 1982, which 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. For further information about the work of the Society and the service we provide please contact us.