

GUIDE TO UNDERSTANDING SLY DISEASE (MPS VII)

What is Sly Disease?

Sly Disease is a mucopolysaccharide storage disorder also known as Mucopolysaccharidosis type VII (MPS VII). Sly disease takes its name from William Sly who originally first described the disorder in 1972.

All individuals with Sly disease have a deficiency of the enzyme beta-glucuronidase which results in the accumulation of mucopolysaccharides. The accumulation of mucopolysaccharides is responsible for many problems that affect individuals with Sly disease.

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

What causes Sly Disease?

Mucopolysaccharides are long chains of sugar molecules used in the building of bones, cartilage, skin, tendons and many other tissues in the body. Muco- refers to the thick jelly like consistency of the molecules, -poly- means many, and -saccharide is a general term for a sugar molecule. An alternative word for mucopolysaccharides is glycosaminoglycans or GAGs.

In the course of normal life there is a continuous process of building new mucopolysaccharides and breaking down old ones - a recycling process. The breakdown and recycling process requires a series of special biochemical tools called enzymes. Individuals with Sly disease are missing or deficient in an enzyme called beta-glucuronidase which is essential in the breaking down mucopolysaccharides. The incompletely broken down mucopolysaccharides remain stored inside the cells of the body and begin to build up causing progressive damage. Babies may show little sign of the disease but as more and more cells become damaged by accumulation of mucopolysaccharides, symptoms start to appear.

Does Sly Disease affect individuals differently?

Sly Disease, like most MPS and related disorders, is very variable. In its most extreme form, children are born with a condition called hydrops fetalis. This is a very severe condition in which the child retains an enormous amount

of fluid throughout its body. Babies with hydrops fetalis rarely survive beyond a few weeks to a few months of age. Many individuals with Sly Disease are less severely affected and have clinical symptoms similar to other MPS and Related Diseases.

It is important to remember that Sly Disease is extremely varied in its effects and there is a wide spectrum of severity. A whole range of possible symptoms are outlined in this booklet, however affected individuals may not experience all of them.

How common is Sly Disease?

In the United Kingdom, Sly Disease is the rarest Mucopolysaccharidosis with an average of only one baby every 10 years born with the condition. Worldwide it is estimated to have a frequency of less than 1:250,000 births.

How is Sly Disease inherited?

Sly Disease is an autosomal recessive disease; 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 Sly 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, MPS VI.

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 Sly Disease in pregnancy?

If you have a child with Sly Disease 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 Sly Disease 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.

Life expectancy

Life expectancy is very varied. Babies with hydrops fetalis rarely survive beyond a few weeks to a few months of age. Other individuals with Sly Disease may die in childhood whilst others may live to become adults.

Clinical Presentation of Sly Disease

Growth

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

Physical Appearance

Individuals with Sly Disease tend to bare a close resemblance to each other with many similar features. Their faces are often chubby with rosy cheeks and their heads rather large with a prominent forehead. The neck is short and the nose is broad with a flattened bridge. The lips are often thickened and the tongue enlarged. The hair tends to be thick, the eyebrows bushy and there may be more hair than usual on the body. Individuals with Sly Disease have prominent tummies and a characteristic way of walking and holding their arms due to joint contractures at their hips, shoulders, elbows and knees.

The appearance of individuals with the less severe form of Sly Disease is extremely variable. Adults are often stocky in build and their trunks are shorter than their limbs. The neck may be short and stiff.

Intellectual ability

Individuals with severe Sly Disease usually experience progressive storage of mucopolysaccharides in the brain that is primarily responsible for the slowing of intellectual development by 1 to 3 years of age. This is often followed by a gradual loss of skills until death, however the pattern is very varied. Some individuals will only learn to say a few words while others learn to walk well and to read a little. They can enjoy nursery rhymes and simple puzzles. Emphasis should be on helping infants and children with Sly Disease to learn as much as they can before the disorder progresses. Even when the child starts to lose skills they have learned there may be some surprising abilities left. Children will continue to understand and find enjoyment in life even if they lose the ability to speak. Individuals with less severe Sly Disease may have normal intelligence with mild physical involvement.

Brain

Deterioration of the brain is one of the main features of the severe form of Sly Disease. Individuals with the less severe form of the disease may not be affected in this way. The brain and the spinal cord are protected from jolting by the cerebrospinal fluid that circulates around them. In some individuals with Sly Disease the circulation of the fluid may become blocked over time. The blockage (communicating hydrocephalus) causes increased pressure in the head which can press on the brain and cause headaches and delayed development.

Hydrocephalus

Hydrocephalus can be confirmed using a CT or MRI scan. A lumbar puncture with pressure measurement is another way to assess if hydrocephalus exists. If hydrocephalus is confirmed it can be treated by insertion of a thin tube (shunt) which drains fluid from the brain. The 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 Sly Disease.

Eyes

Clouding of the cornea caused by storage of mucopolysaccharides is seen in all children and adults with MPS VII and can lead to significant visual disability. Severe corneal clouding may reduce sight, especially in dim light. Some individuals cannot tolerate bright lights as the clouding causes uneven refraction of light. A loss of night vision is common which may also be due to damage of the retina. Glaucoma, abnormally high pressure in the eye, may occur and cause damage to the retina and results in optic nerve atrophy.

Ears

Individuals suffering from Sly Disease 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 Sly Disease 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 is known as "glue ear".

Nose and Throat

Frequent coughs, colds and throat infections are common problems for those suffering from Sly Disease. 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.

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 the 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 Sly Disease, 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 in which case it is referred to as "mixed deafness". Nerve deafness is managed by the fitting of hearing aids in most individuals with Sly Disease. 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 Sly Disease have found radio aids and the loop system helpful at school and at home.

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.

Heart

Heart disease is common in individuals with the severe form of Sly Disease but may not develop or cause major problems until later in life when drugs can be prescribed to help relieve the condition. Some individuals with the less severe form of Sly Disease 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.

Respiratory infections

Individuals with Sly Disease commonly suffer from recurrent respiratory infections, particularly within the first year, 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.

Liver and Spleen

In most individuals with Sly Disease the liver and spleen become enlarged by storage of mucopolysaccharides (hepatosplenomegaly). The enlarged organs do not usually cause problems, but they can interfere with eating and breathing.

Bones and joints

Individuals with Sly Disease tend to have problems with bone formation and growth. This may lead to bone as well as neurological problems if nerves are compressed by bone. Over time, bone changes in Sly Disease tend to be mild and when present resemble dysostosis multiplex, i.e. bones and cartilage are not only malformed but also forming in abnormal places. Joint stiffness is a common feature of Sly Disease and the maximum range of movement of all joints may become limited.

Stiffness may cause pain, which 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 Sly Disease 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 backward slippage of the vertebrae can cause a slight angular curve (kyphosis or gibbus) to develop but it usually does need treatment.

Mouth and Teeth

The lips are thick, the gum ridges are broad and the tongue becomes 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 Sly Disease 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.

Hands

Individuals with Sly Disease often 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 Sly Disease 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.

Skin

Individuals with severe form of Sly Disease tend to have thickened and tough skin. There may also be excess hair on the face and back. Individuals diagnosed with Sly Disease may suffer from hyperhidrosis (excessive sweating).

Legs and Feet

Many individuals with Sly Disease stand and walk with their knees and hips flexed. This, combined with the tight Achilles tendon, may cause them to walk on their toes.

General management of Sly Disease

Anaesthetic

Giving an anaesthetic to an individual with Sly Disease 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 Sly Disease 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 Sly Disease

Bone Marrow Transplant (BMT)

For some years Bone Marrow Transplants (BMT) have been used to treat children with Mucopolysaccharide and related diseases.

Enzyme Replacement Therapy

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 Enzyme Replacement Therapy will help some of the physical problems, the blood-brain barrier may prevent Enzyme Replacement Therapy from directly helping the brain.

Good progress is being made in production development for ERT for MPS VII but at present there is no timeline for a human clinical trial. For up-to-date information, please contact the MPS Society.

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.