What is Aspartylglycosaminuria?

Aspartylglycosaminuria (AGU) was first described by Dr Pollitt et al in 1968 and is a rare lysosomal storage disorder of the oligosaccharide family, closely related to the mucopolysaccharidoses.

Whilst there is no cure for individuals affected by this disorder this factsheet explores the presentation and clinical management of AGU. Bone Marrow Transplant and Enzyme Replacement Therapy are also addressed. This guide 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 AGU?

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, “saccharide” is a general term for a sugar molecule. In the course of normal life there is a continuous process of building new oligosaccharides and breaking down old ones. This process requires a series of special biochemical tools called enzymes.

AGU is an enzyme deficiency disorder resulting in defective aspartylglycosaminidase enzyme activity which is essential for the chemical decomposition of oligosaccharides. Without the aspartylglycosaminidase enzyme used materials cannot be completely broken down and remain stored in the body causing progressive damage to cells. Babies may show little sign of the disease but symptoms start to appear as more and more cells become damaged by the accumulation of oligosaccharides.

Does AGU affect individuals differently?

Despite the rarity of diagnosed cases of AGU, follow-ups and studies carried out have shown consistency in the clinical picture. There do appear to be some differences in the severity of the disease between patients who carry the most common Finnish mutations of AGU and individuals from other countries who often have other, less well-known mutations. In these individuals the outcome can be much more severe, leading to a shorter life span than described in literature.

How common is AGU?

The MPS Society which co-ordinates the Registry for Mucopolysaccharide and Related Diseases has been contacted regarding 3 cases in the UK. Approximately 250 cases are reported worldwide. Around 200 patients are living in or originate from Finland. It was initially thought that the disorder was exclusively particular to the Finnish population but a few sufferers from different origins have since been diagnosed with AGU.

How is AGU inherited?

We all have genes inherited from our parents which control, for example, our height and the colour of our eyes. Some genes we inherit are “recessive” which means that although we carry the gene it does not have any effect on our development. AGU is caused by a recessive gene. If an adult carrying the abnormal gene has a partner who is also a carrier, there will be 25% (1:4) chance with every pregnancy that the foetus will inherit the defective gene from each parent and will be affected by the disease. There is a 2 in 3 chance that unaffected brothers and sisters of those affected by AGU will be carriers. However, as the disease is so rare the chance of meeting another carrier is slight.

Can you test for AGU in pregnancy?

If you have a child with AGU it is possible to have tests during any subsequent pregnancy to find out whether the foetus is affected by the disease. Pre-natal tests can be arranged early on during a pregnancy for those families who already have a child with AGU. Both amniocentesis and chorionic villus sampling can be used to diagnose AGU in utero.

Genetic counselling

All parents of children with an oligosaccharide storage disorder should consider genetic counselling before having other children. The counsellor should be able to advise on the risk to close relatives and to suggest whether the wider family should be informed.

Life expectancy

AGU usually leads to death between thirty and fifty. Many deceased patients have passed away following an infection.
Clinical presentation of AGU

Growth
After the age of approximately 3 months diarrhoea, hernias and respiratory infections become more common. Other symptoms appear around the age of 5 years. Speech and development may be delayed.

Physical appearance
Changes in appearance develop gradually as oligosaccharides accumulate. Faces are often broad and the skull is asymmetric. The neck is often short. Folds of skin over the inner corner of the eyes, common in babies, may remain. The nose is usually broad with a flattened bridge. The cheeks tend to sag. Although the body is in proportion, stature becomes restricted and the abdomen tends to protrude.

Intellectual ability
Individuals with AGU suffer from neurological deterioration because of the effect of accumulation of oligosaccharides in the brain. Learning difficulties have been consistently observed in patients. These are usually mild in the early years but can become severe by the time the child is five to seven years old. Speech development becomes progressively delayed. Loss of neurons in the brain causes dementia which in turn is responsible for a tendency towards hyperactive and restless behaviour.

Brain
The brain and the spinal cord are protected from jolting by cerebrospinal fluid circulating around them. In some individuals with AGU circulation of this fluid may become blocked. The blockage (communicating hydrocephalus) causes increased pressure in the head which can press on the brain and cause headaches and delayed development.

Brain

**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 AGU.

Eyes

Cataracts and corneal clouding are common in individuals with AGU. Some individuals may experience photophobia for which protective measures can be taken such as wearing sunglasses.

Ears

Some individuals suffering from AGU 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 AGU 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 running 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 become thick like glue. Hence the condition is 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 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 AGU, 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 AGU. 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 AGU have found radio aids and the loop system helpful at school and at home.
Nose and throat
Storage in the throat causes the voice to become hoarse within the first ten years.

Mouth and teeth
Individuals with AGU tend to have thick lips, a wide gum and 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 AGU 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.

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

Heart
Storage of oligosaccharides in the heart will cause some damage to the heart valves. Systolic murmurs and other general heart abnormalities are common in AGU patients but should not necessitate treatment. The size of the heart in individuals suffering from AGU can be abnormally large.

Liver and spleen
In most individuals with AGU the liver and/or spleen become enlarged by storage of oligosaccharides. The enlarged organs do not usually cause problems but they can interfere with eating and breathing.

Hernias
The 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 large and cause entrapment of the intestine, or are very large and are causing problems. It is very common to have a recurrence of an umbilical hernia after a repair has been made.

Skin
The skin is generally thicker than normal which is the reason for wrinkles being a physical characteristic of the disorder. Angiokeratoma, a collection of warty blood vessels, has been observed on the legs and feet of some patients.

Muscles
Individuals with AGU may suffer from hypotonia (reduced muscle tension).

Mobility
Individuals with AGU can be clumsy. When running they tend to lean forward and have their arms dangling at the sides. It has been observed that motor skills usually deteriorate by the third decade.

Hands
Individuals with AGU 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 wrists in the space between the carpal bones and the ligaments. Thickening of the ligaments causes pressure on the nerves and this can be relieved by an operation.

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Bones and joints
Spine: The bones of the spine are called vertebrae. These vertebrae are normally positioned in a line from the neck to the buttocks. However, the vertebrae in individuals with AGU can create what appears to be a flattened or broad spine. Poor formation of the vertebrae may also cause them to slip upon one another in places where they should in fact be bound together. Scoliosis is also a feature of the disease. Skeletal changes generally occur and are corroborated by radiology examination. Dysostosis multiplex is common in AGU sufferers where bones and cartilage are malformed and form in abnormal places.

Joints: It is very common to observe joint laxity in individuals with AGU. Between 7 and 10 years X-rays start showing thickening of the skull, irregular vertebrae outline and a thinning of the outer layer of the bones (cortex).

General management of AGU
Anaesthetic
Giving an anaesthetic to an individual with AGU 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 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 specialist anaesthetic booklet published by the MPS Society.

Physiotherapy and hydrotherapy
Physiotherapy and hydrotherapy can be useful to help individuals with AGU achieve specific and realistic goals in daily life or to drain mucus from the chest. 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. In adults it is important to remember that passive stretching may be painful and should only be used with caution.

Specific treatment of AGU
Bone Marrow Transplant (BMT)
For some years Bone Marrow Transplants (BMT) have been used to treat children with Mucopolysaccharide and Related Diseases. The few attempts to carry out BMT on AGU patients have not been convincing, complications were many and only one conclusion has been agreed upon: children should be operated on early during infancy.

Enzyme Replacement Therapy (ERT)
Enzyme Replacement Therapy clinical trials for some MPS and Related Diseases are already at an advanced stage and this treatment will be available for some individuals in the near future. This will involve the recombinant enzyme being given by repeated intravenous infusion. Although there is reason to hope that ERT will help some of the physical problems, the blood-brain barrier may prevent ERT from directly helping the brain. However ERT for AGU may be a possibility in the future.

Carpal tunnel syndrome
Although a child or adolescent with AGU 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.

Joint Pain
Pain due to joint stiffness may be relieved by warmth and ordinary painkillers. Limited movement in the shoulders and arms may make dressing 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 ensure that irritation and ulcers of the stomach do not occur.

Legs and feet
Individuals with AGU may have genu valgum (knock knees) resulting in their feet being forced progressively further apart. Bones in the feet become malformed and the cortex of long bones thins out making the leg bones predisposed to break.

Neck: The odontoid peg (the tooth-like bone at the top of the spine holding the skull in place) is often underdeveloped. The neck can therefore be fragile and shorter than usual.
About the MPS Society

The Society for Mucopolysaccharide Diseases was 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.

This guide is not intended to replace medical advice or care.

Society for Mucopolysaccharide Diseases
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