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Guide to Understanding
Metachromatic Leukodystrophy

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What is MLD?

MLD or Metachromatic Leukodystrophy is one of a group of rare genetically inherited diseases known as the lysosomal storage diseases. The condition gets its name from the microscopic appearance of cells with the sulfatide accumulation that occurs in this disorder. The sulfatides form granules which are metachromatic, which means they pick up colour differently than surrounding cellular material when stained for microscopic examination.

Whilst there is no cure for individuals affected by MLD, this factsheet explores the presentation and clinical management of this disease.

This factsheet is produced by the Society for Mucopolysaccharide Diseases (MPS Society) drawing on the experiences of doctors with reference to medical literature.

What causes MLD?

In the course of normal life there is a continuous recycling process; this process requires a series of biochemical tools called enzymes. Individuals with MLD lack a specific enzyme or protein in every one of their cells. This leads to problems with the breakdown of fats called sulfatides (or sulphatides).

In nearly all cases, MLD develops as a result of a deficiency in the enzyme arylsulfatase A (ASA) also known as sulfatidase or cerebroside 3-sulfatase. ASA is responsible for breaking down sulfatide and other fats that contain 3-sulfogalactosyl. The protein produced by ASA is present in the lysosome, a compartment of the cell that specialises in general “cleanup” of the cell.

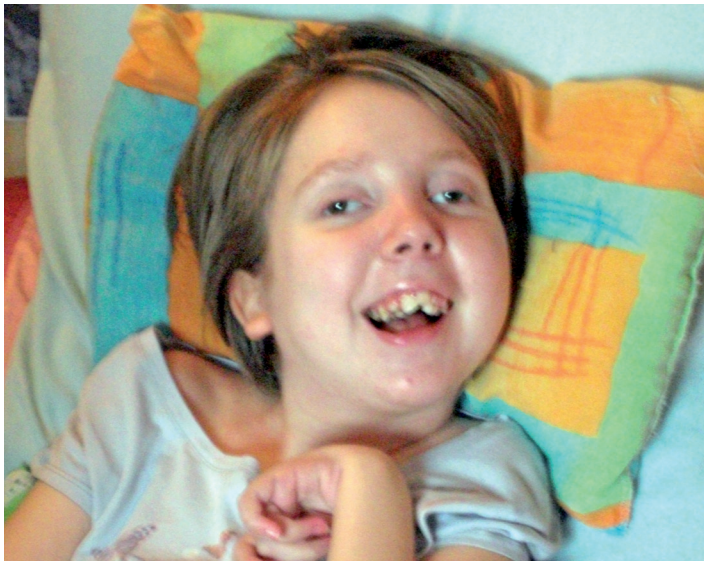
You may hear MLD referred to as a lysosomal storage disorder, since ASA is a lysosomal enzyme. In rare cases, a deficiency of the non-enzymatic activator protein saposin B, which helps arylsulfatase A with the breakdown of these fats, can also cause metachromatic leukodystrophy. When arylsufatase A and saposin B are unable to work together to break down sulfatides, they build up in cells within the nervous system, including the brain.

Are there different forms of MLD?

The severity of metachromatic leukodystrophy varies widely between patients. Although a gross oversimplification, affected individuals are generally described as having one of three main forms of the condition. These forms are identified based on the age of the patient when their first signs and symptoms start to appear. They are known as the late infantile, juvenile and adult forms.

If the disease first develops between 6 months and 4 years of age, the individual is said to have the late-infantile form of metachromatic leukodystrophy. The condition is described as juvenile if it develops between 4 and 16 years of age. Individuals who are older than 16 years when they develop metachromatic leukodystrophy are described as having the adult form of the disease. More recently, it has been suggested that the description of the late-infantile form should be revised to include only children who present before 2-3 years of age.

Kim



How common is MLD?

Metachromatic leukodystrophy is the commonest of all the leukodystrophies. However, it is still a rare disease that affects between about 1 in 54,000 and 1 in 166,650 live births. The adult-onset form of metachromatic leukodystrophy affects 25% of all patients. The remaining patients can be divided roughly equally between the late-infantile and juvenile forms.

How is MLD Inherited?

Metachromatic leukodystrophy is caused by a faulty or 'mutated' gene and it affects both males and females equally. There are known to be more than 60 different genetic faults that can cause metachromatic leukodystrophy. In some cases it is possible to identify the genetic fault that caused the disease.

Inheritance of metachromatic leukodystrophy is autosomal recessive. This means that two copies of the abnormal gene (one from each parent) are required for the disease to develop. Thus, a child who is born to parents who both carry the autosomal recessive mutation has a 25% (1:4) chance of inheriting the faulty gene from both parents and developing the disease. There is a 50% (1:2) chance of the child inheriting one abnormal gene and being a carrier of the disease. Carriers of the faulty gene that causes metachromatic leukodystrophy are not affected by the disease. There is also a 25% (1:4) chance that the child will not inherit the faulty gene from either parent.

Diagnosis of MLD

Although an individual may have signs and symptoms that suggest they have MLD, it is important that the diagnosis is confirmed by biochemical tests. The doctor may ask for a sample of blood from your affected child so that the diagnosis can be confirmed.

Two blood tests are generally carried out to confirm the diagnosis of MLD. The first test assesses the level of arylsulfatase A enzyme activity in the blood and the second looks for a common break in the gene causing a pseudodeficiency of the enzyme. Pseudodeficiency is where the level of enzyme activity is low but it has no effect on the way the body functions. There is one very common break causing this and this is one way of identifying it. The other way is to test the enzyme activity in both parents. Although arylsulfatase A levels are deficient in most patients with MLD, in the rare cases where the condition is a result of saposin B deficiency, levels of arylsulfatase A are normal. Thus, in patients with a clinical picture that strongly suggests MLD who have normal levels of arylsulfatase A, the laboratory will look for saposin D, multiple sulphatase or arylsulphate C.

A second factor that complicates diagnosis is that arylsulfatase A levels are lower than normal in some individuals who are not affected by MLD. Approximately 1-2% of the general population has a so-called pseudodeficiency in arylsulfatase A. These individuals have levels of arylsulfatase A that are 5-15% of normal but they do not show any clinical signs or symptoms and, importantly, they do not excrete sulfatide in their urine. This means that an analysis of the levels of this fat in the urine can be used to tell if the individual has MLD or arylsulfatase A pseudodeficiency.

MLD can sometimes be mistaken for a condition called multiple sulfatase deficiency (also known as mucosulfatidosis or Austin disease) that has some of the same signs and symptoms. Like patients with MLD, those affected by multiple sulfatase deficiency have a deficiency in arylsulfatase A activity; however, they will have other enzyme deficiencies as well. In such cases, levels of total arylsulfatase or another sulfatase should be measured to check for the presence of additional enzyme deficiencies.

Can you Test for MLD in pregnancy?

Pre-natal testing for metachromatic leukodystrophy is possible in early preganacy.

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 whether the wider family should be informed.

Clinical Presentation of MLD

The symptoms can vary widely, although in all cases there is a progressive loss of physical and intellectual function over a relatively extended period of time. In general, the earlier the onset, the more rapid the progression of the disease.

Late Infantile MLD

The most common initial signs and symptoms in patients who develop MLD during the first 2 years of life are, after a period of normal growth and development, abnormal or erratic movements, other changes in the way they move particularly when they are crawling/walking. These children are frequently diagnosed as cerebral palsy as they initially have problems with walking and toe walking is the most common feature. Toe walking can also be innocent so the combination of toe walking and other features are important. There is also deterioration in their development (e.g. a progressive loss of speech and skills). Once clinical symptoms become noticeable, they often appear to progress rapidly over a period of several months, with alternating periods of stabilisation and decline. Affected children usually learn to walk, although they may take longer to learn than their healthy peers. They gradually start to move their limbs in abnormal patterns and their ability to walk diminishes over time as muscles start to become rigid. Speech gradually becomes slower as the disease progresses. Limb movement may become painful as contractures develop. Cognitive development and fine motor skills (e.g. writing, drawing, picking up items) are also affected. There may be difficulties with feeding and weight gain and a feeding tube may become necessary. Mobility and speech are eventually lost and children become bedridden. This is accompanied by a progressive decline in their ability to think, understand and interact with people, eventually leading to dementia. Vision can also deteriorate and seizures may be experienced in the later stages.

Juvenile MLD

Patients who develop manifestations from between 2-3 and 16 years of age often show initial impairments in fine motor skills and concentration and may develop behavioural problems during the early years of schooling. They can have difficulties keeping up with their peers and may sometimes be suspected of having a psychiatric condition such as schizophrenia or depression. In the early stages they may have difficulties with movement, coordination, walking, develop slurred speech and suffer incontinence.

The situation may remain stable for months or even years. As symptoms advance, individuals develop signs of neurological involvement such as involuntary flexion or extension of the arms and legs, tremor, muscle rigidity and they will eventually lose the ability to walk. This is followed by a decline in motor and cognitive function as the final stage of the disease follows that of the late infantile form of MLD.

Adult MLD

Early signs and symptoms in adults who develop MLD may be reflected in poor performance at school or work may be suggestive of a psychiatric disease, particularly schizophrenia. There is generally a slow decline in intellectual capabilities and individuals may become emotionally unstable and experience lapses in memory. This may be reflected in poor performance at school or work. Psychiatric symptoms such as hallucinations and delusions may develop. Movements may become clumsy and they may become incontinent. Paralysis of the arms and legs develop progressively. Signs of peripheral nerve damage and seizures are rare. In the final stages of the disease, affected individuals may reach a vegetative state.

Other symptoms listed below:

- Clumsiness
- Spasticity/Hypertonia: Spasticity is a condition in which certain muscles are continuously contracted. This contraction causes stiffness or tightness of the muscles and may interfere with movement, speech, and manner of walking.
- Nystagmus: Nystagmus is an uncontrolled movement of the eyes, usually from side to side, but sometimes the eyes swing up and down or even in a circular movement. Most people with nystagmus have reduced vision.
- Developmental delay: Significant reduction in physical, cognitive, behavioral, emotional, or social development, in comparison with norms.
- Esotropia: A form of squint in which one or both eyes turns inwards.
- Weakness
- Decreased speech
- Seizures: A seizure is the result of a sudden burst of excess electrical activity in the brain. This causes the brain's messages to become temporarily halted or mixed up. Seizures may take the form of momentary alteration in their level of consciousness (absences). This could be a stare for a few seconds, lack of response or a slight twitch. Some may have more generalised seizures involving either loss of consciousness or physical jerking.
- Ataxia: loss of ability to coordinate muscular movement.
- Quadriplegia: paralysis from the neck down.
- Eventual absence of voluntary functions.

Although the majority of the signs and symptoms seen in patients with MLD are neurological, some patients may have inflammation of the gall bladder and can develop gallbladder polyps.

Life Expectancy

There is a wide range of life expectancy in patients with MLD. Although studies show that the survival of patients with MLD is improving over time, disease progression is faster and life expectancy is shorter in those who develop manifestations early in life than those who develop manifestations later in life. Sadly, infants who develop signs and symptoms during the first two years of life are likely to die during childhood; however, individuals who develop signs and symptoms during adulthood may have a reasonably normal life span.

General Management of MLD

Anaesthetic

Giving an anaesthetic to an individual with MLD 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. Specialist management may be necessary as individuals with MLD may have breathing difficulties after anaesthetics and are sensitive to anaesthetic drugs. 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 MLD 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.

Medication

Children with MLD 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 or they may make the child more irritable. Some medications for seizure will also increase the secretions and sometimes the balance between seizure control and secretion control can be very hard. The use of sedatives can increase the problem of sleep apnoea by depressing respiration.

It is now recognised that frequent use of antibiotics may make them less effective when really needed. Repeated use can also cause thrush (a fungal infection which commonly affects the mouth or vagina and produces a white curd-like deposit). It causes irritation and discomfort and will need to be treated. Your doctor may, therefore, wish to limit the number of times when antibiotics are prescribed for coughs and colds. In some children the use of low dose continuous antibiotics during the winter months may be considered to control infections but again this should be discussed with expert centres.

Diet

There is no scientific evidence that a particular diet has any beneficial effects. Symptoms, such as diarrhoea, tend to come and go naturally. Some parents, however, find that a change in their child's diet can ease problems with excessive mucus, diarrhoea or hyperactivity. Cutting down on milk, dairy products and sugar as well as avoiding foods with too many additives have all been said to help individual children. Sometimes medicines like loperamide to stop diarrhoea are prescribed but these should be prescribed under supervision of those with expert knowledge of this condition.

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 reintroducing foods one at a time to test out whether anything in particular tends to increase your child's symptoms.

Feeding

Most children with MLD enjoy their food although some are reluctant to try anything new. In the later stages, your child may find it harder to chew properly and food may have to be liquidised. In MLD there aren't issues with difficult upper airways (as seen in many other lysosomal storage disorders) so tube feeding is frequently used before or instead of gastrostomy.

Choking

When a child cannot chew and has difficulty swallowing there is a risk of choking. Food, especially meat, should be cut up very small. Even with this precaution the child may start to choke. It is important that after a significant choking episode swallowing should be assessed by a Speech and Language Therapist.

Pain

It is very hard, when a child cannot express him or herself, to know whether the crying is from pain or frustration. Children may have ear infections, toothache, aches and pains in their joints or discomfort from a full stomach. Children with MLD are more prone to develop gallstones and this is an important cause of abdominal pain that doesn't respond to usual medication. Some medication like Morphine may make this worse and is an important consideration and specific treatment may be more appropriate. As with small babies, parents have to learn by trial and error. Sometimes screaming episodes are put down to behaviour problems. Do not hesitate to ask your GP to check whether there is a physical cause for your child's distress.

Home Adaptations

Sufferers of MLD will become progressively less mobile and increasingly dependent on their parents and carers to meet their everyday needs in areas of incontinence, personal hygiene and nutrition. It is important to give thought early on to the ways in which the families and carers will manage when weight bearing and walking or climbing the stairs is no longer possible. An en-suite bathroom and bedroom is ideal with plenty of space for a buggy and carer to manoeuvre around in. When weight bearing is no longer possible a hoist is beneficial with tracking from bed to bath directly in line for ease of use. Adaptations can often take a long time so it is prudent to plan ahead as far as possible.

Palliative Care

Palliative care is provided to the family and child with a life limiting disease in situations where curative treatment is not an option. This support encompasses aspects such as respite care, symptom management and bereavement support and may extend over a considerable period of time. In addition considerable personal care may be required which can take up a large amount of time. This will include feeding and personal hygiene. The stress involved can put a family under immense strain. An assessment of medical needs and a care plan should lead to an approved package of support being provided to both the MLD sufferer and the family and enable both to experience a better quality of life.

Specific Treatment of MLD

Bone marrow transplantation (BMT), sometimes known as haematopoetic stem cell transplantation, has been used to treat patients with MLD. This procedure is not currently recommended for children suffering the late-infantile form of the disease. BMT may potentially be beneficial in individuals with late-juvenile or adult-onset MLD who are in the early stages of the disease.

Future Treatments

Enzyme replacement therapy (ERT) is available for several of the lysosomal storage diseases. Experiments on animals with arylsulfatase A deficiency suggest that ERT reduces sulfatide storage and leads to functional improvement. Clinical trials of ERT for MLD are ongoing. Results are eagerly awaited.

Gene therapy, which is the concept of replacing the faulty gene with a copy of a normal gene, may be a possible treatment in future years.

The approach that is under development involves the injection of an adeno-associated virus (AAV)-based vector, which carries a normal copy of the arylsulfatase A gene into the brain. AAVs are not disease-causing; however, they can infect cells and incorporate their own genes within the host cell. This should theoretically restore enzyme levels in the brain. Experiments in animal models suggest that this may also be a possible treatment for patients with MLD. An AAV-based clinical trial has been initiated in Italy and results are eagerly awaited over the next few years.

These developments offer hope for new therapies in the future; however, it is possible that not all of those affected by MLD will be able to benefit from these advances.

Your Doctor may be able to give you more current information on treatment options.

About the MPS Society

The Society for Mucopolysaccharide Diseases (MPS Society) was founded in 1982 and represents over 1200 children and adults suffering from MPS and related diseases including Fabry, their families, carers and professionals throughout the UK.

Society for Mucopolysaccharide Diseases
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