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Early onset LAL D

Lysosomal Acid Lipase Deficiency

Information for individuals, parents and families

Society for Mucopolysaccharide Diseases
mpssociety.org.uk

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There is huge variability within this condition and some people may experience only some of the symptoms, while the severity of those symptoms can also vary.

This booklet is produced by the multidisciplinary team at the **Willink Metabolic Unit, Manchester with support from the Society for Mucopolysaccharide Diseases (MPS Society).** It is designed to help those affected by early onset LAL D and their families understand its causes and effects. While there is currently no cure for individuals affected by LAL D, this booklet explores how best to understand and manage the disease. It draws on the experiences of patients, carers, families and medical professionals as well as medical literature.

What is Lysosomal acid lipase deficiency (LAL D)?

Early onset LAL D is also known as Wolman disease. It was first identified by Dr Wolman, Dr Abramov and Dr Schorr in 1956

Lysosomal acid lipase deficiency (LAL D) is an inherited autosomal recessive lysosomal storage disease that affects multiple systems within the body. It is caused by a deficiency of the LAL enzyme resulting in storage of cholesteryl esters (cholesterol joined together with fatty acids) in the liver, spleen, gastrointestinal system and cardiovascular system.

In the course of normal life there is a continuous recycling process which consists of building new materials and breaking down old ones ready for disposal. This breakdown and recycling process takes place in a special part of the body's cells called the lysosomes, which is why LAL D and other similar conditions are also known as lysosomal storage diseases. The process requires a series of special biochemical tools called enzymes.

LAL D is a spectrum of disease which ranges from early onset (infants presenting with symptoms under 12 months of age) to late onset (presenting from age one year to adulthood). This booklet focuses on early onset LAL D, although some similar symptoms may be experienced in late onset LAL D. The disease causes many types of clinical symptoms, affecting many systems within the body. It is still a relatively under-recognised condition with many individuals receiving no diagnosis or incorrect diagnosis of non-related liver disease.

What causes LAL D?

In the case of LAL D, the enzyme is called lysosomal acid lipase, and it is either not being produced at all or is not working correctly. This happens when there is a genetic variant in the gene – called LIPA – that gives the body the instructions for making the enzyme. This results in lipids (cholesterol and fatty acids) within the cells and major organs not being broken down.

When these are not completely broken down they remain stored in the body's cells and accumulate in many tissues and organs. The symptoms of LAL D are a result of the build up of waste products, especially in the liver, spleen, gastrointestinal system and cardiovascular system, disturbing the normal functioning of the cells. It is a severe condition that progresses rapidly.

Early onset LAL D, Current understanding is that most infants present with a total loss of enzyme activity, resulting in the severe form of the disease.

Late onset LAL D Those presenting with late onset LAL D tend to have some enzyme activity.

How is LAL D inherited?

Genes are the unique set of instructions inside our bodies that make each of us an individual

We have thousands of genes and they are the blueprint for our growth and development, as well as controlling how our bodies function. If a particular gene is faulty, or altered, then it will not work efficiently.

Genes are carried on structures called chromosomes. It is usual to have 23 pairs of chromosomes that are numbered in pairs, from pair number 1 to pair number 22, plus one pair of sex chromosomes: XX for a female and XY for a male. A child will inherit one set of chromosomes from the mother in the egg, and one set from the father in the sperm therefore we each have two copies of each gene, one of which is inherited from each parent.

Defects in genes are called **genetic variants**

LAL D is inherited in an autosomal recessive pattern, which means that in an affected individual, both copies of the LAL D gene in each cell have genetic variants. The parents each carry one copy of the mutated gene, but they do not show signs and symptoms of the condition. This is known as being a carrier.

A **carrier** will not show symptoms but can pass the defective gene on to their child

When both parents are carriers of the defective LAL D 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. The chance of a baby inheriting LAL D is the same for every pregnancy.

Brothers and sisters of an individual affected by LAL D might also be carriers of the condition and it is recommended that parents seek advice from their local genetic department about the potential risks in future pregnancies.

How common is LAL D?

Early onset LAL D is very rare and estimated to affect 1 in 350,000 births. In the UK it is estimated that one to three babies will be born per year with this condition.

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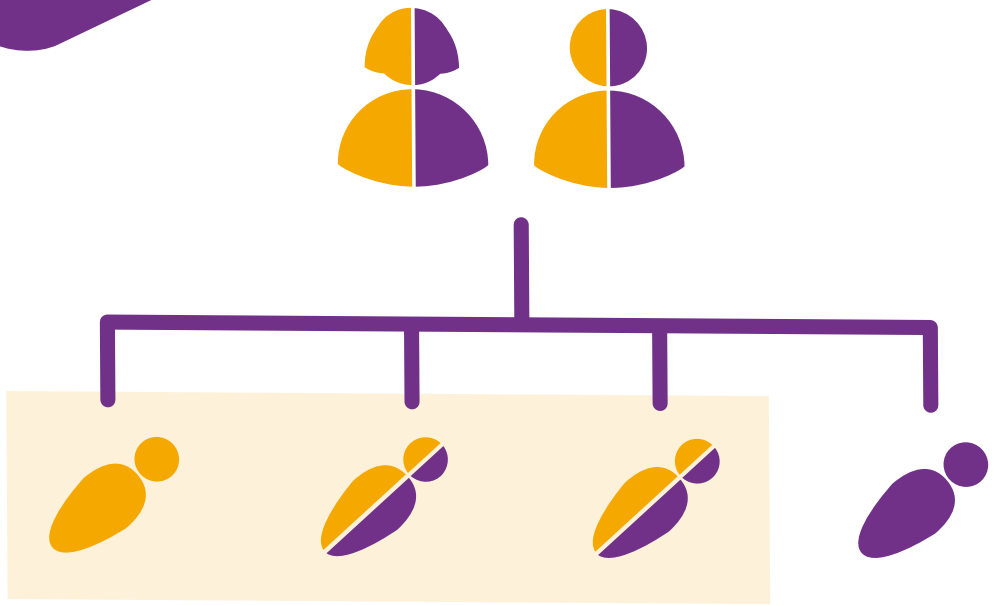

Autosomal Recessive Inheritance Pattern

- AFFECTED BY THE DISEASE 25%
- CARRIERS OF AFFECTED GENE 50%
- UNAFFECTED BY THE DISEASE 25%

How is LAL D diagnosed?

Diagnosis of early onset LAL D is usually made within the first few weeks or months of life, although some babies have been diagnosed before birth during an ultrasound scan.

At birth, although the disease process has already started in the womb, babies appear to look normal; however, it is often the case that they soon start to have problems with vomiting and diarrhoea and start to fail to thrive (indicated by poor weight gain) and over time exhibit more signs and symptoms of LAL D.

There is a wide spectrum of clinical symptoms, not all of which will appear in every individual. This, as well as its rarity, can often delay diagnosis. Many individuals may experience some or all of the symptoms that are outlined in this booklet before receiving an actual diagnosis.

What can I expect in the future?

Without treatment, infants with early onset LAL D have a life expectancy of between six and 12 months and patients will normally die from disease complications.

However, treatments are developing rapidly that make a better outcome a possibility.

How is LAL D tested?

Once LAL D is suspected, a blood test will be done to measure the level of the enzyme in the blood. Those affected will show lower than the normal levels or sometimes they will have no enzyme at all.

Is there a test for LAL D in pregnancy?

Amniocentesis involves testing a small sample of amniotic fluid

Chorionic villus sampling involves testing a small sample of cells from where the placenta attaches to the uterus

In utero means that the tests are done while the baby is still in the womb

In vitro literally means 'in the glass', as the testing is done in a flat glass dish called a petri dish

Pre-implantation genetic testing for Monogenic or single gene disorders (PGT-M) is an assisted fertility treatment

Unless there is a known genetic risk of LAL D in the foetus, it is unlikely that a test in pregnancy would be done. If you have a child with LAL D, or a known history in your family, 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. Ultrasound scans, amniocentesis and chorionic villus sampling can be used to diagnose LAL D *in utero*.

It might also be possible to have PGT-M screening to avoid passing LAL D to the baby. PGT-M is an assisted fertility treatment that involves checking the chromosomes of embryos in vitro before they are implanted in the womb, using IVF techniques. This is a complex process and requires referral from your regional genetics service.

What is the value of genetic screening and counselling?

LAL D is a genetically inherited condition and there is a risk of recurrence in future pregnancies for a couple with an affected child. Therefore all parents of children with LAL D should consider asking for genetic counselling before having other children. The counsellor should be able to provide non-directive advice on the reproductive choices, the risk to close relatives, and to suggest whether the wider family should be informed.

There are several specialist centres in the UK where you can go to be tested and to see a specialist in LAL D. The most up to date list can be found on the MPS website: **mpssociety.org.uk/our-friends**

What are the possible symptoms and how are they managed?

Symptoms are known as **clinical presentations**

LAL D causes a wide variety of signs and symptoms. The most common in infants are:

- Excessive vomiting and diarrhoea
- Poor weight gain and poor growth (failure to thrive)
- Swelling of the abdomen due to gastrointestinal (gut) problems or an enlarged liver (hepatomegaly) and spleen (splenomegaly), which can also cause umbilical hernias
- Appear very lethargic, irritable, distressed and unhappy
- May exhibit delays in their developmental motor skills and muscle tone

Liver disease

Many infants present with jaundice, indicated by a yellowing of the skin and whites of the eyes. Blood tests may indicate the presence of liver disease. Unfortunately scarring of the liver (hepatic fibrosis) can develop rapidly and lead to cirrhosis of the liver.

Some infants with severe liver disease can develop oesophageal varices. Varices are enlarged or swollen veins, which are at risk of rupturing or leaking, causing some level of internal bleeding.

There are many treatments available to manage pain, so speak to your doctor about options

Gastrointestinal and nutritional complications

At diagnosis, the majority of infants with LAL D will have ongoing gastrointestinal problems, resulting in very poor weight gain and growth leading to severe malnutrition and growth failure. Complications include

- Vomiting and diarrhoea (present within the first few weeks of life). Diarrhoea is caused by the build up of fats in the gut which prevents the ability to absorb nutrients and calories
- Stools are likely to be pale, greasy (fatty) and watery with a foul smell (steatorrhea)
- Gut motility complications result in vomiting and abdominal bloating (due to a build-up of gas), abdominal pain

These symptoms in young infants may result in them being misdiagnosed as having reflux, colic or cows' milk protein intolerance. Often infants have already been changed to feeds with an alternative to cows' milk protein with little improvement in overall symptoms or weight gain.

All infants diagnosed with LAL D will require significant, long-term input to manage their nutritional needs in order to support their growth and manage gastrointestinal symptoms.

How is LAL D managed?

General Medical Management

Treatment of early onset LAL D is a combination of:

- Intensive nutritional management
- Intravenous enzyme replacement therapy

Due to the rapid progression of the disease and the involvement of so many different specialists, all infants should be admitted to a designated paediatric lysosomal storage diseases (LSD) centre without delay for stabilisation, evaluation and treatment. Initial inpatient stays are often prolonged, with the average initial stay being around four to six months.

A multi-disciplinary team will be involved and will include many specialities, including the team of metabolic doctors, specialist nurses and specialist dietitians.

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Monitoring and care

The first few months of the baby's life are always spent on a ward in hospital whilst the baby is stabilised, established on ERT and appropriate feeds and is growing well.

Babies are usually very sick when they are first admitted to hospital and can sometimes deteriorate quite suddenly so careful monitoring is crucial. Therefore they will be continually monitored with regular blood tests, abdominal scans and assessments. Parents and carers are encouraged to report any changes that that they feel may be abnormal for their child.

Cuddles and contact

The children often require multiple IV lines and have a nasogastric tube, which can make handling and bathing such babies rather a daunting task. However, these babies need a lot of cuddles and hands-on care just like any other baby and the parents should not feel afraid to ask for help with bathing, dressing and so on as their confidence will increase the more they handle their child.

A flexible tube placed inside a vein which is used to give a person medicine or fluids.

Regular measurements

It is important that there is a detailed record of the infant's fluid balance, so parents usually keep a diary of everything the baby is given and their output of urine, stools and vomit.

The infant's growth will also be measured regularly to monitor their response to treatment.

Measurements will include:

- Weight, usually twice a week
- Length, every two to four weeks
- Mid upper arm circumference (MUAC), once a week; this is assessed to confirm the amount of arm muscle and fat under the skin. This is a more accurate measure of nutritional status when weight is affected by enlarged liver and spleen size or by fluid retention.

Feed Tolerance

Regular monitoring and accurate recording of fluid balance is essential. Giving a description of vomiting and stools is important in the assessment of feed tolerance eg absorption and can impact on their feeding regimen. Parents may be asked to keep a diary.

Output Monitoring

- Vomiting – amount and frequency
- Stools – describe amount, consistency, colour and frequency
- Urine
- Weigh all nappies

Management of acute illness

Babies with early onset LAL D are also susceptible to normal childhood infections and can become unwell quickly with normal childhood infections. Families will be advised on how to manage acute vomiting or diarrhoea to prevent dehydration. Parents will also be advised on what to do if the child has a temperature but no other symptoms as this could indicate a line infection.

Nutritional management

Total parenteral nutrition (TPN) is a method of **intravenous** (IV) feeding that gets nutrition into the body via the veins.

A nasogastric tube (NGT) delivers nutrition to the patient by a tube inserted through the nose and into the stomach.

A **gastrostomy** is a tube inserted into the stomach through the abdominal wall.

All infants with LAL D will require intensive nutritional management to promote normal growth and to help minimise some of the symptoms. The lack of enzyme prevents fats being metabolised correctly causing a build-up of cholesteryl esters in the gut causing difficulties with digestion and absorption.

There are a number of essential dietary considerations.

- On diagnosis infants will be assessed over 24-48hrs and put on specialist infant feeds containing minimal fat
- Feeds will usually also need to have their protein and carbohydrates in a simple form, such as amino acids and glucose
- Due to the severe gut damage, however, even these minimal-fat feeds are often not tolerated initially and infants may need intravenous feeding (TPN).

Infants who require TPN will be restarted on some enteral fluids, after a few days, once their symptoms of vomiting and diarrhoea resolve. Initially this will usually be oral rehydration fluid eg Dioralyte given as a very small volume continuously through a nasogastric tube.

Further components of the diet (protein, carbohydrate, essential fats, vitamins, minerals) will be added, often one at a time, until a complete feed is tolerated.

- Once a minimal-fat feed or TPN is established, infants with LAL D become much more settled rapidly gain weight and start to thrive
- Unfortunately infants may continue to experience vomiting and diarrhoea even when gaining weight and growing well on their special feeds; this is part of the condition and may not mean they are not tolerating feeds
- The majority of children with LAL D have, at some point, a nasogastric tube (NGT) inserted because they may be unable to take enough feed through the mouth to meet their daily nutritional and fluid requirements, or because it is necessary to give feeds as a slow, continuous infusion to maximise tolerance
- If tube feeding is going to be required for a prolonged time, then the NGT can be replaced with a gastrostomy.

Over time attempts will be made to normalise the diet. This will be done over a period of time under the supervision of a metabolic dietician. However, the amount of fat tolerated without reoccurring symptoms may be minimal.

Oral Feeding

It is important that the infant continues to take food normally otherwise they may lose their oral feeding skills, such as the ability to suck, and may become averse to taking food by mouth.

This can happen as a result of a lack of oral experience when the baby is constantly on tube or intravenous feeding. It can also be a response to frequent vomiting. This can adversely affect the babies' ability to suck so it is important to try to keep the sucking reflex going by offering small amounts of water orally or by providing a dummy.

Babies with LAL-D are encouraged to maintain their oral feeding skills by:

- Providing a dummy if the baby is not allowed oral feeds
- Offering small volumes of water or oral rehydration solution, such as Dioralyte, from a bottle when allowed
- Introducing solids with a very low fat content at around six months of age, as part of normal feeding development
- Encouraging fun, messy food play especially where the child dislikes eating and drinking

Looking after a nasogastric tube or gastrostomy

It is helpful if the parents learn to use and test the correct position of the tube before feeding. Some parents also learn how to insert the tube.

Placement of a feeding tube in the stomach is common in LAL D. This is called a gastrostomy, and, unlike an NG tube, it doesn't need replacing as often. This allows more flexibility in the way the infant is fed: for example, it allows continuous overnight pump feeds to be given at home, and can be used alongside oral feeding. Having a gastrostomy tube has other advantages; for example, for giving medicines or extra fluids when the child is unwell.

Oral aversion is when an infant becomes unable to take food by mouth

It is important never to force feed, as this will result in further behavioural feeding issues.

Enzyme replacement therapy (ERT)

A peripheral cannula is a fine, soft surgical tube inserted into a vein in order to administer medication

A **Hickman line** is a surgically inserted tube which can be made up of one, two or three tubes, or lumems. It is attached to a major vein and comes out of the body at the other end

A **port-a-cath** is also a surgically inserted tube but it goes into the major vein behind the collar bone and is completely beneath the skin

ERT is normally started very soon after diagnosis to try to prevent any further progression in the disease and to improve any signs and symptoms already present. ERT does not work on its own but appears to be effective alongside a highly modified diet and close supportive care.

ERT infusions are given on a weekly basis and can take 2–6 hours to administer depending on how the infant tolerates the infusion.

The infusions have to be given in a designated LSD hospital setting for the first 18 months to two years. Once the child is aged between 12 months and two years and stable on infusions, they can have home/school infusions, however close monitoring would still continue.

Reactions to ERT

Infusion reactions appear to be common but are managed with the administration of medications such as antihistamines, and changes to infusion rates.

The most common reactions tend to be:

- Rashes
- Raised temperature
- Increased breathing and heart rate

More information regarding the infusion and infusion reactions and side-effects are given once the decision has been made to start ERT.

Effectiveness of ERT

In clinical trials, ERT has been shown to improve survival rates compared with untreated infants. Though not all children survived the turbulent initial period, around two-thirds of infants in the clinical trials survived past one year compared with untreated infants. The average age of surviving children at the end of each of the two clinical trials was around three years or five years respectively. Clinical experience has shown that children may survive for much longer, though the long-term future of ERT-treated children with this disease is unclear as these are all relatively new developments.

Intravenous (IV) access

Good IV access is vitally important in order to give the weekly enzyme treatment so the infant will be fitted with a cannula, a Hickman line or a port-a-cath.

As treatment starts almost immediately after diagnosis, peripheral cannulas are used at first which can be difficult to site. For the longer term, a permanent in-dwelling line such as a Hickman or a port-a-cath will be inserted. It is crucial that these lines are cared for meticulously as they are also essential for obtaining blood samples and for the administration of intravenous nutrition (TPN), if needed.

Unfortunately children with LAL D appear to have a higher incidence of line infections so it is important to follow strict line care and follow up any rises in temperature in order to rule out a line infection. When lines need replacing this can take months to achieve and this can make the administration of the essential ERT particularly challenging.

Haematopoietic stem cell transplantation (HSCT)

HSCT is a blood stem cell transplant. There are different possible sources of blood stem cells, such as bone marrow, or umbilical cord blood, taken from an appropriate tissue-matched donor. Where bone marrow is used, the treatment is known as bone marrow transplantation (BMT).

HSCT can be a way of replacing the missing enzyme in some lysosomal storage disorders, effectively by replacing the immune system of the recipient with that of the donor. The cells of the donor immune system produce enzymes that can be taken up by cells in the rest of the body.

The use of HSCT for LAL D in the past was very limited, and those children who received it had mixed outcomes, due to the rapidity of disease progression and the difficulty of undertaking this treatment in such critically ill, malnourished children.

More recently, a small number of children have received HSCT after a period of stabilisation with nutritional management and ERT. While the long-term outcomes of this treatment are still unknown, and the experience is currently limited to only a very small number of children, some initially promising results have been reported. Children who received HSCT were able to reduce the dose and/or frequency of ERT infusions, and had improvements in gastrointestinal symptoms and have been able to tolerate, and grow, on more normal diets.

So far, HSCT has been used on an individual case-by-case basis, for example in children who have had a poor response to treatment with nutritional management and ERT. The precise role and indications for HSCT in LAL D are yet to be fully established.

Encouraging development

Babies with LAL D are very poorly so often spend a lot of time in their cot and can often seem their happiest there as it can be seen as a place of safety. However, these babies are likely to be delayed in gaining motor skills and reaching developmental milestones so they need to be stimulated and handled as much as they can tolerate. A regular routine, with specific playtime, can improve their development, and a play specialist may help to introduce some play therapy to help grow their motor skills and to provide some fun!.

The more parents care for and play with their children, the more confident they become, and this is a great benefit. Parents can learn how to make their feeds, test a NG tube or become pump trained. Learning these new skills will also smooth the transition to home care when the baby is ultimately discharged.

The more parents care for and play with their children, the more confident they become

What is the likely impact on the family?

Having a child diagnosed with a life-threatening, lifelong condition is a very stressful and anxious time as the family now face a rather uncertain future.

Commonly parents of LAL D babies feel that something is wrong with their child weeks before the diagnosis is made and they may have made multiple visits to the GP or other health professionals with their concerns. It can therefore be a relief to receive a diagnosis, although they now face a roller-coaster journey as LAL D is very unpredictable and the baby faces months in hospital in order to stabilise their condition. Naturally this has a massive impact on both the parents and the rest of the family.

Life revolves around caring for the child

Parents often have to devote all their time and energy to caring for their affected child and attending all their various appointments and procedures. It is important to draw strength from family members and friends and keep them up to date with what is happening to try and prevent feelings of isolation and confusion.

It can also help to talk to other LAL D families who are further down the line, as they really do know how newer families are feeling. Many parents find it helpful to talk to a professional such as a psychologist who can offer support and ways of coping with an inherited, long-term, chronic illness.

The MPS society is also there to help with both practical and emotional problems and should be contacted soon after diagnosis as they offer a valuable service, including important sibling support and family days out which can help prevent feelings of resentment and provide an enjoyable time away from the constraints of LAL

Living with LAL D

The MPS Society is able to provide more information on the following:

- Pre-school and education advice and support
- Advice on benefits
- Support with your mental health and wellbeing
- Signposting to other places for support

Please contact us on **0345 389 9901** or visit our website **mpssociety.org.uk/advocacy** if you would like to find out more about how the MPS Society can support you.

Visit **mpssociety.org.uk/our-friends** to find out about specialist centres who work with people with lysosomal storage diseases.

Where can I get more information and support?

The Society for Mucopolysaccharide Diseases (MPS Society) is the only registered UK charity providing professional support to individuals and families affected by MPS and related lysosomal storage diseases throughout the UK.

Further information booklets and other resources about MPS, Fabry and related diseases are available from mpssociety.org.uk

Our Support and Advocacy team have specialist knowledge of these diseases and a background in social care. We are here for you whenever you need us.

Phone us on **0345 389 9901** Mon to Fri 9am–5pm

Outside these hours you can call us on **07712 653 258**
Mon to Fri 5pm–10pm
Sat and Sun 9am–5pm

Email us at **advocacy@mpssociety.org.uk**

Members in Northern Ireland and Scotland can also contact their Support and Advocacy Officer on **07786 258 336**

Every effort has been made to ensure that the information in this booklet was accurate and up to date at the time of going to press. This booklet is not intended as a substitute for professional medical advice and the MPS Society and other contributors cannot take responsibility for actions taken as a result of this information.

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