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PRACTICAL INFORMATION
FOR FEMALE CARRIERS
OF ALD

ALDLIFE
helping to cope - helping to hope
A charity to promote awareness, research and prevention of adrenoleukodystrophy

PRACTICAL INFORMATION FOR FEMALE CARRIERS OF ALD

Introduction

You have discovered you are a carrier of a mutation in the ABCD1 gene, the gene which causes ALD (adrenoleukodystrophy).

This will most likely be because a family member has been diagnosed with either ALD (adrenoleukodystrophy) or AMN (adrenomyeloneuropathy).

ALD Life is Britain's leading charity dealing with these conditions, run by people who have been in the situation you are now facing and who can help you.

We were founded to help and support people in your position. Our members have been through the same ordeal and have experienced the problems you now face.

We must stress there is no right or wrong way of dealing with being a carrier, but in researching this booklet, we have spoken to many who have been found to be carrying the ALD gene and have collated much of the information they wished they had been given.

The medical information shown in shaded boxes, has been compiled from reputable sources & checked by medical experts in ALD.

We have a worldwide contact list of people who are willing to chat about all aspects of living with the disorder.

Please contact ALD Life on 020 7701 4388
or email info@aldlife.org
Our website is **www.aldlife.org**

> "IT WAS A RELIEF TO FIND A RELIABLE & TAILORED INFO CENTRE LIKE ALD LIFE."

PRACTICAL INFORMATION FOR FEMALE CARRIERS OF ALD

What is a carrier?

The ABCD1 gene is located on the X-chromosome. Women have two X chromosomes. In women who carry the ALD gene mutation on one X-chromosome, the full-blown disease does not appear because there is a normal copy of the gene on the other X-chromosome. But women can pass the gene to their children, hence the term 'carrier'.

There is more information about the genetic aspects of ALD and AMN on p6.

What are ALD and AMN?

Adrenoleukodystrophy (ALD) is caused by a genetic fault that means those affected are unable to process Very Long Chain Fatty Acids (VLCFAs). It is thought that these VLCFAs accumulate and gradually destroy the myelin sheath that covers the nerves. The myelin acts like the coating around an electric cable, and allows messages to be transmitted along nerve cells. When the myelin is damaged, messages cannot get through and functioning is affected.

The gene at fault in ALD is called ABCD1. The faulty gene can cause several related but different conditions. The most devastating form of the disease, symptomatic cerebral ALD, affects the brain and is only found in males. The other condition caused by a faulty ABCD1 gene is called AMN, which affects nerves in the spinal cord and body to varying degrees. It can affect both men and women.

It's not possible to predict how the ALD gene will affect any one person.

Will I develop AMN symptoms?

Carrying a mutation in the ABCD1 gene puts you at risk of developing AMN, but it is not inevitable. Women are less likely to develop AMN than men, and the symptoms of AMN usually develop at an older age, and progress more slowly in women than men. There are no exact figures, but it is estimated that most female carriers are highly likely to develop some symptoms during their lifetime. Usually these will be later in life and relatively mild.

Symptoms of AMN can include stiffness, weakness and pain in the legs. This starts gradually and can progress over time. The medical term for this is 'progressive spastic paraparesis'. Damage to the nerves supplying the legs means unsteadiness and falls are common. The nerves to the bladder and bowel can also be affected in AMN.

Mobility can gradually deteriorate to the point where the sufferer develops significant problems. In rare cases women with AMN may become wheelchair bound.

Primary adrenal insufficiency, known also as Addison's disease, is caused when the adrenal glands do not produce enough of certain steroid hormones. It is treated by taking replacement hormones. Symptoms include chronic fatigue, muscle weakness and weight loss. People with adrenal failure can become extremely unwell very quickly if they get a viral or bacterial infection.

It is extremely rare for females with the ALD gene to suffer from adrenal failure, and routine testing is not required. On the other hand, males with the ALD gene can suffer from adrenal failure and should go to their doctor to be tested for this.

ALD Life has produced separate leaflets for men and women suffering the symptoms of AMN.

How can I prevent these symptoms?

There is currently no method of predicting which female carriers of the ALD gene will go on to develop AMN. There is also no proven way to prevent AMN symptoms developing. Some choose to follow a very low fat diet and to take Lorenzo's Oil to lower their levels of very long chain fatty acids (VLCFA), which will normally be high.

However, studies in people with AMN who are taking Lorenzo's Oil have shown that, although it can lower VLCFA levels, it probably does not affect the onset or progress of the disease.

It must be emphasised however, that this is a very personal choice and some patients find benefit in keeping their diets low fat and using Lorenzo's Oil to assist in bringing down their VLCFA levels. Research is still ongoing into the consequences of raised VLCFAs on the general health of those with the ALD gene.

Exercise is important for everybody, but some women do choose to make sure their exercise regime includes exercises to ensure their muscles are in the best shape possible in case they suffer future symptoms.

What medical follow-up should I get?

Your GP should be able to refer you to an AMN specialist. They will ask you about AMN symptoms, examine you and do some blood tests. If you do go on to develop symptoms, your specialist will recommend treatments to ease these. You can also discuss options for pregnancy.

If your GP is unsure, ALD Life can help to find a local specialist for you.

Explanation of the genetic implications

ALD is an X-linked disorder, which means that the genetic abnormality involves the X-chromosome.

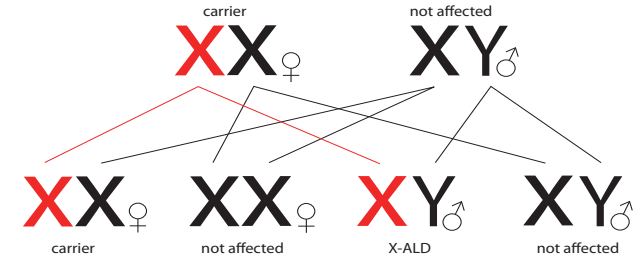
Women have two X chromosomes.
In women who carry the ALD gene mutation on one X-chromosome, the full-blown disease does not appear because there is a normal copy of the gene (Figure 1) on the other X-chromosome.

Men have one X-chromosome and one Y-chromosome (Figure 2). In men who have ALD on an X-chromosome there is no other X-chromosome for protection; therefore the male can develop symptomatic ALD.

For reasons we don't understand, not all males who have the gene are affected in the same way. Some develop cerebral ALD as boys, others have no symptoms for many years and then develop AMN as adults. Some males develop Addison's disease (adrenal failure) rather than ALD or AMN. Most women with the gene will also develop some, usually mild, AMN symptoms later in life.

Figure 1:

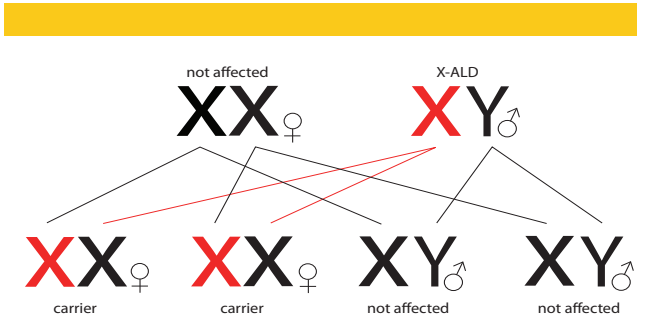
If a woman is a carrier for ALD she has the following possible outcomes with each newborn: With a daughter, there is a 50 % chance (1 in 2) that the daughter is a carrier of ALD and a 50 % chance the child is unaffected. Where the child is a boy there is also a 50 % (1 in 2) chance the son will have ALD and a 50 % chance he will be unaffected.



X **X-ALD X-chromosome**
X **normal X-chromosome**
Y **Y-chromosome**
♀ **Female**
♂ **Male**

Figure 2:

If an affected man has children, then all of his sons will be entirely normal (because sons get the father's Y-chromosome). But all of his daughters will be carriers (because he passes his only X-chromosome to his daughter).



X **X-ALD X-chromosome**
X **normal X-chromosome**
Y **Y-chromosome**
♀ **Female**
♂ **Male**

What about my children?

You have been diagnosed as a carrier of ALD, and as a result you could pass the gene on to your children. If you already have children, we recommend they should be tested immediately to see if they have the ALD gene.

Testing is especially important if you have young sons, because if the gene is discovered early, before symptoms appear, there is a chance of preventing ALD from developing. There is a (50%) 1 in 2 chance that your sons will have the gene. If you have boys with the gene they should be considered for a preventative programme, which is explained in another leaflet - Boys with Asymptomatic ALD.

There is a (50%) 1 in 2 chance that your daughters could be carriers of ALD. If they are, they have a 50% chance of passing the gene on. If you have daughters under the age of 18 testing is usually delayed until they reach adulthood.

The idea of genetic testing for your children can be frightening. Of course, if they are adults, they will need to make their own decision. Your GP or specialist can put you in touch with a genetic counsellor who can talk you or your children through the implications of testing, and help you make an informed choice.

What about future pregnancy?

Female carriers of the ALD gene can pass the gene on to sons or daughters and so need to consider their options carefully when having children. Males can only pass the gene on to their daughter, but they too should consider their options very carefully.

If you are a female carrier and have a boy, there is a (50%) 1 in 2 chance that he could suffer from the life-threatening disease ALD as a child or from AMN in later life (see p 6).

Similary if you have a girl there is a 50% (1 in 2) chance that you will pass the ALD gene to your daughter, who in turn could pass it on to her children or could develop AMN later in life.

Although men cannot pass the gene on to male children, they will always pass the gene on to female children who then have a 50% (1 in 2) chance of passing it on to their own children.

Are there any options available so I can have children who are not affected by the ALD gene?

Some people will choose to go ahead and have a child and take the risk of passing on the ALD gene. Another option would be to have a test during pregnancy (prenatal diagnosis) to find out whether or not your unborn baby has the ALD gene. A third option is to have pre-implantation genetic diagnosis, a form of IVF.

Two main prenatal tests are available: chorionic villus sampling (CVS) which is done at around 12 weeks of pregnancy, or Amniocentesis which is done at 16 weeks of pregnancy. CVS will test if the pregnancy is male or female, and if male will be sent off for a genetic ALD test. Both tests carry a small risk of miscarriage at 2% (1 chance in 50) or 1% (1 chance in 100) respectively. The results would be available about one week after the test and you can then take the decision whether to carry on with the pregnancy.

There are also tests that can detect the sex of a pregnancy at an early stage (around 9 weeks) by testing a maternal blood sample. Some women will opt for this test first and only go on to have a prenatal test if the pregnancy is male.

> “REMINDING YOURSELF THAT THERE IS ONLY A ‘CHANCE’ AMN WILL AFFECT YOU LATER IN LIFE, AS WELL AS BEING POSITIVE ABOUT HAVING HEALTHY CHILDREN, IS THE WAY I DEAL WITH THIS. I FOCUS ON DOING ALL I CAN TO NOT ALLOW IT TO AFFECT ME WHEN I AM OLDER. I LOOK AFTER MY HEALTH MORE THAN MOST PEOPLE.”

Women who are found to be carrying a male with ALD will be offered the choice of termination. This is a very personal decision to make. ALD Life can put you in touch with others who have been in this difficult position.

An alternative way of preventing an ALD pregnancy is pre-implantation genetic diagnosis (PGD). At-risk couples can use IVF technology (even though they do not have fertility problems) to create embryos in a “test tube”.

The embryos are tested to see whether they carry the mutated ABCD1 (ALD) gene. In doing so, the clinic can differentiate embryos which do not carry the mutated gene from those that do.

Embryos that will not lead to an affected child will be transferred to the woman's womb, with the hope that she will become pregnant.

A licensed centre must make an assessment of a couple before providing PGD treatment to them. This is because treatment can only legally be provided if their offspring are at risk of a genetic abnormality which may cause a medical illness or condition on the Human Fertilisation and Embryology Authority (HFEA) PGD approved list, and that the risk of the genetic abnormality is significant and the medical illness or condition resulting from it is of appropriate seriousness (ie it is not just the fact that the condition is on the list).

The HFEA has also stated that "If carrier status in itself does not result in a serious condition then avoiding it cannot be the primary purpose of embryo testing. However, unaffected embryos can be preferred over carrier embryos when choosing embryos to transfer if it is the full serious condition which has been tested for/which the PGD process is aiming to avoid".

PGD should be available on the NHS, and your genetic counsellor should be able to direct you to a centre that can carry out this treatment. The success of PGD is related to female age, so most centres will only offer treatment to women under the age of 40.

We would strongly recommend that you talk to a genetic counsellor about your options. ALD Life know a number of families who have had children using the above techniques and are willing to talk about their experiences.

Some women who have been diagnosed as carriers have advised that it helps to have counselling or someone to talk to. Feelings of guilt towards affected children are a problem for some women.

How can I get more information?

You can get in touch with others in a similar situation through ALD Life, who can also provide practical information, support and advice. ALD Life also runs an annual event which brings together families and individuals suffering from all aspects of carrying the ALD gene to learn about innovations in treatment and research and share experiences.

Listed below are just some of the useful organisations that are there to help you:

ALD Life

ALD Life was founded by Sara Hunt after both her sons were diagnosed with ALD. She has first hand experience of most aspects of dealing with the disorder: her elder son, Alex, had symptomatic ALD and was diagnosed at age 7 in 2001 and passed away in 2012. Her younger son, Ayden, had a successful bone marrow transplant in 2008. The charity provides practical, emotional and financial support for all those affected by ALD and AMN.

www.aldlife.org
Tel: 020 7701 4388
Email: info@aldlife.org

ARC - Antenatal Results & Choices

A charity providing impartial information & individual support to parents whose unborn baby has been diagnosed with a condition that may lead to the decision to end the pregnancy.

www.arc-uk.org
Tel: 0845 077 2290

Pre-Implantation Genetic Diagnosis:

Guy's and St Thomas' hospital in London run one of the world's leading pre-implantation genetic diagnosis (PGD) units and have produced a website with lots more detail on PGD.

www.pgd.org.uk

The Human Feritlisation and Embryology Authority

The Human Fertilisation and Embryology Authority can give you details of pre-implantation genetic diagnosis services near to your area and give advice on funding.

www.hfea.gov.uk

What Clinic
What Clinic also have a list of centres around the UK offering PGD services.

www.whatclinic.com/fertility/uk/pgd-preimplantation-genetic-diagnosis

PGD in Scotland
PGD has been available in Scotland since 2002, based at Glasgow Royal Infirmary Assisted Conception Services Unit, Walton Building, 84 Castle Street, Glasgow, Scotland, United Kingdom, G4 0SF.

Tel: 0141 211 0505

INFORMATION SOURCES

The medical information in this leaflet, shaded in orange, has been compiled from the following references, and reviewed by an expert doctor.

Jangook P et al. Adrenoleukodystrophy in female heterozygotes: Underrecognized and undertreated. Molecular Genetics and Metabolism 105 (2012) 180–185

X-linked adrenoleukodystrophy in woman: a cross sectional cohort study
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All medical information is correct at time of going to press January 2015.