alpha-1 ORGANISATION AUSTRALIA INC

Alpha Times

Newsletter of Alpha-1 Organisation Australia inc

Issue 5 Spring 2021

From the President's Pen

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Welcome to our Spring edition. I hope you are keeping safe and if you are in lockdown that you are managing to keep busy and in touch with friends and family.
This is the first time I am addressing you as the elected President of the A1OA. We held our first AGM in August 2021, in accordance with the requirements of registered charities. Our Annual Report was accepted and can be found on our website (www.a1oa.org.au) under Resources. Following Board nominations, I am pleased to announce that Ian Saunders will hold the position of Treasurer during 2021-2022 and Leonie Robison and Sandra Baxendell will serve on our management committee as general members. We have a vacancy for Secretary and Vice-President. Members with an interest in volunteering in one of these roles should contact me at president@a1oa.org.au.
During the last few weeks, I have met with Australian research groups who are undertaking research related to alpha-1 antitrypsin deficiency, including liver and lung research. It is wonderful to learn about their work and how we may be able to support the research. A rare opportunity to support a group of Australian alpha-1 liver researchers has emerged but requires the generous donation of a diseased alpha-1 liver. If you are on a liver transplant list, this may be something that you would like to consider – details inside.
Our charity is always advocating for treatment access, a cure and for clinical trial access. I recently had a zoom meeting with KAMADA staff in Israel, exploring if they might be able to bring their trial on inhaled antitrypsin to Australia. We will share information if this looks like happening. We have also learnt via our A1OA Face Book page that a Phase 2 alpha-1 liver trial may be coming to Melbourne later this year. Trial information will be provided via social media as soon as it is available.

Looking at Livers

In this edition we look at some of the issues around liver problems associated with Alpha-1 Antitrypsin Deficiency.

A common problem for sufferers of Alpha-1 Antitrypsin Deficiency is liver disease, potentially leading to liver failure.

Itchiness and liver failure

Itching (pruritus) is one symptom of chronic liver disease, though not everyone with liver disease develops it.
You might have a localised itch, such as on your lower arm, or it might be an all-over itch. Either way, it can lead to a distracting, often overwhelming, desire to scratch. Scientists have yet to identify a single substance responsible for itching in liver disease. It may be that it's caused by a combination of factors.

Alpha-1 Antitrypsin Deficiency (A1AD) Starts in the Liver

A1AD is caused by a mutation in the Serpina -1 gene that codes for the manufacture of Alpha-1 Antitrypsin in your liver. The protein is then carried around the body via the bloodstream to protect the lungs and other organs. One variant, designated Z, codes for a misshapen molecule of antitrypsin, which is unable to be transported out of the liver. The protein builds up in the liver over time and can lead to cirrhosis, scarring and liver cancer.

Sufferers can experience swelling or pain in the abdomen, vomiting, loss of appetitive, diarrhoea, tiredness, jaundice. Sometimes a child can be born already exhibiting signs of liver disease, such as jaundice, poor growth, diarrhoea, or itching, and require a transplant.

You can help prevent the development of liver disease by avoiding alcohol, getting vaccinated against Hepatitis A and B, and keeping your diet and weight healthy.

These are thought to be good for your liver

Coffee-may help lower the risk of inflammation, cirrhosis, cancer by preventing the build-up of fat and collagen.

Green tea- high antioxidant level improves liver enzyme levels and reduces oxidative stress and fat deposits in the liver and decrease the likelihood of developing liver cancer.
Green tea as a supplement should be avoided as there are reports of liver damage resulting from its consumption.

Grapefruit- contains antioxidants that reduce inflammation and decrease the amount of fat in the liver and increases the number of enzymes necessary for burning fat.

Blueberries and cranberries- antioxidants protect against liver damage, increase immune cell response, have been shown to slow the development of lesions and fibrosis and scar tissue.

Grapes- especially red and purple- antioxidants lower inflammation preventing damage.

Prickly pear- (used in traditional medicine with liver disease and hangover) helps reduce inflammation and stabilises antioxidant and enzyme levels.

Beetroot juice- contains nitrates and antioxidants to help reduce oxidative damage and inflammation.

Cruciferous vegetables- beneficial effect on enzyme levels and may help prevent tumours and fatty liver.

Nuts- high in nutrients, may be associated with decreased risk of non-alcoholic fatty liver disease.

Fatty fish- contain omega-3 fatty acids, which help reduce inflammation. Remember to balance this with omega-6 fatty acids found in many plant oils.

Olive oil- can improve liver enzymes and fat levels and blood flow in the liver.

What are the Stages of Liver Failure?

Infections, alcohol abuse, and genetics can all lead to liver disease and damage. Liver failure happens when your liver can't work well enough to perform its many vital functions, such as producing bile to help you digest food and clearing your blood of toxic substances.

Damage to your liver can accumulate through several stages. Each stage progressively affects your liver's ability to function properly.

It's important to distinguish between liver disease and liver failure.

Liver disease refers to any condition that causes inflammation or damage to your liver. Liver disease can affect the overall function of your liver.

Liver failure is when your liver has lost some or all of its functionality. It can occur due to the damage that's caused by liver disease.

Inflammation

In this early stage, your liver becomes enlarged or inflamed. Many people with liver inflammation don't experience symptoms. If the inflammation continues, permanent damage can occur.

Fibrosis

this happens when an inflamed liver begins to scar.

The scar tissue that's generated in this stage takes the place of healthy liver tissue, yet the scarred tissue can't perform the same functions. This can start to affect your liver's ability to function optimally.

Fibrosis can be hard to detect because symptoms aren't often present.

Cirrhosis

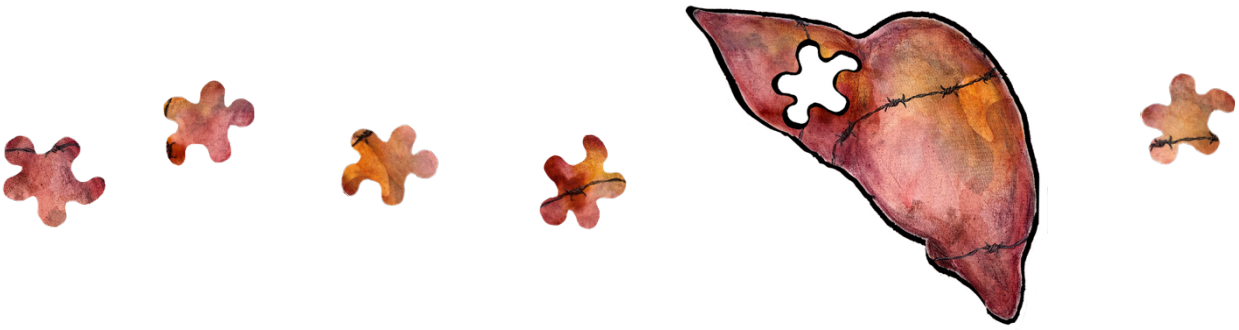
In the cirrhosis stage, severe scarring has built up on your liver. Because there's even less healthy liver tissue, it becomes very difficult for your liver to function properly.

While symptoms may not have been present before, you may now begin to experience symptoms of liver disease.

End-stage liver disease (ESLD)

People with ESLD have cirrhosis in which liver function has deteriorated dramatically.

ESLD is associated with complications such as ascites and hepatic encephalopathy. It can't be reversed with treatments other than a liver transplant.



Liver Research Gives Great Hope

A number of general liver studies (i.e., not alpha-1) plus alpha-1 antitrypsin specific liver research give hope to the alpha-1 community.

Alpha-1 Liver Studies

a) INTERVENTIONAL STUDIES

- The Phase 2 AROAAT2002 study has not been offered in Australia but positive interim 48-week liver biopsy results have been announced. Results indicate that treatment leads to improvements in multiple measures of liver health including fibrosis with substantial and sustained reductions in the level of mutant Z protein.

- The Estrella study, using the experimental Belcesiran drug trial has been undertaken in New Zealand. The intervention (an RNAi therapy) targets the gene responsible for the production of abnormal antitrypsin in the liver. Further information can be found at www.clinicaltrials.gov. We hope to see this trial offered in Australia soon.

b) OBSERVATIONAL STUDIES

- Four alpha-1 observational studies are underway overseas which will shed light on the natural history of alpha-1 liver disease. Information from these trials will support future treatments and cures. Information can be found at www.clinicaltrials.gov.

Non-Alpha-1 Australian Liver Research

DONOR LIVER INJURY

- The increased rate of fatty liver disease is decreasing the number of suitable donor livers for transplantation as these livers tend to fail after transplant. Australian researchers are exploring markers called alarmins to understand the injury profile of livers post-transplant with the aim of blocking the injury pathway and improving transplant success rates and making more donor organs suitable for transplant. (Ref: gallipoliresearch.com.au)

LIVER CIRRHOSIS AND CANCER

- Most patients with liver cancer have underlying cirrhosis. Liver cancer is potentially curable if detected early.
- Researchers from the University of NSW Microbiome Research Centre have recently been awarded $4 million to develop microbial based biomarkers for the early detection of liver cancer which will improve outcomes among patients with liver disease.
- Researchers from the University of WA Medical School have received $3.2 million to support a nation-wide trial to identify cirrhosis and liver cancer in patients sooner. This study will recruit 2,800 patients with risk factors for cirrhosis and liver cancer. This research uses a cirrhosis detection pathway that has been developed to examine its effect on early diagnosis and surveillance compared to usual care.

Non-Alpha-1 Liver Research

Regenerative liver research is being undertaken at King's College London on diseased livers with stem cell like properties being examined which may be able to be repair diseased livers. Regenerated livers may stop the need for liver transplant.

Research at the Children's Medical Research Institute (CMRI)

AATD Gene Therapy Program at Children's Medical Research Institute

Children's Medical Research Institute (CMRI) focuses on the prevention and treatment of childhood diseases with world-leading research in the areas of gene therapy, embryology, neurobiology, and cancer. Our group, the Translational Vectorology Research Unit (TVRU) led by Associate Professor Leszek Lisowski, develops novel bioengineered gene therapy delivery tools to enable safe and efficient correction of genetic diseases and other conditions.

The delivery tools we develop are called AAV vectors and they enable long-term therapeutic correction of disease in a wide range of human tissues. They are also easy to manufacture at scale making them an excellent choice for gene therapy applications. Natural and bioengineered AAV vectors have been developed to treat Spinal Muscular Atrophy (SMA) (Zolgensma™) and prevent the blinding eye disease RPE65 deficiency (Luxturna™), and they are the technologies underpinning a large number of late-stage clinical trials targeting conditions in other human organs, including the liver.

While there have been several AAV-based clinical trials conducted over the past 20 years in the U.S. for AATD, the therapeutic successes were limited. We believe our unique insight into AAV vectorology, which enables us to develop better AAV vectors for precise cell targeting, combined with our knowledge of liver biology, vector-based genome engineering and our experience understanding of the unique challenges associated with translation of gene therapeutics, puts us in the rare position to support development of a safe and effective treatment option for AATD. Specifically, using our already optimised proprietary tools and biologically-predictive preclinical model systems, we will develop a novel bioengineered AAV-based gene therapy targeting the affected liver cells of AATD individuals to replace the mutant gene with the normal gene.

However, to do this we need your help! Cells isolated from explanted livers of AATD patients, livers that are normally discarded, are invaluable in our research. They enable us to develop and validate the gene therapy tools to increase the chance of clinical success. Specifically, we can use the affected cells isolated from these livers to test our developed treatments, which can give us insight to how the gene therapy would work inside a human body.

The liver donated by the family of a young girl, Charlize, with a metabolic liver condition, has proved invaluable to gene therapy research. Charlize and her family feel empowered by this donation and what they are doing to help find cures for other children (you can read the story here https://www.cmrijeansforgenes.org.au/get-involved/real-stories/charlize .

For those AATD patients who will undergo a liver transplant, we ask if you would please consider donating your explanted livers to support our research program and help us develop an advanced gene therapy to help all of those effected by this illness. Your donation would be a direct way to support research that will help others with AATD. To find out how you can help please contact us at LLISOWSKI@CMRI.ORG.AU

Newly Diagnosed? Part 4.

Greetings. In Part 1 of this series, we looked at a few things to do as a priority when you're first diagnosed with alpha-1 antitrypsin deficiency (A1AD). In Part 2 we looked at some broader implications, including what it means for your relatives, and in Part 3 we looked at some of the symptoms/health effects of A1AD. If you want copies of these earlier articles let us know and we'll send them out to you.

As promised, in Part 4 we look at some of the mental issues associated with an A1AD diagnosis.

A1AD is normally diagnosed as a result of lung and/or liver issues which have no other obvious cause. While it can be a positive thing to find a reason or cause for your symptoms, it can also be quite worrying to learn of your condition, and it is important to make sure you don't ignore the mental issues which may arise. These may include thoughts such as 'why me', general hopelessness and depression.

You should not be surprised or ashamed at such thoughts – in the circumstances they are perfectly natural and understandable, and asking for help is the best thing to do. This may be from a good friend or via your GP, who will be able to refer you to an appropriate specialist and/or prescribe medication which may help. In addition, most states and territories have genetic counselling units who deal specifically with the issues associated with such conditions. Doing all you can to learn about the condition and it's impacts is also helpful as it will help you rationalise the thoughts you are having.

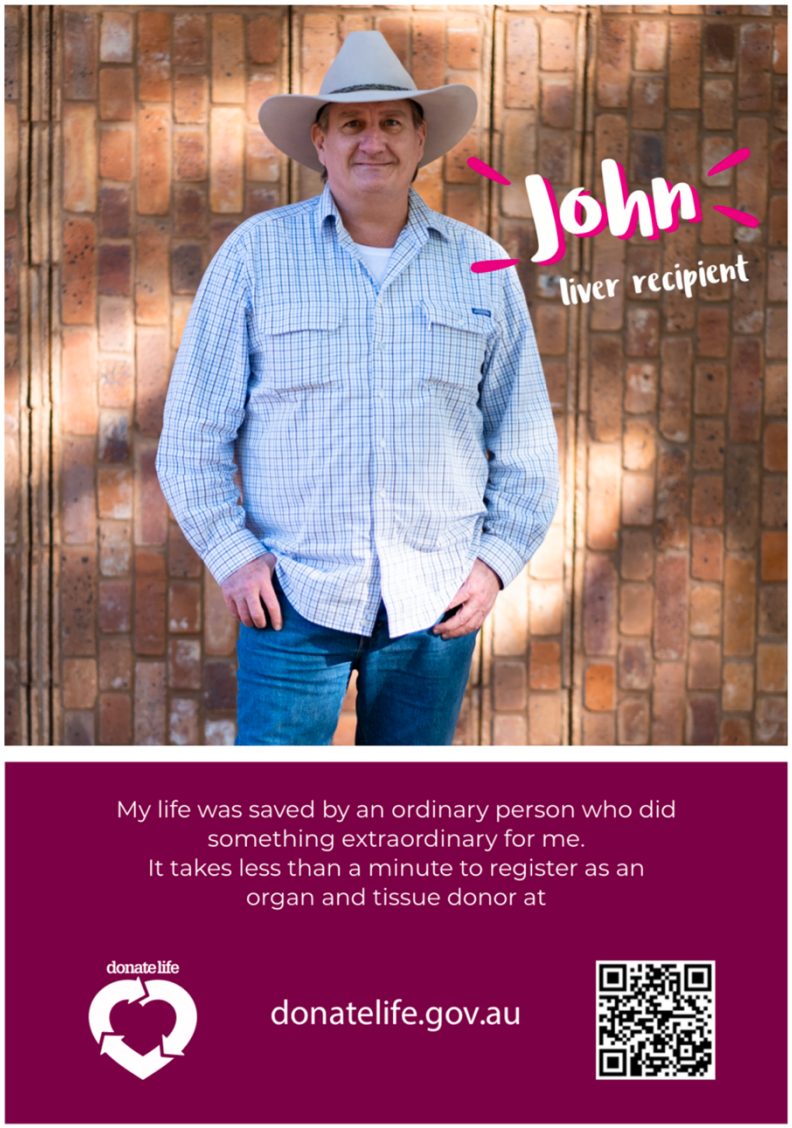
You may also be concerned about the impact on others, be they spouse/children etc or siblings/relatives – being the bearer of bad news isn't normally fun. In this context it is important you don't take on others' issues – you can only explain the situation to them, advise them to seek their own alpha-1 status if appropriate and let them process the situation themselves.

Be kind to yourself – stay active and involved as much as possible and accept A1AD as part of your unique journey.

An Alpha Story

John Hammond

John Hammond feels that every day he has is a gift. Two years ago, the farmer and former miner, was being kept alive in hospital, facing death, and being prepared for palliative care. John had been diagnosed in 2010 with A1AD, ZZ variant, when his lung function was found to be declining but it was his liver that failed him first.
After 18 months in hospital, with his wife only able to visit in school holidays, medical staff was able to make John strong enough to receive a liver transplant if a suitable liver became available. Due to the seriousness of his condition, John was put to the top of the transplant list in Australia and New Zealand. Within thirty- two hours of being placed on the list, he was wheeled into surgery, where a liver transplant saved his life. John is grateful every day to the selfless donor who has given him a second chance at life and the gift of spending more time with his family.



John's liver continues to work well, though as with all transplants, the recipient must take anti-rejection drugs for the rest of his life as well as other medications to counter the side effects of these. He also needs to cover up in the sun and use 50+ sunscreen due to the increased risk of developing skin cancer and melanoma and other cancers, because of the immunosuppressing drugs. There are also week-long stays in Brisbane every three months for doctor's appointments and clinic visits. Unfortunately, John's choice of career as an underground miner has impacted badly on his lungs and he is facing a lung transplant in the near future as his lung function continues to decline.
He is philosophical and takes every day as it comes, living life to the fullest as he feels he owes this to the generosity of his anonymous donor.

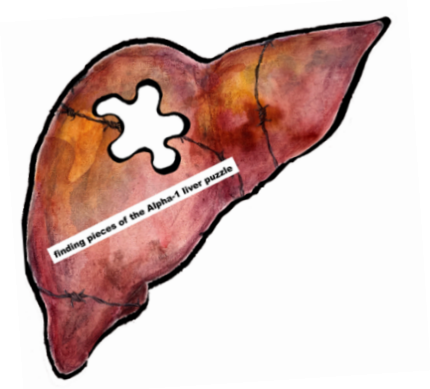
Organ donors save lives. Be an organ donor. Register here

https://www.donatelife.gov.au/

Aunty Alpha

Dear Aunty Alpha,
I've recently been diagnosed with A1AD so I know that we can develop liver problems. I have been feeling itchy lately. Should I be worried?
Regards, Kate

Dear Kate,
Itchiness can be a symptom of liver disease but can also be attributed to other causes. Possible causes are skin conditions, viruses, nerve disorders, psychiatric disorders, allergies, drug reactions, pregnancy. Talk to your GP about eliminating these.
Causes of itching in liver disease are not well understood and research is being done into different substances that might be responsible; bile salts accumulating under the skin, histamine which doesn't respond to antihistamines, serotonin, serum alkaline phosphatase, and lysophosphatidic acid.
Try to avoid scratching. Talk to your GP or specialist about the different treatments. You might need to try a few different treatments to find the right one or a combination that works for you. Some are discussed in this edition of Alpha Times
Regards, Aunty



Have a question about Alpha-1 Antitrypsin deficiency? Write to Aunty Alpha at contactus.a1oa@gmail.com

Does itching indicate anything about liver disease progression or prognosis?
You can develop problem itching at any stage, including before you know you have liver disease. This alone says nothing about liver disease severity, progression, or prognosis.
When to see a doctor
Always see your doctor if you develop new symptoms or your symptoms worsen, including itching.
How to treat itching associated with liver disease
It can take a bit of trial and error to find the right treatment for your particular itch as there are different causes of itching related to liver disease.
Avoid scratching because that can irritate the skin leading to further irritation and infection.
If you find yourself scratching too much, try to avoid temptation by keeping your skin covered.
If you tend to scratch a lot during the night, wear gloves to bed.

1. *Apply anti-itch topicals*

If you have a mild, localized itch, you can try aqueous cream with 1 percent menthol or over the counter corticosteroids and calcineurin inhibitors.

2. *Take prescription oral medications*

a) Cholestyramine- *helps remove bile salts from circulation.*
b) Rifampicin- *inhibits bile acids. It requires regular monitoring due to the potential for serious side effects such as hepatitis or renal impairment.*
c) Naltrexone- *blocks the effects of opioids. It requires regular monitoring.*
d) ***Sertraline-*** *an antidepressant that can be used to treat chronic itch.*

3. *Light therapy- exposes the skin to specific types of light to promote healing. It can take several sessions to start working.*
4. *Liver transplant. When treatment doesn't work and quality of life is severely affected, your doctor may want to discuss the possibility of a liver transplant.*

