



Notes from ALD Connect's Symptomatic Women Community Call

April 26, 2021

Featuring ALD expert neurologist Dr. Ali Fatemi

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****Disclaimer****

These notes are from ALD Connect's Symptomatic Women Community Call with guest Dr. Ali Fatemi on April 26th, 2021. These notes are for informational purposes only. They are not intended to be a substitute for professional medical advice, diagnosis or treatment. If you or a family member are ill or suspect that you or a family member are ill, seek professional medical attention immediately. ALD Connect does not recommend or endorse any specific physicians, treatments, procedures or products even though they may be mentioned in these notes.

Background Information on ALD (From Dr. Fatemi's Presentation)

- ALD shows an X-linked inheritance pattern because the gene that gets mutated to cause ALD, called the *ABCD1* gene, is on the X chromosome. This means:
 - If a father having XY chromosomes has the mutation, there is a 100% chance every one of his daughters will have mutation and a 0% chance any of his sons will have it. This is because he always passes his Y chromosome to his sons and his X chromosome to his daughters.
 - If a mother having XX chromosomes has a mutation on one of her Xs, there is a 50% chance that any child (50% for boys or girls) will inherit the mutation. This is because both males and females receive an X chromosome from their mother.
- While traditionally doctors thought that X-linked diseases seldom affect women, we now know this is not true and that many women with ALD do have symptoms. Part of the biological reason for this is due to the process of "X-inactivation".
- In individuals with two X chromosomes, "X-inactivation" is a process by which one X chromosome (either from mom or dad) gets turned off in each cell. This occurs in order to normalize the expression of X-linked genes – just because women have two X chromosomes doesn't mean they should be doubling the expression of genes on the X chromosome, so they turn one X off in each cell.
 - Generally, this is thought to occur randomly, meaning that on average a woman with one healthy X chromosome and one mutated X chromosome should have ~50% of her cells with the healthy *ABCD1* gene and 50% of her cells with the defective gene.
 - However, sometimes the process appears to be "skewed", leading to non-random X inactivation. In this case, one copy of the X chromosome can be preferentially turned on in more than 50% of cells in the body. If the mutated X chromosome in ALD becomes skewed, this could mean that more than 50% of cells could have the defective *ABCD1* gene instead of the healthy gene.
 - This process seems to vary by individual and by tissue system (brain vs. liver) because it can begin at any point in development.



- Practically this means that some women with ALD may have more of their cells using the mutant *ABCD1* copy than others, which could lead to more severe symptoms. This is one of the reasons that ALD symptoms in women can be so variable, and part of the reason why it's important to regard women with ALD as patients and not only carriers of the disease.
- Doctors have known for a long time that adult women with ALD can show severe symptoms
 - Axonopathy (defects in the part of nerve cells that send signals, called axons) and loss of myelin (an insulating sheath that coats axons) can occur in the long tracts of the spinal cord in both men and women with ALD
 - General disability from movement disorder and bowel/bladder issues are very common in women with ALD
 - Bowel and bladder control are highly impacted in both males and females due to impacted spinal cord
 - Bowel and bladder symptoms can precede other symptoms (i.e. walking) by up to 10 years in men and women
 - Peripheral neuropathy is common in women and can cause:
 - Pain, tingling, burning, and numbness in limbs
 - Muscle weakness
 - Dysautonomia, which is when the autonomic nervous system is not working properly, leading to improperly functioning blood vessel regulation and bladder dysfunction
 - Dysautonomia can have similar symptoms to Adrenal Insufficiency, such as confusion and fatigue
 - According to best estimates of the Dutch experience with ALD (which is easy to track because there is one main ALD expert center in the country), 80% of women with ALD may experience symptoms. However, we are not sure about the real proportion of ALD women with these symptoms because the method of study recruitment was biased towards those with symptoms. The main symptoms in middle aged and elderly women are:
 - Urinary incontinence
 - Gait disorder
 - Sensory disturbances (tingling, numbness, burning sensation and pain in legs)
 - Balance problems occur in both men and women with ALD and worsens in both men and women at a similar rate
 - Study with a force plate done at Kennedy Krieger Institute (placebo arm of Lorenzo's Oil study done in the past)
 - At the same age, men tend to sway more on the force plate (have earlier onset of symptoms) than women, but the rate of worsening over 2 years was constant regardless of sex
 - The doctors now need to show that abnormal swaying is clinically meaningful. For example, that it is correlated with how much you are going to fall and how much disability you have
 - FDA needs to see this evidence



- Now they are going to do a home study with sensors for women that can be done at home (**contact Dr. Fatemi to learn more**)
- ALD experts are now trying to get the sway test approved by the FDA as a primary outcome measure for clinical trials. The problem is that 6-minute walk test in women (which is primary outcome in Minoryx trial for AMN men) does not change sufficiently enough over 2 years, so it is not a good measure to use in a clinical trial for ALD women, but it is currently the only primary outcome accepted by the FDA.
- Adrenal dysfunction
 - Almost all men with ALD develop adrenal symptoms.
 - Most women have normal adrenal function (but not all). Estimated prevalence of Adrenal Insufficiency in women with ALD is around 2-5%.
- Cerebral ALD
 - Very uncommon in women with ALD but not impossible.
 - Dr. Fatemi now estimates he has seen 5/300 women who showed MRI changes that could be cerebral ALD from his time at Kennedy Krieger Institute)
- Discussed scientific article that Dr. Fatemi wrote alongside other ALD doctors:
 - **“MRI and proton MRSI in women heterozygous for X-linked adrenoleukodystrophy”** A. Fatemi, P.B. Barker, A.M. Uluğ, L.M. Nagae-Poetscher, N.J. Beauchamp, A.B. Moser, G.V. Raymond, H.W. Moser, S. Naidu. Neurology Apr 2003, 60 (8) 1301-1307; DOI: 10.1212/01.WNL.0000059546.15529.CB
 - <https://n.neurology.org/content/60/8/1301.long>
 - Three female patients from this study showed cerebral ALD and Adrenal Insufficiency, which are traditionally thought to be symptoms only seen in men. The proportion of women with severe symptoms in this study is likely not representative of the overall patient community however, because the recruitment method of the study was skewed towards women with more severe symptoms.
- Mechanism of ALD disease
 - The *ABCD1* gene, which is mutated in ALD patients, codes for the ALD protein, which normally functions as a transporter on the surface of peroxisomes that allows for the uptake of C24:0 Very Long Chain Fatty Acids (VLCFAs) into peroxisomes for degradation.
 - Mutation of *ABCD1* leads to a buildup of VLCFAs, which can cause dysfunction of mitochondria (cellular components that produce energy for the cell), oxidative stress, cell membrane changes, altered autophagy (a system of recycling cell components), and stress in the Endoplasmic Reticulum (a structure in the cell that makes proteins among other functions). All together this leads to a pro-inflammatory state which can contribute to neurodegeneration and endothelial dysfunction.



Question and Answer Session with Dr. Fatemi

Q. How do you distinguish between symptoms of ALD vs aging or childbirth (i.e. bladder control)

A.

- It's very difficult, no definitive test, at home you cannot tell yourself
- Urodynamic study at a urologist can help distinguish the cause
 - This involves inserting a catheter and measuring pressure to assess the ability of the bladder muscles to contract and urinate normally
- Nerve conduction study can also work for neuropathy
 - This may distinguish between a herniated lumbar disc in the back and demyelinating disease

Q. When can a male be sure he won't develop cerebral ALD?

A.

- While it becomes less likely that men with AMN will develop cerebral lesions as they age, Dr. Fatemi has seen men in their 60s and 70s develop cerebral ALD and it doesn't seem to correlate with severity with AMN symptoms either, so it's really difficult to tell
- Several factors may influence development of cerebral ALD, but so far we don't really know how to predict if someone will develop cerebral disease, so the best way is to monitor all men via yearly MRIs

Q. My calves have atrophied. How does ALD cause this? Any suggestions for minimizing this? Walking does not seem to help.

A.

- Motor neuron decay can cause atrophy in muscles
- Certain guided exercise can strengthen hips and improve strength and walking speed in women with ALD
- But the disease is a nerve disorder so if the nerves are affected there may be little you can do ultimately to prevent or reverse the damage

Q. How many women with ALD are wheelchair bound by age 60?

A.

- Very few, probably 2-5%, more towards the 2%
- However, many more people will require gait support (cane, walker) than wheelchairs
- Those that do use a wheelchair may require one because of a fall and a bad recovery
 - Second hit (fall, disease) on top of the ALD can cause problems to be more severe
- It's a good idea to check your Vitamin D levels to make sure bones are less likely to break after a fall

Q. Is the COVID vaccine safe for women with ALD?

A.

- No reason to be concerned at all for Moderna or Pfizer vaccines because of the way the vaccines are made
- In terms of AstraZenca and Johnson & Johnson vaccines:



- Slight risk for blood clots after the vaccines but overall COVID is a lot riskier than the vaccines still
- So far there is no indication that an altered immune disorder can be made worse by the vaccine, so there is no reason to think people with ALD should not receive the vaccine

Q. How does ALD cause joint pain?

A.

- Any disease that causes spasticity or imbalance can cause joint pain
 - This is because you have to compensate for your symptoms by standing/walking in an unnatural position because of your disorder
- Can often go hand in hand with neuropathy
- Bad positioning can cause pain, sometimes it can be simply fixed by correct shoe inserts
 - Very important to see a whole team of doctors, including orthopedic doctors (hard to find an ALD expert orthopedic doctor - best to find someone with experience with neurological/spasticity disorders), rehab doctors, etc., not just neurologists

Q. How can you get testing for *ABCD1* genetic mutations?

A.

- At Kennedy Krieger Institute, their Genetic Counselor (Julie Cohen) can meet via telehealth to discuss testing opportunities for *ABCD1* (they use a commercial lab but must this be ordered through a health care provider)
 - [Contact Dr. Fatemi's center](#) to set this up

Q. Can the *ABCD2* protein compensate for loss of the *ABCD1*/ALD protein?

A.

- Several drugs in the pipeline now are attempting to upregulate *ABCD2* to compensate for *ABCD1*, so hopefully yes

Q. Could hand, head, and voice tremors be symptoms of ALD?

A.

- Dr. Fatemi has not seen voice tremors in men with AMN unless they develop cerebral ALD, but now has met several women with voice, head, and hand tremors with ALD. Dr. Eichler in Boston is trying to look in more detail at these symptoms.
- Overall, it is a rare phenomenon, but seems to be true. Unclear how bad it can get, but one individual has this to the extent that she is in a wheelchair because of these symptoms. It's an emerging picture, but still not sure what causes it. Odd that it isn't seen in men. With these symptoms, it would have to originate from brain stem or cerebellum, not the spine, but MRIs of these individuals tend to be normal, so it is not indicative of cerebral involvement.

Q. How can we volunteer for the at-home study mentioned?

A.

- None of the interventional clinical trials are on yet



- Ongoing studies (natural history) by Dr. Fatemi and Dr. Eichler (but no interventions yet) – contact [Dr. Fatemi](#) or [Dr. Eichler](#) if interested in participating
 - As a part of this natural history study with Dr. Fatemi, they are doing in-person and at-home assessments
 - Looking at walking speed variables and how much you sway

Q. If symptoms start early does that mean they will become worse?

A.

- Dr. Fatemi doesn't think so
- Often seems like symptoms get worse and then plateau for women with ALD
- Some women have mild symptoms for 30 years
- However, there is not good data to show this conclusively

Q. Is Ampyra (dalfampridine) a good medicine for support with gait and fatigue?

A.

- This is a drug that seemed to work very quickly for Multiple Sclerosis patients (in a matter of minutes to hours)
- A doctor in Germany did an open label study for ALD patients (no placebo group) with an in-house version of the drug, and a couple of people in the study developed seizures with this in-house version (a known side effect of the in-house version)
 - This doctor thought the walking speed improved in ALD patients, but it seems like there is not enough data to conclude whether it really works, so unclear
- Most insurance companies would not cover it for ALD right now
- Definitely will not get at the base of the disease, just symptoms

Q. Do any of the trials done in men with AMN translate to women?

A.

- The FDA will probably not explicitly approve drugs tested in AMN men for women with ALD based on trials only in men, but most prescriptions are prescribed off label, so many doctors might prescribe a drug approved for men to women with ALD.
 - UNLESS the FDA specifically prohibits this which they can do, but there's no scientific reason they would do this

Q. Should symptomatic women get a baseline MRI, EEG, and EMG?

A.

- EMG (electromyography which measures muscle and nerve function) could be recommended
- EEG (electroencephalogram which tests electrical activity in the brain) is not necessary unless someone has seizures
- MRI (magnetic resonance imaging, could detect changes in white matter in the brain or spinal cord) is a tough question - usually not recommended if the symptoms are consistent with "AMN", so it would be only based on symptoms if it's necessary (for example if someone displayed symptoms consistent with cerebral ALD)



Q. Is there any way to make adjustments to shoes to keep running?

A.

- Get an evaluation, including a physical therapist
- Keeping active is helpful
- Maybe need to switch to a different type of exercise to avoid falling (biking is good), but definitely a good idea to keep exercising

Q. How should we label women with ALD?

A.

- Dr. Fatemi thinks the label "AMN" is reasonable since some women do have adrenal symptoms and some men don't. "ALD" would also be appropriate.

Q. Is there anything we can do to keep young girls asymptomatic?

A.

- Not at this time, but one idea would be to prescribe medications that get approved for AMN men to everyone with *ABCD1* mutation to see if it can prevent them developing symptoms. BUT this would be a political issue because insurance companies wouldn't want to pay for lifelong treatment.
 - It also will be hard to conclusively prove these medicines can prevent symptoms because we are never really going to be able to do a 40 year-long study to see if intervention in babies affects symptom development in 40 year-olds, so if there is a good medication with few side effects then it may be recommended to try the medication. However, we may have to keep in mind the potential side effects of any drug especially for children who are growing.

Q. If a mother has a quick escalation of disease burden, should a daughter worry she will have the same quick progression?

A.

- It's unlikely that we can predict progression of disease based on genetics (i.e. mother and daughter may have very different symptoms)

Q. I have upper body neuropathy and weakness but am told it's not likely related since it's in the arms. I don't have carpal tunnel. Could it be ALD related?

A.

- Dr. Fatemi has had several female patients with peripheral neuropathy in arms but not in males, so it could be ALD-related but we are uncertain
- It may be that nerves are generally fragile in ALD patients, so if an ALD patient sustains a second injury to nerves it may cause more damage than it ordinarily would in a non-ALD patient