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Keys to Avoiding an Adrenoleukodystrophy Misdiagnosis

Dr. Nacinovich:
Even though adrenoleukodystrophy, or ALD for short, only affects 1 in 18,000 people, the impacts of this rare and fatal genetic disease cannot be underestimated; but because it's so rare, that often leads to misdiagnosis and even missed diagnosis, which lessens the chances that it will be amenable to treatment. So, how can we get better at recognizing ALD earlier on?

Welcome to the ***Clinician's Roundtable*** on ReachMD. I'm Mario Nacinovich, and here with me today is Dr. Paul Orchard, a Professor of the Division of Pediatric Blood and Marrow Transplantation at the University of Minnesota. Thanks for joining us today, Dr. Orchard.

Dr. Orchard:
Absolutely. Thanks for having me.

Dr. Nacinovich:
So, Dr. Orchard, to get us started, can you provide us with an overview of what adrenoleukodystrophy, or ALD, is?

Dr. Orchard:
Absolutely. So, ALD is an X-linked inherited disorder, and as you mentioned, the incidence is about 1 in 17,000, 1 in 18,000. Because it's an X-linked disorder, it primarily affects boys and has several different phenotypes that can become apparent as the child gets older. The babies, for instance, that are born with ALD are totally asymptomatic and have no physical findings, have no disease-related manifestations, but as they get older, they tend to develop these. The adrenal insufficiency is one of those. There's an adult form of the disease that happens in the third and fourth decade generally called adrenomyeloneuropathy, or AMN. And the most severe form of the disease is called cerebral adrenoleukodystrophy, which is an acute neuroinflammatory process that occurs in 35–40% of boys in school-aged population, so the peak is around 7 years of age in terms of cerebral disease.

Dr. Nacinovich:
What are some of the symptoms of ALD in children, and when do they typically start developing?

Dr. Orchard:
Well, some of the boys that have adrenal insufficiency can have some subtle changes, such as hyperpigmentation and whatnot, that they may develop primarily in the school-aged population, but sometimes these boys can actually get into significant trouble. If they have a viral infection, for instance, they can get quite severely ill, end up in the emergency room, may need IV fluids because of their adrenal insufficiency issues, and some of the boys end up quite hypotensive and in the intensive care unit, so that's commonly what we tend to see with boys that have the adrenal insufficiency manifestation of the disease.

The cerebral disease tends to occur at a peak of about age 7, or at least becomes apparent then, and this is only about 35% of the boys develop this disease or this form of the disease for reasons that aren't apparent. But those boys may start to have some attention deficit issues. Sometimes the handwriting deteriorates. They tend not to do quite as well in school. They tend to lose peripheral vision as they progress and get more white matter disease in the brain and can actually have seizures and other types of problems. So, sometimes the initial manifestations of the cerebral form of the disease are quite subtle, but as the disease progresses, it becomes much more obvious.

The AMN form of the disease, adrenomyeloneuropathy, is a disorder that tends to happen more in the third and fourth decade of life. In those circumstances, those are primarily motor issues, and they may have difficulty running, walking, may end up using a cane and then eventually a wheelchair. They may have issues with incontinence and whatnot as they progress. That's a very slowly progressive form of the disease, and that does not affect the brain like the cerebral form does but is mostly a spinal cord issue.

Dr. Nacinovich:
Now, Dr. Orchard, some of those symptoms you just described seem very similar to the symptoms of ADD and ADHD. So, can you tell us, how can we avoid mistaking ALD for something else?

Dr. Orchard:
Well, this is a significant problem because many of the issues that we see in the boys early on as they develop cerebral disease and white matter tends to be affected can be quite subtle, and picking up the disease at a relatively early stage is extremely important in maintaining function down the road following intervention. Again, the school performance can be subtle in its early phases. Attention deficit is an issue that is pervasive. Again, it is in many boys in this age group, so those types of things can be difficult. If their handwriting is starting to deteriorate, for instance, and a boy was doing quite well in school and has significant changes over 6 months or a year, those can be red flags; but again, they are not specific, and they can be quite subtle in the early phases, so it's a diagnostic challenge.

Dr. Nacinovich:
For those just tuning in, this is the ***Clinician's Roundtable*** on ReachMD. I'm Mario Nacinovich, and today I'm speaking with Dr. Paul Orchard from the University of Minnesota about a rare yet fatal genetic disease called adrenoleukodystrophy.

So, Dr. Orchard, let's dive into this discussion a little bit more. Are there different types of ALD we should be aware of, particularly during the diagnostic stage? And if we suspect a patient has ALD, is there a way of knowing which type of ALD they have?

Dr. Orchard:
Well, there are a number of issues that are important here. The disease is caused by mutations within the ADCD1 gene. That gene is a peroxisomal transporter of very long-chain fatty acids, and this transporter takes very long-chain fatty acids in the peroxisome where they are degraded, and if that does not happen, then you accumulate very long-chain fatty acids. Very long-chain fatty acids can be stored in a number of different places in the body but especially go to the adrenal glands and to the brain, to the testes, and those are areas that we can see are affected by the disease.

Dr. Nacinovich:
And once a patient is diagnosed with ALD, can you walk us through those next steps?

Dr. Orchard:
Well, it depends a bit on the age at which someone is diagnosed. Most commonly the boys are diagnosed relatively early in age. It would be important to have them have adrenal insufficiency tested for to help determine if they may need supplemental hydrocortisone, for instance, so that is a common thing that we would do as a boy is newly diagnosed. If the boys are 3–4 years old or older, that is an age group where they are at risk for developing cerebral disease, and so the best way to determine whether that is happening is to do serial MRIs and in the area of the splenium is the characteristic place where this starts some changes in demyelination that have become apparent on T2 MRIs, and that's what we would be looking for. So, if a boy is picked up based on a family history, for instance, or because they were shown to have adrenal insufficiency earlier, we would set them up in a monitoring program to have MRIs done essentially every 6 months from the time they are 3 up at least until the time of puberty, and then we tend to back off a little bit on the MRI monitoring at that point because the age of highest risk is in that 4–12 age group.

Dr. Nacinovich:
What is the prognosis and life expectancy for someone with ALD?

Dr. Orchard:
The life expectancy can dramatically change based on what types of disease become apparent. Adrenal insufficiency, if it's unrecognized, can put someone at risk for a life-threatening complication with a relatively standard viral infection, for instance. And we do hear about boys that are otherwise undiagnosed that have a lethal outcome with an ineffective episode, so that is certainly one risk of the disease. The most common one though is the cerebral form of the disease. So in those boys, over a period of years generally, start from an early lesion of demyelination that is associated with inflammation, and this inflammation spreads throughout the white matter of the brain and becomes crippling and ultimately lethal over a period of years, so untreated that generally is something that will lead to someone's demise in a relatively short period of time. If we can identify cerebral disease early, there is an intervention, which is letter marrow transplantation historically, and there is interest in gene therapy now that may prove useful as well, but the outcomes based on those interventions are quite clearly linked to the amount of disease present at the time that the intervention takes place. So, if this lesion is very small, the boys tend to do quite well. They don't recover any lost myelination, but it can help stop further progression of the disease and result in good function on a long-term basis, but if the disease is quite advanced and the patients go to transplant with extensive demyelination, those patients have tended to lose ground going through the procedure and may end up with significant deficits and disabilities—even assuming that the transplant can stop further progression of the disease. So, early diagnosis, especially

for the cerebral form of the disease, is key.

Dr. Nacinovich:
Unfortunately, we're almost out of time today, Dr. Orchard, but before we close, is there anything else you'd like to share with our audience regarding ALD?

Dr. Orchard:
Yes. I think one of the things that is the most encouraging thing that has come down the road in the last few years is newborn screening. Very long-chain fatty acids can be tested for in a heel stick at the time of birth, and boys can be identified—and some girls that are carriers for that matter as well—but boys can be identified long before any affects of the disease become apparent, and then we can start on an ongoing monitoring program for the boys that are tested for adrenal insufficiency, and intervention takes place if there is any sense that that needs to happen. And then, if they start to develop cerebral disease, then we have the opportunity to intervene at the very earliest stages, which is absolutely crucial in maximizing outcomes. So many boys historically have only been diagnosed after they have significant cerebral disease and have motor problems and seizures and other issues, and that is clearly too late for us to be able to intervene effectively, so the newborn screening, which is now ongoing and developing in more and more states on an ongoing basis, is going to be critical for helping identify the disease and effectively intervening.

Dr. Nacinovich:
Well, with that parting comment, I'd like to thank Dr. Paul Orchard for joining me to bring this rare and often overlooked genetic disorder into the spotlight. It was great having you on the program today, Dr. Orchard.

Dr. Orchard:
My pleasure.

Dr. Nacinovich:
I'm Mario Nacinovich, and you've been listening to ***Clinician's Roundtable*** on ReachMD. To access this episode and others in the series, visit ReachMD.com/cliniciansroundtable where you can Be Part of the Knowledge. Thanks for listening.