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A Deep Dive into the Pathophysiology of CAH and Its Impact on Treatment

Announcer
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Neurocrine Biosciences. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is Clinician's Roundtable on ReachMD, and I'm Dr. Charles Turck. Here with me today to discuss our current understanding of how the pathophysiology of congenital adrenal hyperplasia, or CAH, impacts its therapeutic landscape is Dr. Craig Alter. He's a pediatric endocrinologist and the Director of the Neuroendocrine Center at the Children's Hospital of Philadelphia.

Dr. Alter, welcome to the program.

Dr. Alter:
Thank you very much.

Dr. Turck:
So jumping right in, Dr. Alter, would you tell us about CAH and the genetic mutations that cause it?

Dr. Alter:
In practical purposes, the CAH that we're seeing are due to the 21-hydroxylase deficiency. This is a defect on chromosome 6. It's well worked out. Most of the time, parents do not know they're carriers of the mutation, so it's a surprise when they have a child with CAH. The second child would have a 25 percent chance of having CAH if both parents are carriers. Now there are some unique situations, for example, I have a situation where the dad actually has CAH, so he's what we call an obligatory carrier. He for sure will pass on the mutation. The mother, though, was not a known carrier of the condition, and so when they had their first child, the mother had to ask the obstetrician, "What is the chance, given that my husband has CAH, what's the chance that I have a child with CAH?" And the obstetrician incorrectly said, "There's no chance. You don't have this condition." But actually, she turned out to be a carrier. Many of us are actually carriers and don't know it. So they had a child with CAH, and now they are having a second child with CAH, and the mother, again, asked the question, "What's the chance that I have a second child with CAH?" Now typically, we're used to saying 25 percent, but in this case, since we know Dad is going to pass on the defective gene and Mother is 50/50, the answer is 50 percent chance. And low and behold, it turned out they did have a second child, and this child was a girl. So she was treated, the mother, in utero with dexamethasone, and unlike the older sister, this child was born without any overt concerns about the genitalia. She would have, of course, lifelong need for treatment of CAH, but she has 21-hydroxylase deficiency, and treatment started in utero.

Dr. Turck:
And what are the effects of the 21-hydroxylase enzyme deficiency that you briefly mentioned before? How do they figure into the pathophysiology of CAH?

Dr. Alter:
Yes. The enzyme is actually quite fascinating. The adrenal gland, which is an amazing hormone producer has several avenues. It makes glucocorticoids, like hydrocortisone. It makes aldosterone, which controls the potassium and the blood pressure, that's the mineralocorticoid pathway. It makes androgens, which are, of course, what's responsible for advanced bone age and early pubic hair, etc. It also makes epinephrine, adrenaline, but that's a different part of the gland, so that's not a discussion here. The 21-hydroxylase enzyme is necessary for the glucocorticoid production and the aldosterone production, but not the androgen production, which is why, when the brain senses that the body does not have enough glucocorticoids, it in turn, puts out tons of ACTH to stimulate the adrenal

gland to overproduce everything it can. So as a result, excessive androgens come out, which is not a desirable effect, but a net result of that feedback loop and the high ACTH.

Dr. Turck:
Now, Dr. Alter, how has our understanding of these mechanisms evolved over the years and is more research on CAH pathophysiology needed? What do you see as the practical impacts of gaps in our research and understanding of CAH on clinical practice?

Dr. Alter:
Sure. I'm going to speak from the clinical end because I see a lot of children with this condition. It's not an easy condition to treat. We know the strategies for treatment. We give steroids to reduce the excessive androgens, and also to make sure the child has enough glucocorticoids for crises. We know how to replace the aldosterone in the oral form using fludrocortisone. We know, in infancy, to give salt. That's all fine, we've known that for decades. The problem is that it's not easy to avoid excessive steroids or excessive androgens. If you give too small of amount of glucocorticoids you're going to get excessive androgens, rapid growth, advanced bone age, early pubic hair, things like that. If you completely suppress the androgens, which is great on one hand, but then the child becomes Cushingoid, and they gain a lot of weight, and the growth slows down. So it's really not so easy.

There's a lot of debate on what labs to follow. There are guidelines, such as with the Endocrine Society. Dr. Speiser is on those guidelines. They're excellent to read, but it's still unclear, even if you read that, what labs to follow. I like to follow androstenedione. I also get 17-hydroxyprogesterone, but what to do with that result is really perplexing. Although, you may say, I want to suppress the 17-hydroxyprogesterone, while that may be true, if you suppress that, typically your way overtreating with glucocorticoids. So you really have to put the whole picture together. How the child's growing, the amount of steroids they are getting in milligrams per meter squared per day, the compliance level, the growth chart, the bone age, and then make a decision based on the labs. So I don't think I can look at someone else's patient's labs alone and tell you what I would do. It really depends on the whole picture.

Dr. Turck:
For those just tuning in, you're listening to Clinician's Roundtable on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Craig Alter about the pathophysiology and treatment of congenital adrenal hyperplasia, or CAH.

So, Dr. Alter, I was wondering if you would tell us about any challenging patient cases you've encountered over the years in the treatment of CAH.

Dr. Alter:
Sure. I have several patients who were not so compliant, so they weren't getting enough glucocorticoids. Their bone ages jumped up significantly. They were the tallest kid in the class until seventh grade, and then after seventh grade the bone age was essentially at fusion at 16 years of age, and they barely grew after that. So the tallest kid in the class until sixth grade ended up only five foot two. That person eventually went into central precocious puberty, and we treated them with pubertal suppressive drugs as well, but it was a challenging case given their degree of compliance and the excessive androgens and exposures throughout the first 10 years of life. Other kids, they have good suppression, but their weight gain is a little excessive. And other kids seem to do really, really well with good suppression and good growth that end up at a perfectly acceptable height for the family.

Dr. Turck:
Do you have any stories about when CAH was suboptimally treated and how we could have done a better job of treating those patients?

Dr. Alter:
I would say that there are times when I've had to give hydrocortisone at doses well above the standard dose range of 10 to 15, even 20 milligrams per meter squared per day. I'm on 25 to 35. Why? Because the androgens are significantly elevated. The 17-hydroxyprogesterone is well over 1,000 nanograms per deciLitre. Really uncomfortable labs showing that there's not enough steroids. You can argue that maybe the compliance isn't excellent, sure, but either way I'm going to point where, on paper, it looks like I need higher doses of glucocorticoids where they're already in a very high range above the typically recommended levels. So in that case, what I really want is a medication, which could lower the feedback of ACTH stimulating the adrenal glands to make excessive androgens, so I can give them a lower dose of steroids, and at the same time, lower the levels of androgens.

Dr. Turck:
Now, Dr. Alter, let's look ahead for just a moment. Are there any emerging therapies or clinical trials stemming from our understanding of CAH pathophysiology that we should keep an eye on or that you're excited about?

Dr. Alter:
Yes. I'm absolutely excited by a new attack of this condition. I will tell you I'm not involved with any of the companies, I'm not in any of

the studies, but I'm highly interested as a clinician and the results of these studies. There are medications, which will block the excessive ACTH release. How are they doing that? They are blocking the effect of the CRH on stimulating the pituitary gland to make ACTH. Now this is a great approach because it's the one thing that I'm missing. I'm missing the ability to lower the dose of steroids, and at the same time, keep the androgen levels in check. And my hope is that by having one of these medications added to the mix that a child could be on lower doses of glucocorticoid with good control of the androgens. Of course, it means another medication added to a situation where they're already taking two medicines. They're taking the fludrocortisone, typically once a day, and they're taking the hydrocortisone, glucocorticoid, typically three times a day.

Dr. Turck:
And finally, Dr. Alter, overall, do have any other thoughts about how we're doing treating CAH, or any other takeaways you'd like to leave with our audience?

Dr. Alter:
Well, I think that we've done amazing progress since the year 2000 that other speakers have talked about how every state in the United States has a screen for congenital adrenal hyperplasia, and that's true. So after, maybe 2009 or 2011, all the states now have that. They all have different protocols though. They have some false positives, some false negatives, but we're much better at picking up, especially, the boys with CAH. Why the boys? Because when CAH occurs in girls, there's typically a clue on examination. For the boys, there's no obvious clue and they could, essentially, go into adrenal crisis and hyperkalemic crisis from five days to 15 days of life if they're not picked up. So the screen has been really good. It's not perfect, and there are situations where it's missed because, like any other test, nothing's perfect, and we're always trying to make the screening test better. But that's where there's been great advances; not losing newborns to this terrible condition.

Dr. Turck:
Well, it's clear that we've come a long way in our understanding of the pathophysiology of congenital adrenal hyperplasia and how that's impacted our current practice and the future treatment landscape. And I'd like to thank my guest, Dr. Craig Alter, for sharing these key insights. Dr. Alter, it was great having you on the program.

Dr. Alter:
Thank you for having me. I enjoyed it.

Announcer
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