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Managing Patients with Congenital Adrenal Hyperplasia

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

Dr. Turck:
Welcome to *Clinicians Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me to share her insights on managing patients with congenital adrenal hyperplasia, or CAH for short, is Dr. Maria Vogiatzi. She's an Attending Physician in the Division of Endocrinology at the Children's Hospital of Philadelphia. Dr. Vogiatzi, thanks for being here today.

Dr. Vogiatzi:
My pleasure.

Dr. Turck:
So diving right in, Dr. Vogiatzi, would you explain what CAH is and its prevalence?

Dr. Vogiatzi:
Sure. CAH is a group of genetic disorders of the adrenal gland that result in variable deficiencies of cortisol. In about 90 to 95 percent of the cases, CAH is caused by lack of the enzyme that is called 21-hydroxylase. So when we usually talk about CAH, we refer to 21-hydroxylase deficiency. Now depending on the residual enzymatic activity, CAH, due to 21-hydroxylase is classified as either classical or non-classical. The classical form represents the severe form of the disease, is rare, and occurs in about one to 15,000 live births. Non-classical CAH, on the other hand, is much more frequent, represents the mild form of the condition, and has an estimated prevalence of about one in 200 people.

Dr. Turck:
Now with that in mind, what symptoms do patients typically present with? And could these conditions be confused with any other disorder?

Dr. Vogiatzi:
Let me start by discussing first classical CAH. Classical CAH represents the severe phenotype and is characterized by cortisol deficiency, and most of the patients have also additional aldosterone deficiency. Now cortisol deficiency removes the normal negative feedback inhibition on the hypothalamus and the pituitary gland and leads to excessive ACTH secretion. Excessive ACTH secretion results in adrenal hyperplasia and accumulation of adrenal androgens. Accumulation of adrenal androgens can be significant, can happen in fetal life, and therefore, can cause prenatal virilization of the external genitalia in girls.

Classical CAH presents during the first week of life with signs of adrenal insufficiency and adrenal crisis. We call it salt-wasting adrenal crisis. It can be life-threatening. And for this reason, CAH is included at this point in the newborn screening programs that are run by the states. CAH can also present later on in life, can present during childhood with signs of androgen excess. These signs can be early puberty and more specifically, early pubarche, and growth acceleration that eventually can lead to short adult height. In adolescent girls, we can again see signs of androgen excess, manifested as irregular menses, severe acne, or hirsutism. And for the same reason, young women may also struggle with infertility.

Classical CAH, again associated with adrenal insufficiency, should be differentiated from other causes of adrenal insufficiency, including rare forms of CAH. Babies who present with genital atypia can also be confused with other disorders of sex development.

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Dr. Turck:
And how about non-classical CAH?

Dr. Vogiatzi:
Non-classical CAH is not life-threatening, does not cause prenatal virilization, and overall has a mild, variable phenotype. Many individuals can be completely asymptomatic and never come to medical attention. However, some people may present with signs of androgen excess, and again in children, we see early pubarche and growth acceleration that compromise height. And adolescent girls with non-classical CAH can present with symptoms, such as irregular periods, acne, and hirsutism. The signs can be very similar to the signs that we see in girls with polycystic ovarian syndrome, or PCOS. So we recommend screening for non-classical CAH in all children who present with premature adrenarche or in girls with signs of androgen excess, such as irregular periods.

Dr. Turck:
And once we suspect a patient may have one of these genetic conditions how do we diagnose them?

Dr. Vogiatzi:
So the diagnosis is primarily done hormonally by measuring a steroid that's called 17-hydroxyprogesterone. This is the steroid precursor that accumulates above the enzymatic block in 21-hydroxylase deficiency. Very high levels are consistent with the diagnosis. One thing to remember is to ask the patient to have the measurement done first thing in the morning because adrenal androgens peak around seven to eight o'clock in the morning.

If 17-hydroxyprogesterone is borderline, the next step is to do an ACTH stimulation test. During this test, we again measure 17-hydroxyprogesterone levels, and we measure them before and 60 minutes after ACTH administration. And based on the results, we put the diagnosis. And finally, the diagnosis can be confirmed with genetic analysis that is now available in commercial labs.

Dr. Turck:
For those just tuning in, you're listening to *Clinicians Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Maria Vogiatzi about congenital adrenal hyperplasia, or CAH.

So, Dr. Vogiatzi, now that we have some insight into the prevalence, presentation, and diagnosis of CAH, let's take a look at how we can treat it. What therapies are available?

Dr. Vogiatzi:
So congenital adrenal hyperplasia is associated with adrenal insufficiency. And the cornerstone of management is hormonal replacement with glucocorticoids. Individuals who also have aldosterone deficiency will receive replacement with fludrocortisone.

Now therapy with glucocorticoids has two goals. The first is to replace the cortisol deficiency that these individuals experience. The second goal of glucocorticoid therapy is to suppress the excessive ACTH secretion, and therefore, lower the adrenal androgen secretion. Now as in every other patient with adrenal insufficiency, we recommend that patients and families receive instruction on how to manage physiologic stress. Physiologic stress refers to an acute illness or severe injury or a procedure, and there is a very specific stress dose management that we recommend for cases like this.

Now let me take a moment and talk a little bit more about glucocorticoid therapy in CAH. So the principle of therapy sounds simple. In reality, the treatment can be challenging. And the reason that the glucocorticoid treatment in CAH can be challenging is because the doses that we have to use to suppress adrenal androgen secretion are frequently supraphysiologic, so we use doses of hydrocortisone in the range of 12 to 15 milligrams per meter squared per day. So this chronic, supraphysiologic treatment with glucocorticoids can lead to various comorbidities, like weight gain, metabolic syndrome, increased risk for cardiovascular complications.

To minimize these problems, we frequently monitor adrenal androgen concentrations, and we try to titrate the glucocorticoid dose accordingly. In other words, we try to strike a balance between undertreatment and androgen excess, versus overtreatment and problems like obesity and metabolic syndrome.

Let me take a moment now and clarify typical treatment for non-classical CAH. As we discussed, non-classical CAH is mild. The phenotype is variable. Many patients don't have any symptoms, and of course, in cases like this, no treatment is needed. But for cases that present with signs of androgen excess, again, the primary treatment is therapy with glucocorticoids to suppress adrenal androgen secretion.

Dr. Turck:
And before we end, today, Dr. Vogiatzi, what further research is being done to support the management of this group of genetic conditions?

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Dr. Vogiatzi:
Well, thank you for this question because we are now in an exciting time for research in CAH as we have a new, promising, emerging therapy, and there are also additional efforts for drug development in CAH. First of all, we have the results of a trial that looked at a new CRH receptor antagonist. The name of the drug is called crinecerfont. The trial was done in both pediatrics and adults with CAH. The principle of therapy is as follows; by blocking CRH, you expect to see a decrease in ACTH secretion and a decrease in adrenal androgens, allowing the patient to cut down on the daily glucocorticoid dose. And indeed crinecerfont was found to be effective in reducing both daily glucocorticoids and elevated adrenal androgens. Beyond crinecerfont, we have another CRH receptor antagonist that is under development. There is a new drug that blocks the ACTH receptor itself. And there is also a gene therapy that is going on. So hopefully more to come.

Dr. Turck:
Well, that's a great look ahead for patients with congenital adrenal hyperplasia. And I want to thank my guest, Dr. Maria Vogiatzi, for joining me to share her insights. Dr. Vogiatzi, it was great having you on the program.

Dr. Vogiatzi:
Thank you.

Announcer:
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