CONGENITAL ADRENAL HYPERPLASIA

Developed by Kimberly Young and Dr. Diane Wherrett for PedsCases.com.
May 4, 2022

Introduction:

Hello! Welcome to this PedsCases podcast on congenital adrenal hyperplasia. My name is Kimberly Young and I'm a first year Paediatrics resident at the University of Toronto. This podcast was created in collaboration with Dr. Diane Wherrett, a Paediatric Endocrinologist at the Hospital for Sick Children in Toronto.

By the end of this podcast, the learner should be able to:

1. Define congenital adrenal hyperplasia
2. Describe the pathophysiology of congenital adrenal hyperplasia
3. Delineate the difference between classic and non-classic congenital adrenal hyperplasia
4. Recognize signs of congenital adrenal hyperplasia in a neonate, as well as signs of a salt-wasting adrenal crisis
5. List the initial investigations and review the management for congenital adrenal hyperplasia

Clinical Case

Before we dive in, let's start off with a clinical scenario. You are a third-year medical student on your paediatrics rotation. You have been asked to perform a newborn exam on Mia, a one-day old female in the Mother & Baby Unit. Mia was born at 37+3 weeks gestation to a G1P0 mother. While conducting your physical, you have the opportunity to speak with Mia's parents, who share that the pregnancy and delivery were uncomplicated. They had undergone routine antenatal screening tests, including early first trimester screening and an anatomy ultrasound, and no concerns were reported. The initial portion of the exam is unremarkable; however, upon opening up her diaper, you notice that her genitalia appear abnormal, specifically noting that her labial folds appear enlarged. What is your approach to this presentation of ambiguous genitalia?

Introduction

There are a number of possible etiologies behind ambiguous genitalia in a neonate, ranging from those affecting sex determining genes, differentiation of external genitalia, and everything in between. In a newborn presenting with ambiguous external genitalia, it is important to rule out congenital adrenal hyperplasia so appropriate and timely management

can be initiated, especially as these babies are at risk of a salt-wasting adrenal crisis, which we will discuss later on in the podcast.

Pathophysiology

Let's start off with the pathophysiology of congenital adrenal hyperplasia. Given the name, you can probably guess that dysfunction of the adrenal glands is involved. You may recall that the adrenal glands can be found sitting atop the kidneys and that their primary function is hormone production. The adrenal gland is comprised of an inner adrenal medulla, which produces catecholamines like epinephrine and norepinephrine, and an outer adrenal cortex, which produces various steroid hormones from cholesterol. The adrenal cortex is divided into three zones: an inner zona reticularis, where the sex steroids are produced; a middle zona fasciculata, where the glucocorticoid cortisol is produced; and, an outer zona glomerulosa, where the mineralocorticoid aldosterone is produced.[1] Cortisol has metabolic functions and also serves as the major stress hormone in the body. Aldosterone, which is regulated by the renin-angiotensin-aldosterone system, helps with blood pressure control and stimulates the reabsorption of sodium and secretion of potassium into the urine.

As with many endocrine organs, the function of the adrenal gland is governed by a neuroendocrine pathway, namely the hypothalamic-pituitary-adrenal, or HPA, axis. Corticotropin-releasing hormone (CRH) is produced in the paraventricular nucleus of the hypothalamus. CRH binds to CRH receptors in the anterior pituitary, stimulating the release of adrenocorticotropic hormone (ACTH) into the systemic circulation. In turn, ACTH stimulates the synthesis and release of glucocorticoids and androgens in the adrenal gland. As with other neuroendocrine pathways, the HPA axis is regulated by negative feedback mechanisms. When high levels of cortisol are produced in the body, it feeds back to decrease CRH and ACTH production. Conversely, when cortisol levels are low, the body produces more ACTH in an effort to stimulate production in the adrenal gland.

Congenital adrenal hyperplasia, or CAH, describes a group of autosomal recessive genetic disorders that affect approximately one in every 20,000 live births. These disorders affect the enzymes involved in the biosynthetic pathway converting cholesterol to cortisol.[2,3] In approximately 95% of CAH cases, there is a deficiency of the enzyme 21-hydroxylase. 21-hydroxylase converts 17-hydroxyprogesterone to 11-deoxycortisol, which is the precursor to cortisol. Therefore, deficiency in 21-hydroxylase results in the underproduction of cortisol.[2,3] In response to the low levels of cortisol, there is increased ACTH secretion from the pituitary gland. High levels of ACTH result in adrenal hyperplasia, as well as elevated levels of the precursor 17-hydroxyprogesterone, as it is upstream of the enzyme deficiency. The excess 17-hydroxyprogesterone, which cannot be converted to cortisol, is shunted to alternative synthetic pathways in the adrenal cortex, leading to increased production of the androgen testosterone.[6] When the XX fetus is exposed to excess androgens, especially during the critical period for sexual differentiation from nine to 15 weeks' gestation, masculinization of the external genitalia results.[6] On the other hand, XY infants are typically born with normal male genitalia and are not overly virilized. 21-hydroxylase is also the enzyme responsible for converting progesterone to deoxycorticosterone, which is a precursor of aldosterone. Thus, aldosterone deficiency can also be seen in specific subtypes of CAH, which we will discuss later.

21-hydroxylase is the most common, but not the only, enzyme affected in CAH. Deficiency of 11®-hydroxylase, which converts 11-deoxycortisol to cortisol, is the second most common cause of CAH.[1]

Classic vs. Non-classic CAH

There are two main subtypes of CAH: classic and non-classic CAH. Non-classic CAH is often referred to as late-onset CAH, as it tends to present in childhood, adolescence, or even young adulthood. Non-classic CAH is characterized by mild androgen excess, which tends to present itself in females with hirsutism, acne, oligomenorrhea or amenorrhea, or premature adrenarche. Males can also present with similar symptoms, minus the ones associated with menstruation, of course! If these features sound familiar, that's because they also describe the presentation of polycystic ovarian syndrome, or PCOS, and females with non-classic CAH are frequently misdiagnosed with PCOS.[7]

Classic CAH, on the other hand, typically presents with virilization of female external genitalia at birth. Classic CAH can be further classified as either salt-wasting or non-salt-wasting forms. Recall that 21-hydroxylase is a key enzyme in the biosynthetic pathways for both cortisol and aldosterone. The differentiating factor between salt-wasting and non-salt-wasting CAH is whether aldosterone production is affected in addition to cortisol. 1 in 4 individuals with classic CAH have the non-salt-wasting form, also known as simple virilizing CAH. These individuals have impaired cortisol production, but intact aldosterone production. Conversely, 3 out of 4 individuals with classic CAH have the salt-wasting form, which is the most severe subtype of CAH. In salt-wasting CAH, deficiency of 21-hydroxylase results in both cortisol and aldosterone deficiency. The lack of aldosterone limits the amount of sodium that can be reabsorbed into the body; instead, sodium is lost in the urine – hence, "salt-wasting". Males with classic CAH tend to present with salt wasting crises or early adrenarche.

Presentation

As mentioned, females affected by classic CAH tend to present with virilized external genitalia at birth, due to the masculinizing effects of excess testosterone produced by their adrenal glands. This virilization can range in presentation from mild clitoromegaly to severe clitoromegaly with fusion of labial folds. However, the internal reproductive organs, like the ovaries, fallopian tubes, and uterus, are unaffected. Males with classic CAH tend to have normal genitalia at birth, though they may develop penile enlargement or hyperpigmentation later on.[7]

Clinical Case

Let's return to our clinical case. You review Mia's physical exam findings with your staff and share your top differential diagnosis of CAH. After examining Mia, your staff agrees with your finding of ambiguous genitalia and asks which investigations you'd like to do to explore a diagnosis of CAH. They also ask you to think about a possible management plan moving forward if a diagnosis of CAH is confirmed.

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Investigations

CAH is one of many disorders investigated through newborn screening. This is especially helpful in trying to identify affected males, as they do not present with clinical signs of CAH at birth. Screening tests aim to measure serum 17-hydroxyprogesterone levels. Since this hormone is the substrate for 21-hydroxylase, elevated serum concentrations are characteristic of CAH. Salt-wasting CAH is associated with the highest 17-hydroxyprogesterone levels, followed by non-salt-wasting CAH, and non-classic CAH is associated with the smallest rise in 17-hydroxyprogesterone.

Confirmatory testing is done with the ACTH stimulation test, also useful in classifying disease severity. This test involves measuring 17-hydroxyprogesterone and cortisol levels both at baseline and 60 minutes after the administration of a bolus of cosyntropin (ACTH).

Treatment

In patients with classic CAH, the mainstay of treatment is long-term glucocorticoid therapy. The benefits of this are two-fold: glucocorticoid replacement provides negative feedback to the HPA axis to shut off ACTH production, as well as suppressing excess androgen production.[7] Hydrocortisone remains the preferred glucocorticoid for maintenance therapy requiring doses from 10-15 mg per m^2 of body surface area per day divided TID.[1] It's important to contrast these therapeutic doses from physiological concentrations, which typically range from 6-9 mg/m^2/day; mildly supraphysiological doses are chosen to ensure androgen production is adequately suppressed.[4] Doses used in CAH are still much smaller than doses used for treatment of inflammatory conditions.

Infants with the salt-wasting form of classic CAH also require supplementation with a mineralocorticoid and salt.[7] In addition to hydrocortisone, these patients are often treated with a combination of fludrocortisone, at a dose of approximately 0.1-0.2 mg per day, and NaCl, at a dose of approximately 1-2 grams per day.[1,6,7]

It's also worth noting that glucocorticoid and mineralocorticoid replacement serves to manage ongoing CAH and suppress continued androgen production, but will not reverse virilization to external genitalia that has already occurred. In situations where a female demonstrates ambiguous genitalia, namely classic CAH, surgical correction is an option.

Clinical Case

Let's revisit our case one last time. After confirming Mia's diagnosis of CAH with serum 17-hydroxyprogesterone testing, you counsel her parents on her management plan. You initiate glucocorticoid therapy, a low dose of fludrocortisone, and answer questions about surgical options that may be pursued in the future. Mia is subsequently discharged from the hospital.

Two weeks later, you are still on your paediatrics rotation and have received a consult to see a two-week old infant in the emergency department. The referring physician shares that

the parents are concerned about difficulty feeding and note that the infant has had poor weight gain since leaving the hospital after birth. You arrive in the emergency department and are surprised to see Mia, the newborn with ambiguous genitalia you had previously examined. They had missed their initial follow-up with Endocrinology for a check of Mia's electrolytes, specifically sodium and potassium. You recall that patients with classic CAH are susceptible to developing an adrenal crisis, which warrants timely identification and management, and decide to promptly review her presentation with your staff.

Adrenal Crisis

When patients with CAH lose large amounts of salt, they are at risk of a salt-wasting adrenal crisis. These episodes commonly present at around one or two weeks of life if CAH has not been adequately diagnosed and managed; for example, affected males with unaffected external genitalia or highly virilized females, who do not arouse suspicion of a CAH diagnosis, may only be identified after presenting in an adrenal crisis.

Since aldosterone is low in salt-wasting CAH, the body is unable to reabsorb sodium and secrete potassium, which results in hyponatremia and hyperkalemia. Where sodium goes, water tends to follow due to osmotic diuresis; therefore, another feature of a salt-wasting adrenal crisis is dehydration, which tends to be coupled with failure to thrive, difficulty feeding, and ultimately leads to hypovolemic shock.[6]

Initial treatment of an adrenal crisis centres around adequate fluid resuscitation in order to achieve hemodynamic stability. Rehydration should be initiated with IV 20 mL/kg normal saline boluses, followed by maintenance fluids with IV D5NS. Careful monitoring of potassium and glucose levels is important in order to adequately correct hyperkalemia or hypoglycemia as needed. Patients then require a stress dose of hydrocortisone, totaling 100 mg/m^2/day.[8]

Key Learning Points

Before we conclude this podcast, let's review some key learning points regarding congenital adrenal hyperplasia:

1. Congenital adrenal hyperplasia is caused by enzymatic deficiencies that affect the body's production of cortisol and, in some cases, aldosterone
2. The most common enzyme affected in congenital adrenal hyperplasia is 21-hydroxylase
3. There are two main subtypes of congenital adrenal hyperplasia: non-classic CAH tends to present later in life with mild symptoms of androgen excess. Conversely, classic CAH may present at birth in females with ambiguous genitalia
4. There are two subtypes of classic CAH: non-salt wasting (or simple virilizing) and salt-wasting. Both subtypes are characterized by cortisol deficiency, but the salt-wasting form also involves significant aldosterone deficiency, which affects the body's ability to reabsorb sodium and secrete potassium

5. Diagnosis of congenital adrenal hyperplasia is often done through newborn screening, which is sensitive for elevated concentrations of serum 17-hydroxyprogesterone
6. The mainstay of treatment of classic CAH is glucocorticoid replacement with hydrocortisone. Salt-wasting CAH also requires a mineralocorticoid, fludrocortisone, and NaCl supplementation.
7. Salt-wasting adrenal crisis are acute presentations requiring urgent fluid resuscitation and stress doses of hydrocortisone

We hope you enjoyed this PedsCases podcast on congenital adrenal hyperplasia! Thank you for listening!

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