

# CONGENITAL ADRENAL HYPERPLASIA

## • THE FACTS YOU NEED TO KNOW •

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### **What is CAH?**

Congenital adrenal hyperplasia (CAH), also termed adrenogenital syndrome in older literature, is a common inherited form of adrenal insufficiency. This group of diseases is due to mutations (genetic defects) in the genes coding for several enzymes needed for the production of adrenal cortex hormones. About 95% of cases of CAH are caused by 21-hydroxylase deficiency. This enzyme is necessary for efficient production of two vital adrenal steroid hormones: cortisol and aldosterone. Deficient production of these substances causes disruption in the delicate balance of hormones. Sensing low levels of cortisol, the adrenal glands, directed by the master hypothalamus and pituitary glands, go into high gear. Because cortisol production is impeded, the adrenal cortex instead manufactures androgens, or male steroid hormones, an undesired byproduct. In short, while one part of the adrenal functions poorly, making inadequate amounts of cortisol and aldosterone, another portion of the gland over-produces androgens. This last feature distinguishes CAH-21-hydroxylase deficiency from Addison's disease, since in Addisonian patients, the adrenals are most often completely non-functional.

#### *Classic CAH-21-hydroxylase deficiency:*

Lack of both cortisol and aldosterone predispose 3/4 of severely affected individuals to "adrenal crises" with dehydration and shock, or even death, if not properly diagnosed and treated. Excess adrenal androgen production begins in early fetal life in classic CAH-21 affected infants, and causes abnormal growth of girls' clitoris and masculinization of the genital-urinary structures. Severely affected girls may be mistaken for boys at birth. Affected boys have no genital malformations at birth, but continued androgen excess causes unusually fast body growth. Inappropriately early puberty leads to premature completion of growth and short adult height. Proper medical treatment resets the abnormal balance of hormones, permits near-normal growth and puberty. Proper surgical treatment by an experienced pediatric urologist reconstructs near-normal female genitals. Some surgeons are now able to reconstruct the vagina at the same time as they reduce the size of the clitoris in early infancy, whereas in the past surgery was at least a two-step process, finished in late adolescence. Some families may opt to defer genital surgery.

#### *Nonclassic CAH-21-hydroxylase deficiency:*

A milder, non-life-threatening form of CAH-21 becomes manifest in later childhood or even young adult life, and is not characterized by ambiguous genitalia in girls. Rather, these individuals have partial enzyme deficiency, and thus have better cortisol production, normal aldosterone production, and lower levels of adrenal androgens. They do not suffer "adrenal crisis." Generally, such patients seek medical attention because of premature development of pubic hair, irregular menstrual periods, hirsutism (unwanted body hair), or severe acne. Some people affected with nonclassic CAH are not at all symptomatic, and are identified only because of an affected relative.

### **Diagnosis:**

The diagnosis of CAH has traditionally rested on hormone measurements combined with clinical evaluation, including history and physical examination. A number of states in the U.S. as well as several

foreign countries now perform a hormonal test for CAH within the first few days of life. These heel-prick blood specimens are obtained at the time when blood is drawn for thyroid tests and a number of other inherited diseases. The rationale for newborn screening is that mainly in boys, who have no outward sign of the disease, the mortality from "adrenal crisis" is high, and this could be entirely prevented by early diagnosis and medical treatment. Since the incidence of classic CAH worldwide is about in 10,000 total births, this amounts to a substantial number of potentially preventable infant deaths. These screening programs have achieved their goals. Diagnostic methods are continually being refined, both for the hormonal methods, and for the newer genetic typing discussed below. Since the advent of molecular genetic technology, we can now examine the genes of CAH patients and family members. This type of study has application for prenatal testing, neonatal screening, and genetic counseling, as well as confirming diagnosis in questionable cases. Molecular diagnosis is available in several specialized laboratories. Just as there are potential inaccuracies in hormonal testing, there are pitfalls in genetic testing, as now has become clear from published reports concerning CAH, as well as in the diagnosis of other diseases, and in forensic use of DNA testing. Nonetheless, for the most part, these techniques are verifiable and accurate in the proper hands. Genetic testing can resolve ambiguities that arise from hormonal testing, and can help provide accurate information to parents of CAH patients as to their risk of having another affected child during the early weeks of pregnancy.

It should be understood that carriers of a mutant gene for 21-hydroxylase deficiency are not themselves predisposed to having symptoms or signs of CAH. Some individuals carry 2 nonclassic, mild mutations, and are minimally affected, not requiring medical or surgical therapy. Furthermore, there are also rare instances of people with classic gene mutations who have an attenuated form of the disease. Genetic testing is probably best done only in cases where the individual or family will stand to gain from this knowledge and make significant treatment decisions. In most cases, treatment decisions can readily be made based solely on hormone measurements in blood.

#### **Standard CAH treatment:**

Currently, standard medical treatment consists of giving a glucocorticoid (a cortisol-like steroid medication, e.g., oral hydrocortisone in children, or prednisone or dexamethasone in older patients). In addition, those who have aldosterone deficiency ("salt-wasters") need another drug, fludrocortisone (a mineralocorticoid, which acts like the missing hormone, aldosterone) to be able to retain salt. Infants and small children may also receive salt tablets as a dietary supplement, whereas older patients eat salty foods. Although many patients are wellmanaged on these types of medical regimens, it is very difficult to precisely mimic the native adrenal hormone rhythms and achieve perfect hormonal balance. Thus, most CAH patients have intermittent periods of fluctuating control with peaks and valleys in the hormones doctors use to monitor the effectiveness of treatment (specifically, 17-hydroxyprogesterone and androgens). This leads to increases in the steroid medication doses, and sometimes these become excessive. A known complication of high dose glucocorticoids is growth inhibition. Endocrinologists may find they are "between a rock and a hard place" treating some difficult-to-control CAH patients, since either over treating or under treating will ultimately stunt growth. Most CAH patients do not reach the target height predicted based on parental heights. They are on average about 1 to 2 standard deviations below the population average in height, meaning they are "short normal." A particularly important factor in determining final height in CAH patients is the amount of steroids given as treatment in the first 2 years of life. Doctors are now advocating more modest treatment doses to preserve height potential. All children with CAH should be seen frequently by a pediatric endocrinologist who not only measures blood hormone levels, but also carefully assesses height, weight, blood pressure, and an annual x-ray of the wrist (bone age x-ray).

Nonclassic CAH patients, if they require medical therapy, are usually effectively treated with low dose hydrocortisone (children) or prednisone (adults) only. They do not require genital surgery.

#### **Newer treatment modalities:**

Because of these difficulties in fine-tuning medical treatment of classic, severe CAH with standard therapy, doctors are investigating experimental types of drug therapy. It will take many years to fully understand the safety and effectiveness of the experimental therapy, since a large number of patients will have to reach final height to determine whether the short term benefits are sustained. There are potential harmful side effects to experimental drugs, and it remains to be seen if long-term benefits outweigh such adverse effects. Finally, patient compliance is an important issue, since it is more difficult

to remember to take 3 drugs up to 3 times daily than it is to take 1 or 2 drugs twice daily.

A more radical suggestion for alternative CAH therapy is a surgical one: adrenalectomy. This therapy was in common use in the days before physicians had access to steroid medications. It is now suggested again for selected patients, particularly those with little-to-no enzyme activity, to avoid high dose glucocorticoids and/or persistently high adrenal androgens. A major motivation for considering this type of surgery is that it can now be accomplished by laparoscopy. Laparoscopy is surgery done through one or more 1-inch incisions, with insertion of a fiberoptic light containing a tube with openings for surgical instruments. Laparoscopic appendectomy, for instance, has minimal morbidity and low potential for operative complications. In girls with severe CAH, adrenalectomy could be done at the same time as clitoral reduction and/or vaginal reconstruction. There have been no controlled trials of these procedures to date. Obviously, removing both adrenals leaves the patient in an Addisonian state, and one would still have to supplement both cortisol and aldosterone equivalents. Advocates of adrenalectomy point out that replacement hormone doses in Addisonian patients are lower than in CAH patients, and Addisonian children do not suffer from short stature, overweight, or masculinization and ill-timed puberty. On the other hand, we do not know how much of the adverse effects of excessive adrenal androgens are pre-programmed in prenatal life and early infancy.

### **Prenatal therapy:**

Prenatal therapy has been in use for more than two decades. In families where one child is already known to be affected with CAH, parents can benefit from genetic counseling explaining how the disease is inherited, and what their options are during subsequent pregnancies. The aim of giving dexamethasone to the pregnant woman at risk for a second CAH-affected child is to reduce secretion of androgens from the female fetus' adrenal gland, and thus reduce the chance that the baby will be born with male-like genitals. Because adrenal production of androgen begins in the mid-to-late first trimester before prenatal diagnosis is done, the treatment is begun before it is known whether the fetus is male or female, and before it is known whether the child has CAH. Since CAH is a recessive disease, one has a 50% chance of inheriting a mutant gene from each carrier parent, and the risk of an affected child is 25% in each pregnancy. Since only half of the children are female, only 1/8 fetuses may benefit from prenatal treatment. Thus, 7/8 fetuses would be exposed unnecessarily to steroid treatment via placental passage of the drug given to their mothers. Several hundred children have undergone such prenatal treatment, and surveys show no major ill effects. Endocrinologists urge caution in the use of prenatal dexamethasone therapy and strict monitoring of its application by hospital institutional review boards and ethics committees. Some negative feelings about the therapy are derived from cross-species comparison of rodent and primate studies to humans, and from anecdotal reports in small series of complications incurred by either treated pregnant mothers or infants. It is nevertheless prudent to consider the long-term potential for unrecognized complications when experimental therapies are used. The most cogent argument for restricting prenatal therapy to research studies, is that there are few data for comparison in the first trimester use of glucocorticoids in human pregnancy, and we do not truly know all the long-term risks.

### **Present and future directions:**

For the present, most patients with CAH can be reasonably well-managed with the standard medical and surgical approaches. Molecular diagnosis does not directly add to patient well-being, and is of use mainly in prenatal diagnosis. Looking toward the future, important diagnostic issues are improving the precision and cost-effectiveness of newborn screening. Treatment questions to be resolved will include whether either newer experimental drug therapies or adrenalectomy improve patient outcomes substantially. Enzyme replacement and gene therapy are possible future research applications.

For additional information you may want to read:

1. <http://caresfoundation.org/what.html>
2. [http://www.dshs.state.tx.us/newborn/hand\\_cah.shtm](http://www.dshs.state.tx.us/newborn/hand_cah.shtm)

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