

Congenital Adrenal Hyperplasia

What are the ill-effects of this disorder?

Three main forms of congenital adrenal hyperplasia (CAH) exist: the severe salt-wasting and non-salt wasting forms, and a milder form. An infant with the salt-wasting form may have any or all of the following symptoms within the first few weeks of life: vomiting, poor weight gain, poor feeding, drowsiness, diarrhea, and dehydration. Blood tests would reveal a lower than normal level of salt in the blood. The infant may go into shock. Without proper treatment, this infant will die. Male newborns with the salt wasting form of CAH will have no outward physical signs except possible increased pigmentation around the genitalia.

Female newborns with the salt-wasting form of CAH have ambiguous genitalia which may make the infant appear partially or very much like a male. The clitoris of a female newborn with the salt-wasting form is enlarged and sometimes looks like a penis, and the labial folds may be somewhat joined and wrinkled to look like a scrotum.

The non-salt wasting form of CAH does not generally cause severe illness in newborns. The external genitalia of females with the non-salt wasting form of CAH are also ambiguous, having an enlarged clitoris with or without the joining of the labial folds. The degree to which the clitoris is enlarged and the labia are grown together will reflect how much the infant appears male. Other symptoms of the non-salt wasting form of CAH develop with age in both males and females, including rapid growth in early childhood, and seemingly early sexual development with pubic hair growth.

A milder form of CAH may appear anytime between early childhood and puberty. In early childhood, the mild form causes rapid growth and early pubic hair growth. At puberty, girls with the mild form generally develop excess body hair growth, acne, menstrual irregularity, and sometimes infertility. Infertility may also occur in males with this milder form of CAH, although it is not common.

Heredity

Congenital adrenal hyperplasia (CAH) is an inherited disorder which causes an enzyme deficiency (most commonly 21-hydroxylase) resulting in the inability of the adrenal glands to make hormones necessary to maintain life (cortisol, and in the salt-wasting form also the salt-retaining hormone). The adrenal glands are located on top of the kidneys, in the area of the back near the waistline. Cortisol is responsible for maintaining the body's energy supply, blood sugar, and control of the body's reaction to stress. The salt-retaining hormone (aldosterone) is necessary for maintaining a normal balance of salt and water in the body. An enzyme is a protein substance naturally occurring in the body which facilitates chemical changes in the body. Production of

adrenal enzymes is controlled by genes. Genes are areas on the chromosomes with specific function. The chromosomal composition of an individual comes from the parents, each contributing one half. The genetic make up determines the child's features before birth. CAH results when two defective genes for adrenal enzyme production, one from each parent, are inherited by a child. The parents usually do not have this disorder because they are only carriers of this disorder, that is, they have inherited one normal gene and one affected gene for the enzyme from their parents. The normal gene is dominant and blocks the expression of the defective gene. When one carrier marries another carrier, there is a 25% chance their child will inherit both the defective genes and therefore have the disorder, there is an equal chance their child will inherit both normal genes and not have this disorder, and there is a 50% chance the child will inherit one normal and one defective gene and will therefore be a carrier of the genetic trait. Severe form of CAH occurs with frequency of one in 10,000 to 15,000 live births in general population. As of 1992, seven regional public health newborn screening programs mandatorily screen all newborns for CAH.

Effects of the Enzyme Deficiency

The core problem in CAH is the inability of the adrenal glands to make enough cortisol in the non-salt wasting form, or enough cortisol and salt-retaining hormone in the salt-wasting form. This inability of the body to produce these hormones is the reason newborns and children not receiving treatment get very sick with this disorder. Instead of making cortisol, the hormonal raw materials which usually make cortisol, are shifted away to make other hormones, specifically male sex hormones (androgens). As a result more androgens are produced than necessary. Before birth, the excess androgens stimulate the growth of the genitalia. When the child is male, this is not a problem, however excess androgens in a female with this disorder causes the child's genitalia to have the appearance of a male although the internal genitalia are normal female. This is called masculinization of the female genitalia. Excess androgens produced during childhood causes rapid growth and ages the bones. This growth initially causes the child to be taller than most children their age, however the end results of this growth and bone aging if untreated is a short adult height.

Diagnosis

CAH can easily be diagnosed by measuring hormones in a small blood sample. This blood test measures cortisol and the hormonal raw material (17-hydroxyprogesterone) which make cortisol. Since children with CAH are not able to make cortisol, the blood test would show very low levels of cortisol if the child did have this disorder. As a result of not making cortisol, the hormonal raw material which usually makes cortisol, builds up in excess, the raw material (17 Hydroxyprogesterone) if the child did have this disorder. Families can determine if they are carriers of this disorder by a blood test which stimulates the adrenal gland to produce hormones.

The gene for 21-hydroxylase enzyme which determines whether or not a person has congenital adrenal hyperplasia is always coupled with the gene for a white blood cell protein called human leukocyte antigen (HLA). The genes for HLA and CAH are located close together on chromosome number six from each parent. Because of the close proximity of the HLA gene and CAH gene, the HLA test can serve as a marker for the presence or absence of the CAH gene. By determining the HLA type of the parents, and

their child affected with CAH, it can be determined if other family members are also carriers of the trait. Carrier detection serves the important function of alerting parents to the possibility of having a child affected with CAH.

The gene for the 21-hydroxylase enzyme can also be evaluated by DNA analysis which determines whether the gene is present or absent, or if the DNA make-up is changed in the patient.

When there is a family history of CAH, it is possible to diagnosis a child before birth through tests performed during pregnancy. Prenatal diagnosis of CAH may be done by hormone tests, HLA typing, and/or DNA analysis of amniotic fluid obtained from amniocentesis at 14-20 weeks gestation. Early in the pregnancy, chorionic villus sampling is performed at 8-9 weeks gestation to establish through HLA typing or DNA analysis whether or not a fetus is affected with CAH. Prenatal treatment of female fetuses affected with CAH is possible and may possibly prevent the ambiguous genitalia. However this treatment must be started very early in the pregnancy and requires the mother to take a strong synthetic hormone similar to cortisol (dexamethasone).

Treatment

Regardless of whether the newborn is male or female, early diagnosis and medical treatment of congenital adrenal hyperplasia is crucial. Without treatment a newborn with the salt-wasting form of congenital adrenal hyperplasia is in a life-threatening position. Generally, in the non-salt wasting form of CAH, only cortisol replacement is necessary. In the salt-wasting form, replacement of both cortisol and the salt-retaining hormone and extra salt are necessary. Since the body cannot produce enough cortisol in the non-salt wasting form, or cortisol and salt-retaining hormone in the salt-wasting form, synthetic cortisol (hydrocortisone) and synthetic salt-retaining hormone (florinef) are given to supplement those the body cannot produce.

The aim of treatment is to provide the body with the ability to maintain a normal energy level, and balance of salt and water in the body, normal growth and sexual maturation at puberty, and fertility later in life. Therefore treatment of CAH is ongoing, involving periodic medical evaluations and monitoring for medication dose adjustment.

The masculinization of a female's genitalia will require corrective surgery as an infant and possibly again later in life. However treatment started early in the pregnancy may reduce the degree of masculinization and may also reduce the risk or need for surgery later.

Cortisol is a hormone which is essential to maintain life, without this hormone the body cannot respond to stress. A child affected with CAH can go into shock from infection, injury, or surgery. Extra doses of hydrocortisone are important at these times. Therefore during illness, the dose of synthetic cortisol (hydrocortisone) is doubled or tripled. However if the child is not able to take the medications by mouth due to vomiting or severe diarrhea, parents should give the child an injection of hydrocortisone into a muscle at home and notify their doctor immediately. The child should also drink salt water if vomiting does not recur. If at any point a child with CAH requires surgery, it is imperative that the child's endocrinologist be notified. For the stress of surgery, a child with CAH will require special doses of hydrocortisone either through injection into a

muscle or injection into a vein. The endocrinologist will be able to inform the other doctors of the necessary precautions. It is generally a good idea to obtain a special Medic Alert bracelet which will carry important information for a doctor in the event of an emergency.

Treatment of congenital adrenal hyperplasia is life-long, however periodic medical check-ups would allow for a full and otherwise normal healthy life.

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The MAGIC Foundation

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