Heredity:

Congenital Adrenal Hyperplasia (CAH) is an inherited disorder which causes an enzyme deficiency (**most commonly 21-hydroxylase**) in the adrenal glands resulting in the inability of the adrenal glands to make hormones (cortisol and aldosterone) necessary to maintain life. The adrenal glands are located on top of the kidneys, in the area of the back near the waistline. Cortisol is necessary for maintaining the body's energy supply, blood sugar level, blood pressure, and control of the body's reaction to stress. Aldosterone is the salt-retaining hormone at the kidneys and is necessary to maintain a normal balance of salt and water, and blood pressure in the body. These hormones are produced from the adrenal glands by several steps of chemical changes by enzyme(protein substance) actions. Production of adrenal enzymes is controlled by genes(DNA). Genes are areas on the chromosomes with specific function. The chromosomal composition of an individual comes from the parents, each parent contributing one half and determines genetic make up of a child before birth.

CAH results when two defective genes for adrenal enzyme production are inherited by a child, one from each parent. The gene (DNA) for 21-hydroxylase enzyme is located on chromosome number six. The parents usually do not have CAH because they are only carriers of the defective gene that is they have inherited one normal gene and one abnormal gene for the enzyme related to CAH from their parents.The normal gene is dominant and blocks the expression of the abnormal gene. When one carrier marries another carrier, there is a 25% chance their child will inherit both the defective genes and therefore have CAH, there is an equal chance their child will inherit both normal genes and not have CAH or a trait of CAH, 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 for CAH.

Classic 21-hydroxylase deficiency CAH as based on Newborn screening study occurs with frequency of one in 15,000 live births in diverse population in North America but ranging from 1 in 8,000 to1 in 29,000 live births depending on the ethnicity and racial background. CAH is most prevalent among certain natives in Alaska.

Other enzyme deficiency CAHs (11-ß hydroxylase, 3-ß hydroxysteroid dehydrogenase, 17-α hydroxylase, Star, Cholesterol side chain cleavage enzyme) are uncommon or rare and its effects may be similar to a degree but differs from 21-hydroxylase deficiency CAH.

Congenital Adrenal Hyperplasia

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Effects of 21-hydroxylase Enzyme Deficiency CAH(Clinical Presentation) :

The core problem in CAH is the **inability** of the adrenal glands to make enough cortisol in all clinical forms of CAH and in addition, inability to make enough aldosterone in the salt-wasting form. The inability of the adrenal glands to produce theses life essential hormones is the reason why newborns and children not receiving treatment get very sick with CAH from salt wasting leading to dehydration, poor weight gain, and failure to thrive, or low blood sugar level, and lethargy . In CAH, due to defective action of the enzyme, hormonal raw materials to make cortisol are shifted away to make other hormones, specifically male sex hormones (androgens). As a result more androgens are produced than necessary from early fetal life.

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 CAH cause the child's genitalia to have the appearance of a male although the internal genitalia are normal female. This is called virilization of the female genitalia. Excess androgens produced during childhood cause rapid growth and ages the growth plates in bones called bone age. This growth initially causes the child to be taller than most children of their age, however the end result of this inappropriate premature growth and bone aging if untreated is also early cessation of growth and short adult height.
There are clinical spectrum of CAH : The severe classic Salt-wasting form is manifested by loss of sodium and water from the kidneys leading to dehydration and low blood sodium level in both male and females from neonatal life and if untreated, life threatening , and females have varying degree of the external appearance of a male genitalia at birth while males have normal appearance of genitalia except at times darkened color of scrotum. The classic Non-salt wasting or simple virilizing form is manifested by no gross salt-wasting or its symptoms but females at birth are virilized as in the salt-wasting cases. Mild non-classic form is manifested by no gross genital abnormality at birth in females or males except mild clitoral enlargement in some females; these children generally have no symptoms but develop early pubic hair growth with modestly rapid growth in childhood and adolescent or adult females develop increased body hair and or acne, and menstrual problem or infertility in many. These clinical spectra of CAH largely reflect the degrees of severe to mild inherited structural problem (mutation) within the DNA dictating 21-hydroxylase enzyme action.

Diagnosis:

21-hydroxylase deficiency CAH is generally diagnosed by high 17-Hydroxyprogesterone level with or without low cortisol level in a blood sample of patient. The hormonal raw material, 17-Hydroxyprogesterone is not able to be metabolize to cortisol due to lack of or diminished 21-hydroxylase action, this leads to low cortisol hormone level . When Cortisol level is low, body's mater gland called pituitary produces more adrenal stimulating hormone called ACTH to stimulate adrenals to produce cortisol but CAH adrenals are not able to do so. Instead, the extra ACTH effects in the CAH adrenals will stimulate more 17-Hydroxyprogesterone production in CAH people. The excess 17-Hydroxyprogesterone is metabolized to produce unwanted excess androgen hormones in CAH, thus, androgen hormones like androstenedione, testosterone, and DHEA levels are elevated for the given age and sex of CAH people.

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 (mutation) in the patient. By obtaining blood sample in general and examining the structure of the DNA from affected CAH person in the family, it can be determined if other family members are also carriers or patient with CAH with the affected DNA . Carrier detection serves the important function of alerting the person to the possibility of having a child affected with CAH.

Newborns Screening for CAH:

Newborn screenings for CAH. has been mandated by law in US since 2008 and is performed by measuring17-Hydroxyprogesterone level in a tiny blood spot obtained on a filter paper by heel prick of the newborns usually at age 2-3 days in US. The screening test is performed by the laboratory of Department of Public Health in most state's regional programs. Check with your regional Department of Public Health on Newborn Screening for CAH for current status..

Prenatal Diagnosis:

When there is a family member with CAH, it is possible to diagnosis a child before birth through tests performed during pregnancy. Prenatal diagnosis of CAH in early pregnancy is performed by a chorionic villus sampling at 8-9 weeks gestation to establish through DNA analysis whether or not a baby is predicted to have CAH and whether the baby is female or male. Analysis of fetal cells from Maternal blood sample as early as 5-8 weeks of pregnancy is also used to determine the presence of male sex chromosome(Y) material to determine the sex of the baby.

It is important to know the sex of the baby as early as possible as any male babies are not recommended for prenatal therapy. Prenatal diagnosis of CAH can be made during second trimester by amniocentesis and performing DNA analysis of amniotic cells and measuring 17-Hydroxyprogesterone level which is generally elevated in classic cases.

Prenatal treatment of CAH:

This treatment is to be offered for only affected female baby with classic CAH to prevent genital abnormality that would requires surgical intervention. Prenatal treatment in female fetuses affected with CAH is possible and prevents the ambiguous genitalia in the majority of treated females from early fetal life. This treatment must be started from 5-7 weeks of fetal age and requires the mother to take a strong synthetic hormone called Dexamethasone(drug similar to but 30 times more powerful than cortisol) throughout the entire duration of the pregnancy. Thus, there is a potential for occurrence of significant side effects of Dexamethasone on the mother. The long term impact of exposure of the baby to Prenatal Dexamethasone is not fully established, thus, this is not recommended as a standard therapy at this time. Those families considering prenatal therapy of CAH will need a balanced and informed counseling by experienced teams and will be best to make informed decision on this issue by understanding the benefit and potential untoward side effects as well as not fully established long term outcome of treated cases.

Treatment of CAH in children, adolescents, and adults :

The aim of treatment is to provide the body with the ability to maintain a normal energy level, balance of salt and water in the body, normal growth, sexual maturation at appropriate pubertal age, and fertility later in life. This is accomplished by replacing the inadequately produced cortisol hormone by synthetic hormone Hydrocortisone in growing children and or prednisone or similar family drug in growth completed CAH people life time. In salt wasters, a synthetic salt retaining hormone called fludrocortisone (florinef) helps to retain sodium and water in the body. Therefore, treatment of CAH is ongoing, involving periodic medical evaluations and monitoring for medication dose adjustment and checking compliance..

The virilized female genitalia will require corrective surgery as an infant and if needed, again later in life. Proper and adequate Prenatal treatment may reduce the degree of virilization and reduce the need of cosmetic surgery..

Special care needs for CAH :

Without cortisol hormone, 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 and take child to a near ER. The child should also drink salt water if vomiting does not recur. In the ER, child may need to receive IV Saline with glucose if child is dehydrated and continues to have diarrhea or vomit. It is recommended to carry a special care instruction prepared by your(child's) endocrinologist to any ER for their info.

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 mandatory to obtain a special Medic Alert bracelet which will carry important information for other health care people 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.