

Disease
Name:

**CONGENITAL ADRENAL HYPERPLASIA; 21
HYDROXYLASE DEFICIENCY**

Classification: Inborn error of cortisol synthesis

Genetic
Information:

Inheritance: Autosomal recessive

Population Incidence: 1:15,000 (salt wasting), 1:50,000 (simple virilizing),
1:1,000 (non classical)

Ethnic Incidence: Yupik Eskimos: 1:300

Gene & Location: CYP21; 6p21.3

Common Mutation: A>G intron 2 (25%)

OMIM # 201910

Disease
Information:

Symptom Onset: Prenatal onset to adult, but generally at birth for classical disease

Symptoms: **Classical Salt Wasting:** These represent 3/4 of classical cases. Diminished cortisol production stimulates the fetal pituitary to produce ACTH and excessive adrenal androgens. In female fetuses this causes varying degrees of virilization that is usually recognized at birth. Reduced production of mineralocorticoids in both sexes leads to hypotensive, hyperkalemic, salt-losing crisis in the first few weeks of life which can be fatal.

Classical Simple Virilizing: These represent 1/4 of classical cases. Salt losing crises generally do not occur, but androgen excess and virilization remain a problem.

Non-classical: individuals have variable presentation. Some have symptoms of androgen excess with precocious pubarche and hirsutism, oligomenorrhoea, infertility or acne, while others remain asymptomatic.

Physical Findings: Virilization of external genitalia in females.

Treatment: Treatment with hydrocortisone and mineralocorticoids. Surgical correction of virilized genitalia may be required, but is increasingly being deferred until adolescence. Adrenalectomy has been proposed for those with null mutations and poor control with medication.

Natural History without treatment:

Death from salt losing crisis unless recognized and treated aggressively. Virilization of females can be severe enough that incorrect sex assignments may be made. Adults may have fertility problems.

Children with the “simple virilizing” form have rapid growth with advanced skeletal age, early puberty and short stature as adults. In adulthood, there is hirsutism and acne. Women have irregular menses and infertility.

Non classical patients may remain asymptomatic or develop symptoms of androgen excess.

Natural History with treatment:

Fertility and gonadal function are potentially normal for both males and females with optimum treatment, however, about 30% of males have infertility associated with the presence of adrenal rests in testes and women with classical disease have severely reduced fertility with live birth rates of up to 10% (normal 65-91%).

Height for both males and females is generally 1-1 1/2 SD below predicted height. Final height is correlated to the severity of CAH and the degree of biochemical control during infancy and puberty.

Large prospective studies of early diagnosed, well-treated patients are not yet available.

Metabolic Information:

Missing Enzyme:

21-hydroxylase deficiency

Newborn Screening profile:

17 hydroxyprogesterone is elevated. Degree depends on gestational age, weight and age at testing.

Prenatal testing:

Prenatal testing is possible, although genotyping of fetus is the preferred method.

Miscellaneous Information:

1. AAP Section on Endocrinology and Committee on Genetics. Technical report: congenital adrenal hyperplasia. Pediatrics 2000;106:1511-1518.
2. Lawson Wilkins Pediatric Endocrine Society/European Society for Pediatric Endocrinology working group. Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins pediatric society and the European society for paediatric endocrinology. J of Endo & Metab 2002;87(9):4048-4053.
3. Stikkelbroeck NMML, Hermus ARMM, Bratt DDM, Otten BJ. Fertility in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Obstetrical & Gynecological Survey 2003;58(4):275-284.
4. Cabrera MS, Vogiatzi MG, New MI. Long term outcome in adult males with classic congenital adrenal hyperplasia. J Clin Endo & Metab 2001: 86(7)3070-3078.
5. White PC, Speiser PW. Long-term consequences of childhood-onset congenital adrenal hyperplasia. Best Practice and Research Clinic Endo and Metab 2002;16(2)273-288.