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Congenital Adrenal Hyperplasia Information for Physicians and Other Health Care Providers

Definition Congenital adrenal hyperplasia (CAH) is an inborn error of steroid biosynthesis. Individuals with CAH due to 21 hydroxylase enzyme deficiency cannot produce adequate amounts of cortisol and, in some cases, also are aldosterone deficient. These hormones are essential to glucose metabolism and salt reabsorption; untreated CAH can very suddenly lead to adrenal insufficiency with dehydration, shock and even death.

Clinical Symptoms Female infants with 21 hydroxylase deficient CAH usually have some degree of virilization (ambiguous genitalia) due to their exposure to excessive androgen levels in utero. Although male infants usually appear normal at birth, they may have an enlarged penis and scrotum with increased pigmentation. Symptoms of salt wasting CAH include frequent urination and, in some cases, poor feeding, which can rapidly progress to vomiting, dehydration, electrolyte changes and cardiac arrhythmia. **Infants with CAH who are not diagnosed and treated early are particularly susceptible to sudden death in the first few weeks of life.** In older children, CAH may result in rapid growth and precocious puberty with premature skeletal maturation.

Newborn Screening and Definitive Diagnosis In Illinois, newborn screening for CAH due to 21-hydroxylase deficiency is by fluorometric assay to measure the 17 hydroxy (OH) progesterone level. False positive and false negative results are possible with this screening. Specimen collection prior to 24 hours of age, prematurity and illness can affect this screening, as physiological stress can cause a normal elevation of the 17-OH progesterone level. Treatment with hydrocortisone or dexamethasone may result in false negative screening results. **Infants with a presumptive positive screening test (seriously elevated 17-OH progesterone level) require prompt follow-up and, when notified of these results, the clinician should *immediately* check on the clinical status of the baby and refer the infant to a pediatric endocrinologist.** Measurement of serum 17-OH progesterone level and serum electrolytes is also recommended. Suspect abnormal (moderately elevated 17-OH progesterone) results require repeat filter paper screening as soon as possible. The seriousness of CAH requires additional testing for **all** abnormal test results, although monitoring of pre-term or sick neonates in a neonatal intensive care setting may be at the discretion of the neonatologist.

Treatment Treatment for CAH includes lifetime daily medication. Oral hydrocortisone in children, and prednisone or dexamethasone for older individuals, replaces missing cortisol. Hydrocortisone is usually given at regular intervals three times a day. In cases of salt wasting CAH, in addition to hydrocortisone, fludrocortisone is prescribed to correct aldosterone deficiency. Infants and small children with salt wasting CAH also may require salt tablets as a dietary supplement. Regulation of medication dosage is vital, as improper dosage can result in either growth delay or premature bone epiphyseal closure. Female infants with ambiguous genitalia may require re-constructive surgery.

Incidence Congenital adrenal hyperplasia occurs in one of every 15,000 births. Illinois began screening for CAH in 1987 and has since identified more than 190 cases. On average, 10-15 new CAH cases are identified each year.

Inheritance Pattern The vast majority (90 percent) of CAH cases result from 21-hydroxylase deficiency. The only form of CAH detected by newborn screening, 21-hydroxylase deficiency is inherited in an autosomal recessive pattern. As with other autosomal recessive disorders, the parents of a child with CAH are unaffected, healthy carriers of the condition and have one normal gene and one abnormal gene. With each pregnancy, carrier parents have a 25 percent chance of having a child with two copies of the abnormal gene, resulting in CAH. Carrier parents have a 50 percent chance of having a child who is an unaffected carrier and a 25 percent chance of having an unaffected, non-carrier child. These risks hold true for each pregnancy. All siblings of infants diagnosed with congenital adrenal hyperplasia should be tested; genetic counseling services should be offered to the family.

Physiology The adrenal gland converts cholesterol into glucocorticoids (cortisol), mineral corticoids (aldosterone) and sex hormones (androgens, estrogens and progestins) in response to ACTH stimulation by the pituitary gland. **Cortisol**, the body's stress hormone,

controls protein and carbohydrate metabolism and is vital to the body's response to physiological stresses, such as infection, surgery or trauma. **Aldosterone** helps to maintain the body's fluid and electrolyte balance by promoting sodium reabsorption and potassium excretion within the kidneys. **Androgen**, the male sex hormone, helps to control growth and sexual development. Prior to 12 weeks gestation, fetal genital tissues are alike in both males and females. At 12-14 weeks, androgens from the testes in a male fetus result in normal male genital development. In CAH, excess cortisol precursor is converted to excess androgen. In females, this excess androgen exposure in utero results in virilization of the external genitalia.

Infants with CAH may very quickly develop adrenal insufficiency, hypoglycemia, metabolic acidosis, dehydration and shock. There are two classifications of CAH due to 21 hydroxylase deficiency: **simple virilizing CAH**, with cortisol deficiency, and **salt wasting CAH**, with both cortisol and aldosterone deficiency. Salt wasting CAH may result in severe dehydration with electrolyte imbalance (hyponatremia and hyperkalemia). In both forms of CAH, there is excess androgen production, which may cause precocious puberty.

Key Points for Parents Avoid overly alarming the child's parents if the diagnosis of CAH has not yet been confirmed. If the child needs additional testing or diagnostic evaluation, make certain that the parents understand the importance of following the pediatrician's and/or specialist's recommendations for additional testing and referrals.

Follow-up After Confirmation of Diagnosis These guidelines should be followed after a diagnosis of congenital adrenal hyperplasia has been confirmed:

1. Parents should understand that treatment is lifelong and that compliance with medication and frequent blood monitoring are imperative to the child's health, growth and development. **Although children with CAH are usually healthy, any illness (for example, fever, vomiting or injury) requires prompt notification of the child's physician, as the cortisol dosage may need to be increased. In addition, parents should keep injectable hydrocortisone on hand at all times. If the child has repeated vomiting or is unable to hold down fluids, parents should call the specialist immediately. In emergencies, parents must be prepared to administer injectable hydrocortisone if instructed to do so by the physician.** Children and adolescents with CAH should wear medical identification bracelets or necklaces to alert health care providers to his/her condition and to insure proper medication is provided in an emergency
2. Parents should understand that treatment is not curative and that all morbidity cannot necessarily be prevented. Long-term management, monitoring and compliance with treatment recommendations are essential to the child's well-being. A multidisciplinary approach is recommended and should include the following specialties: pediatrics, endocrinology and, in some cases, pediatric reconstructive surgery. Infants and children with congenital adrenal hyperplasia should have regular follow-up appointments with a pediatric endocrinologist to regulate medication regimens.
3. Genetic counseling services are recommended. A list of genetic counselors and geneticists, whose services are available through the Illinois Department of Public Health, should be given to the parents if they have not already seen a geneticist.
4. Provide a list of available support services within the community, such as the local health department and Early Intervention service providers.
5. Additional information about newborn screening can be found at:
 - Baby's First Test: <http://www.babysfirsttest.org/>
Health Resource and Service Administration (HRSA), Grant no. U36MC16509, Quality Assessment of the Newborn Screening System.
 - National Center for Biotechnology Information: <http://www.ncbi.nlm.nih.gov/gtr/>
National Center for Biotechnology Information, U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda MD, 20894 USA.