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GENOMICS

Congenital Adrenal Hyperplasia

Background

The deficiency in one of the five enzymes required in the steroidogenic pathway for the biosynthesis of cortisol (hydrocortisone) results in a group of diseases known collectively as Congenital Adrenal Hyperplasia (CAH). The diseases are inherited as autosomal recessive disorders. As a result of impaired cortisol synthesis by the adrenal cortex, there is excessive secretion from the pituitary of adrenocorticotropic hormone (ACTH), or corticotrophin, which stimulates the adrenal cortex to synthesize and secrete more cortisol. ACTH stimulation causes diffuse hyperplasia of the adrenal gland, and usually the disease is recognized in infancy. Greater than 90% of cases of CAH are caused by reduced or absent activity of the steroid 21-hydroxylase enzyme, known as CYP21, or Classic CAH. This form of CAH presents in early infancy, early childhood or adoles-cence, depending upon the magnitude of the deficient enzyme activity. In severe cases, very low CYP21 activity causes low aldosterone secretion, salt loss and hypovolemia. Combined with hypotension and hypoglycemia from cortisol deficiency, this results in neonatal death during the first month of life if not recognized and adequately treated. Because the androgen synthetic pathway does not require CYP21 activity, there is excess androgen secretion, and virilization in the female fetus causing varying degrees of sexual ambiguity at birth.

Clinical

Male infants with CAH are normal at birth. In severe cases, salt wasting becomes evident within 7-10 days. By 2-3 weeks, failure to thrive, unexplained vomiting, poor feeding, hypovolemia and shock develop. The same sequence of symptoms develops in untreated female infants with CAH, but virilization with sexual ambiguity at birth leads to an early diagnosis of CAH and adequate treatment in many patients. However, complete female virulization presents at birth with the clinical phenotype of a male infant with bilateral cryptorchidism. In this presentation, the diagnosis of CAH may be missed and the incorrect sex assigned. Approximately 75% of children with classic CAH have the salt-losing CAH. Milder forms of CAH, the so-called Simple Virilizing CAH, have normal aldosterone secretion and present with virilization in infant girls, but the diagnosis in boys may not be evident until childhood when androgen excess causes sexual precocity without testicular enlargement. Late diagnosis is associated with markedly advanced skeletal maturation and accelerated linear growth initially, but early natural puberty and ultimately short stature. In the mildest form of CAH (attenuated, or late onset 21-hydroxylase deficiency), both cortisol and aldosterone secretion are normal, but at the expense of chronic mild-to-moderate excess production of androgenic hormones. These children present in childhood or adolescence with early onset of sexual hair (premature pubarche) and/or hirsuitism, oligomenorrhea and acne in females, or infertility in both sexes.

Testing

The immediate steroid precursor in classic CAH and the substrate for CYP21 is 17-hydroxyprogesterone (17-OHP). The measurement of 17-OHP in the newborn blood spot can discriminate infants with salt-wasting or Simple Virilizing CAH from non-affected infants. The newborn screening test usually does not detect attenuated or late onset non-classical CAH patients. When values exceed the normal range, 17-OHP analysis is repeated using organic extraction to remove interfering substances. The normal values for 17-OHP vary with birth weight and gestational age, and cutoffs should be adjusted accordingly.

Serum confirmation tests include a repeat 17-OHP value, other steroid precursors to be certain that a mildly elevated 17-OHP is not caused by another form of CAH (e.g.,11-hydroxylase deficiency), and tests related to salt loss, such as serum Na and K, and renin activity. Confirmatory DNA testing is also available.

Treatment

Oral hydrocortisone in a physiologic replacement dose is the treatment of choice for CAH. The more potent glucocorticoids are contraindicated in the growing child and adolescent because of the difficulty in determining a physiologic versus pharmacologic dose. In children with salt-losing CAH, 9·-fluorohydrocortisone should maintain normal electrolyte balance without excessive natriuretic or glucocorticoid effects. Monitoring plasma 17-OHP and androstenedione levels, growth velocity, and an occasional bone age offer the basic tools for adequate, effective therapy.

Because the tests to select and interpret at the time of initial diagnosis and during therapy are often complex, the pediatrician is advised to manage the patient with CAH in close collaboration with a consulting pediatric endocrine specialist. It is recommended that parents travel with a letter of treatment guidelines from the patient's physician, and the child should wear a bracelet or necklace for emergency identification that they are Cortisol deficient.

Inheritance

The forms of CAH are each inherited as autosomal recessive diseases. DNA carrier testing of families and prenatal diagnostic testing is available. Early identification of affected fetuses is important to avoid virilization of female infants. For families at risk for an affected child, oral dexamethasone is started as early in pregnancy as possible after pregnancy is diagnosed. If started before six weeks of fetal life, virilization is prevented or considerably limited. Once the sex of the fetus is determined, maternal therapy can be discontinued for a male fetus; once DNA tests of the female infant are known, maternal therapy can be discontinued for an unaffected female fetus.

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