Congenital Adrenal Hyperplasia

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Outcome without screening:
Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that results from diminished synthesis of cortisol by the adrenal glands. In 75% of cases, there is also diminished synthesis of aldosterone. The clinical consequences are shock, hypoglycemia, and circulatory collapse from the cortisol deficiency, and salt wasting and dehydrated from aldosterone deficiency. In addition, adrenal androgen production is increased and the genitalia of affected females are masculinized *in utero*, often making them appear to be of indeterminate gender at birth or even to resemble males with undescended testes.

The indications for newborn screening for this disorder are compelling: the salt wasting adrenal crisis that is precipitated by cortisol and aldosterone deficiency typically does not begin until at least 5 days of life, and the non-specific symptoms of this life-threatening state are often misdiagnosed, resulting in unacceptable mortality. Appropriate therapy is often delayed or never given. Vomiting also ensues as another consequence of cortisol deficiency, but is often misdiagnosed as a metabolic disorder, an infection, or an anatomic problem, such pyloric stenosis or gastroesophageal reflux. With aldosterone deficiency, there is excessive loss of sodium in the urine, and the development of low serum sodium and elevated potassium.

Because of their genital virilization, girls with CAH are more often identified before the symptoms of salt-wasting and shock appear. Excessive androgens can result in enlargement of the clitoris and rugation of the labia in females so that they resemble a scrotum. In severely affected cases, the clitoris and urethra can be so virilized as to resemble a normal penis. These girls can be misassigned as cryptorchid males, and the diagnosis of CAH potentially delayed. More commonly, the degree of virilization is intermediate, so that appropriate gender assignment is questioned, and the diagnosis of CAH is entertained. Male infants, in whom no discernable physical changes are evident, are far more likely to be undiagnosed and die.

Incidence:
The incidence of 21-hydroxylase deficiency varies considerably depending on the ethnic origins of the local population. In western cultures, the incidence of this disorder varies from 1 in 5,000 births in Switzerland to 1 in 67,00 births in Maryland. The frequency among Yup'ik Eskimos in Western Alaska is between 1 in 280 and 1 in 684.

Outcome with screening:
Surveys at academic medical centers in the era before newborn screening for CAH clearly documented a preponderance of female patients with CAH, when the genetics of the condition would predict a 1:1 ratio. The implication of these surveys is clear: that males with this disorder were not diagnosed and presumably died. After the widespread adoption of CAH screening, however, a review of 29 programs from 13 countries concluded that newborn screening led directly to the diagnosis of CAH in 70% of cases; the other 30% having been clinically

suspected before screening results were known. The ratio of males to females diagnosed with CAH in newborn screening programs is the expected 1:1.

Causes of congenital adrenal hyperplasia:
A number of separate genetic disorders comprise CAH, each one resulting from a defect in the activity of a distinct enzyme required for cortisol synthesis. The adrenal gland products three classes of steroid hormones: glucocorticoids, principally cortisol; *mineralocorticoids*, principally aldosterone; and *androgens*. Depending on the location or severity of the enzymatic block, mineralocorticoid production may or may not be affected (saltwasting or non-saltwasting forms), and androgen output could either be augmented or diminished (virilizing or feminizing forms). The name of the condition derives from the fact that with low cortisol output, the pituitary gland secretes massive amounts of ACTH causing the adrenal glands to hypertrophy. There is a flow of precursor steroids into androgen-synthesizing pathways, which are unaffected by the enzymatic block.

The most common form of CAH results from diminished activity of the 21-hydroxylase enzyme: 90% of cases result from this deficiency, and *this is the only form detected by newborn screening methods.* The cortisol precursor, 17-hydroxyprogesterone (17-OHP), accumulates to high levels because of the enzymatic block. Serum measurements of 17-OHP are generally used to diagnose 21-hydroxylase deficiency.

A second form of CAH, accounting for less than 5% of cases, results from 11-hydroxylase deficiency; the precursor that accumulates to the highest levels in this disorder is 11-deoxycortisol, also called compound S. Children with 11-hydroxylase deficiency tend not to waste salt, and may actually retain sodium and become hypertensive.

Much rarer forms of CAH involve enzymatic steps that are crucial to the synthesis of androgen hormones. Rather than resulting in virilized female infants, these conditions result in male infants whose external genitalia are female or indeterminate because of inadequate testosterone production during critical periods *in utero*. These disorders are not detected in screening programs measuring 17-OHP such as those used in Tennessee.

Treatment:
Infants in adrenal crises require intensive management with intravenous fluids, glucose, and cortisol. Chronic management of infants with CAH is complex and should include the close involvement of a pediatric endocrinologist. Medical management includes provision of cortisol or other glucocorticoid, and in saltwasting individuals, a mineralocorticoid, 9 -flurocortisol (Florinef) as well as supplemental sodium chloride. Treatment is lifelong. Salt craving characterizes many of these individuals their whole life. In situations of metabolic stress such as fever, major trauma, or the need for anesthesia, individuals with CAH will require a doubling or tripling of their daily glucocorticoid dose to compensate for the fact that they can not generate the increased cortisol secretion that is required of normal adrenal glands under periods of metabolic stress.

Although the uterus, ovaries, and fallopian tubes are present, the internal genitalia of affected female children are also altered by adrenal andorgens, and reconstructive surgery may be required to generate an introitus for the vagina. Reconstruction of the external genitalia is often performed to restore female anatomy.

Screening tests and confirmation:

Screening for 21-hydroxylase deficiency is accomplished by measuring 17-OH progesterone on filter paper blood specimens. Confirmation is made on a serum sample analyzed at an appropriate reference laboratory. Optimal measurement of 17-OHP involves organic extraction and chromatographic separation of the serum sample to remove cross-reacting steroid molecules. Genetic testing for some of the multiple mutations in the 21-hydroxylase gene is available as well.

Special Concerns and Issues:
Newborn screening measurements of 17 OH progesterone will identify only children with the 21-hydroxylase form of CAH. In some instances, infants with 11-hydroxylase deficiency will have sufficient elevation of 17 OH progesterone to be detected, although 11-deoxycortisol levels are significantly higher. Placental production results in elevated levels of 17-OHP in normal newborns within the first 24 hours of life. These levels may overlap with the pathologic levels of 21-hydroxylase deficiency; so that screening specimens are ideally obtained after the first 24 hours. Cutoff values are significantly higher in preterm infants than in term infants. Some infants with CAH, especially the non-salt wasting forms, have only modest elevations in 17 OH progesterone on their initial screen and may escape detection. Only later do their hormone levels rise into clearly diagnostic range. To find those individuals some states have mandated a second screen of 17-OH progesterone between one and four weeks of age. Older infants with suggestive physical findings or symptoms should be retested for CAH, regardless of the newborn screening results.