CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) is a family of inherited disorders of the adrenal cortex that impair steroidogenic enzyme activity essential for cortisol biosynthesis.[20,21] Newborn screening focuses exclusively on the most common 21-hydroxylase (21-OH) deficiency CAH (>90% of all CAH cases [OMIM database No. 201910]),[22] which impairs production of cortisol and often aldosterone.[20,21] Prompt diagnosis and treatment of CAH is essential to prevent potential mortality as well as physical and emotional morbidity.[20–23]

Incidence

Health organizations in 13 countries (including 36 US states) screen or will screen for CAH in their newborn screening programs. On the basis of newborn screening data, the incidence of CAH ranges from a low of 1 in 21270 (New Zealand) to a high of 1 in 5000 (Saudi Arabia) live births.[24] The incidence is 1 in 15981 live births (Hispanic > American Indian > white > black > Asian) in North America, 1 in 14970 live births in Europe, and 1 in 19111 live births in Japan.[25] An exceedingly high CAH incidence (1 in 282 live births) exists among Yupik Eskimos in western Alaska.[26]

Clinical Manifestation and Variability

The spectrum of disease in CAH ranges from the "classic, severe" salt-wasting (SW) form, to "classic, less severe" simple-virilizing (SV), to "mild, nonclassic" forms.[20,21]

Symptomatic Presentation and Morbidity

Neonates with the SW form exhibit adrenal crisis during the first through fourth weeks of life, peaking at approximately 3 weeks of age. This manifests as poor feeding, vomiting, loose stools or diarrhea, weak cry, failure to thrive, dehydration, and lethargy. These symptoms may not be evident until serum sodium concentrations are below 125 mEq/L. If untreated, circulatory collapse, shock, and death are inevitable. Permanent brain injury attributable to shock, lower cognitive scores, and learning disabilities are observed in some with the SW form.[20] Affected females have ambiguous genitalia (AG) (but normal internal reproductive anatomy), prompting a clinical diagnosis in many. Affected males have no obvious physical signs of CAH. Therefore, without newborn screening and in the absence of a positive family history, all male and a minority of female neonates are undiagnosed until adrenal crisis. The SW form affects approximately 70% of patients with CAH that is diagnosed through newborn screening programs.[25,26] If inadequately treated, postnatal virilization (girls), pseudo- or true-precocious puberty (boys), and premature growth acceleration (boys and girls) occur, leading to early growth cessation.[20–23] Patients with the SV form do not manifest adrenal-insufficiency symptoms unless subjected to severe stress but exhibit virilization as in patients with SW.[20,21] Males and some females with the SV form are not diagnosed until much later when symptoms of virilization, precocious pseudopuberty, or growth acceleration occur.[20–23] The markedly advanced skeletal age of patients with the SV form diagnosed late contributes to their short adult stature. Late discovery of incorrect male sex assignment in females with the SW and SV forms causes extreme distress to the family and matured patients. Mild 21-OH deficiency produces no symptoms at birth and manifests as premature sexual hair, acne, and mild growth acceleration in childhood and hirsutism, excessive acne,

menstrual disorder, and infertility later in life.[20,21] This milder disorder may be missed by newborn screening programs.

Mortality

The mortality rate for infants with the SW form not detected through newborn screening was 11.9%, which was fivefold higher than that of the general population (2.29%).[23]

Pathophysiology

21-OH deficiency results in cortisol deficiency with or without aldosterone deficiency. Cortisol deficiency from early fetal life leads to increased adrenocorticotropic hormone (ACTH) secretion,[20,21] which then stimulates excess secretion of the precursor steroids including 17-OH-progesterone (17-OHP) and causes hyperplastic changes of the adrenal cortex.[20,21] The precursor steroids can only be metabolized by way of the androgen biosynthetic pathway, resulting in excess androgen production that virilizes the genitalia.[20,21] Aldosterone deficiency contributes to SW. The increased circulating 17-OHP concentration is diagnostic for 21-OH deficiency.

Inheritance and Genotype

21-OH deficiency is an autosomal recessive disorder caused by a mutation of the *CYP21* gene.[20,21] There is an active *CYP21* gene and an inactive pseudo-*CYP21P* gene in normal individuals. Both genes are in the HLA complex on chromosome 6p21.3.[20,21] Most mutations in the *CYP21* gene are the pseudogene sequences, suggesting that the mutations in *CYP21* were caused by a gene conversion or recombination between *CYP21* and *CYP21P*. The genotypes from 5 different populations of individuals with CAH correlated well with the phenotype in approximately 90% of affected subjects but did not correlate well in the remaining patients.[21]

Rationale for and Benefits of Newborn Screening

The goals of newborn screening are to (1) prevent life-threatening adrenal crisis, thereby averting shock, brain damage, and death, (2) prevent male sex assignment for life in virilized female newborns, and (3) prevent progressive effects of excess adrenal androgens, which cause short stature and psychosexual disturbances in boys and girls. Kovacs et al[23] found the average serum sodium concentration at diagnosis of the SW form of CAH to be 135 mEq/L in individuals detected through newborn screening programs and 125 mEq/L in those detected after development of clinical symptoms. Thus, prevention of severe SW CAH by newborn screening was demonstrated. Worldwide newborn screening data showed that screening prompted early diagnosis of CAH before clinical suspicion in 67% of newborn infants with CAH, including many females with AG.[26] The mortality rate of individuals with CAH identified through newborn screening has not been established yet. Other newborn screening benefits include (1) improved case detection evidenced by twofold higher incidence versus that of case-survey reports (North America and Japan), (2) improved detection of patients with SW CAH (70% with newborn screening vs 43%–60% in patients with clinical symptoms), and (3) improved detection of males, as evidenced by a 1:1 sex ratio in subjects identified through newborn screening versus a male/female ratio of 0.6:1 in patients with clinical symptoms leading to diagnosis.

Screening

Screening for 21-OH deficiency is accomplished by measurement of 17-OHP concentration in the dried blood spot. Newborn screening for CAH requires a rapid process to prompt the diagnosis before the onset of SW symptoms. Sampling at less than 1 day is associated with a high rate of false-positive results, and sampling beyond 5 to 7 days of age reduces the benefit of screening. Normal preterm infants have higher concentrations of 17-OHP than do term infants; therefore, it is important to have 17-OHP reference concentrations in blood spots of preterm and term unaffected infants according to birth weight or gestational age.[27,28] 17-OHP is not influenced if drawn several hours after transfusion.

Dissociation-enhanced lanthanide fluorescence immunoassay, radioimmunoassay, and enzyme-linked immunosorbent assay with a commercial kit are used to measure 17-OHP concentrations in blood spots.[25,26] The screening 17-OHP assays are nonspecific, and the result on a screening study is not equivalent to the diagnostic serum concentrations.[21,26,29] Affected neonates had screening 17-OHP concentrations of 35 to 900 ng/mL of blood, with preterm infants having higher concentrations.[27,29]

MS/MS may have the advantage of rapid 17-OHP detection and may eliminate the variable 17-OHP cutoff concentrations influenced by different reagents/assays. However, comparative studies of immunoassays versus MS/MS are necessary, and because of the complexity of the MS/MS assay for 17-OHP detection, MS/MS may be used as a complementary test. *CYP21* genotyping is not currently used in newborn screening, but it may be helpful in uncertain cases and for genetic counseling.

Almost all neonates with SW CAH have been identified with the first sample test.[26] Newborn screening for CAH is not intended to detect mild cases, although some are detected. In a study performed in Texas, testing again at 1 to 2 weeks increased detection of SV CAH and the mild form.[29] Despite the birth weight- or age-adjusted 17-OHP cutoff concentrations, preterm birth or low birth weight and samples taken at less than 1 day of age are major factors for false-positive results.[24–30] In an international study, 7% of neonates later determined to have CAH (mostly the SV form) were not detected in newborn screening for a variety of reasons (human error, prenatal dexamethasone therapy, or high 17-OHP cutoff concentrations).[25]

Follow-up and Diagnostic Testing

In most newborn screening programs, 2-tiered 17-OHP cutoff concentrations are established to guide evaluation in term and preterm newborn infants. Exceptionally high (urgent) and moderately high (suspected) 17-OHP concentrations are reported. Pediatricians need to be familiar with these concentrations as reported by their local newborn screening program. Most newborn screening programs that screen for CAH report the presumed positive results with instructions. Immediate evaluation (serum electrolytes, 17-OHP) is necessary in newborn infants with AG, in sick or asymptomatic male newborn infants with urgent or suspected 17-OHP concentrations, and in sick female infants with urgent 17-OHP concentrations. The evaluation is necessary in asymptomatic normal female infants with urgent 17-OHP concentrations and in sick female infants with normal genitalia and suspected 17-OHP concentrations, but these newborns are at low risk of having SW CAH. Normal females with suspected 17-OHP

concentrations are not at risk of SW CAH but need at least a second screening to be sure that a mild deficiency is not missed.

Diagnosis

Quantitative serum 17-OHP concentration is used for the diagnosis of CAH. Concentrations are generally higher in individuals with the SW form.[29] Care must be taken to use the appropriate term or preterm normal values for comparison.[26] With age, serum 17-OHP concentrations decrease in unaffected neonates but increase in those with CAH.[30] Concentrations in neonates with SW and SV CAH are higher than the concentrations in infants with the mild form.[21,29] In neonates with mildly elevated 17-OHP concentrations (4–10 ng/mL), the ACTH-stimulation test helps to rule out nonclassic CAH.[20,21] In asymptomatic infants, serial evaluation of electrolytes throughout the neonatal period is necessary if serum electrolyte concentrations remain normal.

Brief Overview of Disease Management

Treatment for CAH involves replacement of cortisol, which suppresses increased ACTH, 17-OHP, and androgen secretion. Replacement of aldosterone with an analog of mineralocorticoid (Florinef) is required for patients with SW CAH. Adequate medical therapy restores normal energy, glucose and electrolyte concentrations, and fluid balance and prevents excess adrenal androgen effects. Special medical care is needed in case of stress. The rate of mortality is 4.3% for treated patients.[23] In virilized female infants, surgical correction is generally performed before 1 year of age and, if necessary, again before menarche. With standard glucocorticoid therapy, adults with classic CAH do not always reach their genetic potential for height, and obesity is common. Inadequate medical therapy causes infertility. Experimental antiandrogenic/antiestrogenic drug therapy to improve height outcome is ongoing in children with CAH. Adrenalectomy is recommended when medical therapy is ineffective.

Carrier testing for CAH is performed most accurately using *CYP21* genotyping.

Pregnant women known to be at risk of having a fetus with CAH can receive prenatal dexamethasone therapy. First-trimester prenatal diagnosis is indicated for these women. An elevated 17-OHP concentration in amniotic fluid by a specific assay (>6–18 ng/mL) is also diagnostic, but normal concentrations do not exclude SV or nonclassic forms of CAH, and concentrations may be normal in mothers who are on dexamethasone therapy. Prenatal treatment is only indicated for female fetuses with classic virilizing CAH. Maternal dexamethasone therapy at 20 µg/kg per day beginning at 5 to 8 weeks' fetal age prevents or reduces AG in most affected females.[31] Controversy regarding prenatal therapy is related to the fact that (1) this treatment must begin before fetal sex can be determined or CAH diagnosis can be made, and 7 of 8 fetuses are thus unnecessarily subjected to this therapy, and (2) long-term safety of early exposure to dexamethasone in utero is unproven to date.[31] Maternal adverse effects include cushingoid features of excessive weight gain, intense striae, edema, discomfort, and emotional instability. In a consensus meeting concerning prenatal CAH therapy, representatives from the US Lawson Wilkins Pediatric Endocrine Society and European Pediatric Endocrine Society recommended that designated teams undertake this specialized therapy using a national protocol approved by institutional review boards.

Treatment is preceded by informed consent about the risks and benefits of the therapy, and prospective follow-up and evaluation are needed.[31]

Current Controversy

The major controversy regarding newborn screening for CAH is the cost and impact of evaluating those whose test results are false-positive.[32] A second issue is the use of prenatal dexamethasone therapy for CAH. A large national multicenter study on long-term cognitive and psychological development and other health-related outcomes is required to resolve this issue.

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