

Congenital Adrenal Hyperplasia - CAH

Clinical Background

Congenital adrenal hyperplasia is an uncommon autosomal recessive genetic disorder that is caused by several distinct enzymatic defects, usually with subsequent virilization.

Epidemiology

- Incidence – most common adrenal disorder of infancy and childhood (1/3,000-5,000)
- Sex – M>F
- Ethnicity – more frequent in eastern European Jews (1/27 affected with nonclassical 21-hydroxylase deficiency)

Risk Factors

- Genetic
 - Enzymatic defects include:
 - 21-hydroxylase (*CYP21A2*), 11-beta-hydroxylase (*CYP11B1*), 17-*CYP17* alpha-hydroxylase/17,20-lyase, 3 beta-hydroxysteroid dehydrogenase (3 beta HSD) and the very rare mitochondrial cholesterol side chain cleavage enzyme (P450scc)
 - Mutations cause a block in adrenal glucocorticoid and mineralocorticoid synthesis
 - 21-hydroxylase deficiency is the most common defect (90%)

Pathophysiology

- 21-hydroxylase
 - Blocked steroid synthesis causes adrenal insufficiency and compensatory elevation of adrenocorticotrophic hormone (ACTH)
 - ACTH elevation causes adrenal hyperplasia and additional precursor synthesis
 - Precursor excess is shunted into the androgen synthesis pathway, causing virilization in females, premature sexual development in males and adrenal insufficiency
- 11-beta-hydroxylase
 - Impaired conversion of 11-deoxycortisol to cortisol
 - Accumulation of 11-deoxycorticosterone (a potent mineralocorticoid)
 - Leads to mineralocorticoid excess with possible hypertension
- 17-alpha-hydroxylase/17, 20 lyase
 - Rare disorder
 - Decreased cortisol production and shunting of precursors into mineralocorticoid pathways
 - Minimal testosterone or estrogen made

Clinical Presentation

- 21-hydroxylase
 - Classical
 - Ambiguous genitalia (female), males do not have genitalia ambiguity
 - Premature sexual development (male)
 - Salt wasting in about 75% (hyperkalemia, hyponatremia, dehydration)
 - Nonclassical
 - Hirsutism
 - Irregular menses (female)

- Short stature
- Acne
- Infertility
- Alopecia
- 11-beta-hydroxylase
 - Premature sexual development (male), hypertension and hypokalemia
- 17-alpha-hydroxylase
 - Hypertension, hypokalemia, hypogonadism, lack of secondary sexual characteristics in females and males
- 3 beta-HSD2
 - Feminized male, partial virilization of female
- Mitochondrial cholesterol side chain cleavage enzyme (P450scc)
 - Very rare disorder

Treatment

- Steroids to suppress pituitary ACTH secretion
 - May require both gluco- and mineralocorticoid therapy

Diagnosis

- Indications for testing – ambiguous genitalia in infancy; premature sexual development in older children; hirsutism and irregular menses in adult females
- Laboratory testing
 - Initial screen is 17 hydroxyprogesterone (17-OHP)
 - If elevated, perform ACTH stimulation (cosyntropin) but often is unnecessary with marked elevation of 17-OHP
 - If nonclassical form is suspected in adult female, obtain 17-OHP as 8 am value during follicular point of cycle
 - Infants – karyotype to rule out chromosomal disorder
 - Adrenal steroid quantitative panel if ACTH stimulation is abnormal
 - 21-hydroxylase
 - Plasma 17-hydroxyprogesterone markedly increased
 - 11-beta-hydroxylase
 - 11-deoxycorticosterone and 11-deoxycortisol levels increased
 - 17-hydroxylase (17-OH)
 - Elevated pregnenolone
 - Decreased 17-hydroxypregnenolone (17-OH-pregnenolone)
 - 3-beta-hydroxysteroid dehydrogenase deficiency
 - Elevated pregnenolone, 17-OH pregnenolone, DHEA and DHEAS

Differential Diagnosis

- Hirsutism, irregular menses
 - Polycystic ovarian syndrome (PCOS)
 - Cushing syndrome
 - Androgen-secreting tumor
- Salt wasting
 - Adrenal insufficiency
- Ambiguous genitalia

- Maternal hyperandrogenism
- Androgen-secreting tumor
- Chromosomal abnormality
- Premature sexual development
 - Premature adrenarche
 - Androgen-secreting tumor
 - Cushing syndrome

Screening

- Newborn screening in most states (17-OHP)
 - False positives common in premature infants (tend to have elevated 17-OHP)
 - Need to follow-up positive results with ACTH stimulation in all infants unless 17-OHP is markedly elevated
 - Results value for positive tests is set relatively low to prevent missing true positives
- Prenatal diagnosis – via chorionic villus sampling (CVS), amniocentesis is about 90-95% sensitive
 - Allows for prenatal treatment of disease through maternal glucocorticoid treatment

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Congenital Adrenal Hyperplasia Treatment Panel 2002029 Method: Liquid Chromatography/Tandem Mass Spectrometry	Initial screening test for CAH, both classical and nonclassical Components include androstenedione; 17-hydroxyprogesterone quantitative by LC-MS/MS; and testosterone, females or children		
CAH 11-Beta Hydroxylase Deficiency Panel 2002282 Method: High Performance Liquid Chromatography/Tandem Mass Spectrometry	Screen for increased 11-deoxycortisol levels Components include androstenedione; 17-hydroxyprogesterone; testosterone; 11-deoxycortisol, quantitative by LC/MS-MS; and dehydroepiandrosterone		
CAH 21 Hydroxylase Deficiency Panel 2002283 Method: High Performance Liquid Chromatography/Tandem Mass Spectrometry	Screen for 17-hydroxyprogesterone increase Components include androstenedione; 17-hydroxyprogesterone; 17-hydroxypregnenolone, quantitative by LC-MS/MS; and dehydroepiandrosterone		

Adrenal Steroid Quantitative Panel by LC-MS/MS, Serum or Plasma 0092330 Method: Tandem Mass Spectrometry	Detect enzyme deficiencies that result in congenital adrenal hyperplasia Component serum tests are 11-deoxycortisol quantitative; 17-hydroxyprogesterone quantitative by MS/MS; 17-hydroxypregnenolone quantitative by MS/MS, and pregnenolone by MS/MS		
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Additional Tests Available

Test Name and Number	Comments
17-Hydroxyprogesterone 0070005 Method: Radioimmunoassay	Detect enzyme deficiencies that result in congenital adrenal hyperplasia
11-Deoxycortisol Quantitative by LC-MS/MS, Serum or Plasma 0092331 Method: Tandem Mass Spectrometry	Detect enzyme deficiencies that result in congenital adrenal hyperplasia
Deoxycorticosterone 0099731 Method: Radioimmunoassay/Chromatography	Detect enzyme deficiencies that result in congenital adrenal hyperplasia
Pregnenolone by LC-MS/MS, Serum or Plasma 0092334 Method: Tandem Mass Spectrometry	Detect enzyme deficiencies that result in congenital adrenal hyperplasia
17-Hydroxyprogesterone Quantitative by LC-MS/MS, Serum or Plasma 0092332 Method: Tandem Mass Spectrometry	Detect enzyme deficiencies that result in congenital adrenal hyperplasia
17-Hydroxypregnenolone Quantitative by LC-MS/MS, Serum or Plasma 0092333 Method: Tandem Mass Spectrometry	Detect enzyme deficiencies that result in congenital adrenal hyperplasia

Guidelines

Clayton PE, Miller WL, Oberfield SE, Ritzen EM, Sippell WG, Speiser PW. Consensus statement on 21-hydroxylase deficiency from the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society. *Horm Res.* 2002; 58 (4) :188-195.

General References

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References from the ARUP Institute for Clinical and Experimental Pathology®

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