

Overview

Useful For

Diagnosis of suspected 11-hydroxylase deficiency, including the differential diagnosis of 11 beta-hydroxylase 1 (CYP11B1) versus 11 beta-hydroxylase 2 (CYP11B2) deficiency, and the diagnosis of glucocorticoid-responsive hyperaldosteronism

Evaluating congenital adrenal hyperplasia newborn screen-positive children, when elevations of 17-hydroxyprogesterone are only moderate, thereby suggesting possible 11-hydroxylase deficiency

Testing Algorithm

See [Steroid Pathways](#) in Special Instructions.

Special Instructions

- [Steroid Pathways](#)

Method Name

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Serum

Specimen Required

Container/Tube:

Preferred: Red top

Acceptable: Serum gel

Specimen Volume: 0.5 mL

Collection Instructions: Morning (8 a.m.) specimen is preferred.

Specimen Minimum Volume

0.4 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	28 days	
	Frozen	28 days	
	Ambient	14 days	

Clinical and Interpretive

Clinical Information

Corticosterone is a steroid hormone and a precursor molecule for aldosterone. It is produced from deoxycorticosterone, further converted to 18-hydroxy corticosterone and, finally, to aldosterone in the mineralocorticoid pathway.

The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineral corticoids, glucocorticoids, and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see [Steroid Pathways](#) in Special Instructions).

Corticosterone is the first intermediate in the corticoid pathway with significant mineral corticoid activity. Its synthesis from 11-deoxycorticosterone is catalyzed by 11 beta-hydroxylase 2 (CYP11B2) or by 11 beta-hydroxylase 1 (CYP11B1). Corticosterone is in turn converted to 18-hydroxycorticosterone and finally to aldosterone, the most active mineral corticoid. Both of these reactions are catalyzed by CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and 18-methyloxidase (also known as aldosterone synthase) activity.

The major diagnostic utility of measurements of steroid synthesis intermediates lies in the diagnosis of disorders of steroid synthesis, in particular congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17 alpha-hydroxylase activity). In cases of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, <3% of cases) and those with the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies might also suffer mineral corticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH, 11-hydroxylase deficiency (<5% of cases) are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticosterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of females or, in milder cases, hirsutism, polycystic ovarian syndrome or infertility, as well as in possible premature adrenarche and pubarche in both genders.

Measurement of the various precursors of mature mineral corticoid and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type, and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions.

Measurement of corticosterone is used as an adjunct to 11-deoxycorticosterone and 11-deoxycortisol (also known as compound S) measurement in the diagnosis of:

- CYP11B1 deficiency (associated with cortisol deficiency)
- The less common CYP11B2 deficiency (no cortisol deficiency)
- The rare glucocorticoid responsive hyperaldosteronism (where expression of the gene *CYP11B2* is driven by the CYP11B1 promoter, thus making it responsive to adrenocorticotrophic hormone: ACTH rather than renin)
- Isolated loss of function of the 18-hydroxylase or 18-methyloxidase activity of CYP11B2

For other forms of CAH, the following tests might be relevant:

-21-Hydroxylase deficiency:

Â - OHPG / 17-Hydroxyprogesterone, Serum

Â - ANST / Androstenedione, Serum

Â - 21DOC / 21-Deoxycortisol, Serum

-3-Beta-steroid dehydrogenase deficiency:

Â - 17PRN / Pregnenolone and 17-Hydroxypregnenolone

-17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities):

Â - 17PRN / Pregnenolone and 17-Hydroxypregnenolone

Â - PGSN / Progesterone, Serum

Â - OHPG / 17-Hydroxyprogesterone, Serum

- DHEA_ / Dehydroepiandrosterone (DHEA), Serum

- ANST / Androstenedione, Serum

Cortisol should be measured in all cases of suspected CAH.

When evaluating for suspected 11-hydroxylase deficiency, this test should be used in conjunction with measurements of 11-deoxycortisol, 11-corticosterone, 18-hydroxycorticosterone, cortisol, renin, and aldosterone.

When evaluating congenital adrenal hyperplasia newborn screen-positive children, this test should be used in conjunction with 11-deoxycortisol and 11-deoxycorticosterone measurements as an adjunct to 17-hydroxyprogesterone, aldosterone and cortisol measurements.

Reference Values

< or =18 years: 18-1,970 ng/dL

>18 years: 53-1,560 ng/dL

Interpretation

In 11 beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will be low (usually <7 microgram/dL for a morning draw). 11-Deoxycortisol and 11-deoxycorticosterone are elevated, usually to at least 2 to

3 times (more typically 20 to 300 times) the upper limit of the normal reference range on a morning blood draw. Elevations in 11-deoxycortisol are usually relatively greater than those of 11-deoxycorticosterone because of the presence of intact 11 beta-hydroxylase 2 (CYP11B2). For this reason, serum concentrations of all potent mineral corticoids (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range. Plasma renin activity is correspondingly low or completely suppressed. Caution needs to be exercised in interpreting the mineral corticoid results in infants younger than 7 days; mineral corticoid levels are often substantially elevated in healthy newborns in the first few hours of life and only decline to near-adult levels by week 1.

Mild cases of CYP11B1 deficiency might require adrenocorticotrophic hormone (ACTH)1-24 stimulation testing for definitive diagnosis. In affected individuals, the observed serum 11-deoxycortisol concentration 60 minutes after intravenous or intramuscular administration of 250 microgram of ACTH1-24 will usually exceed 20 ng/mL, or at least a 4-fold rise. Such increments are rarely, if ever, observed in unaffected individuals. The corresponding cortisol response will be blunted (<18 ng/mL peak).

In CYP11B2 deficiency, serum cortisol concentrations are usually normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone will be elevated, often more profoundly than in CYP11B1 deficiency, while 11-deoxycortisol may or may not be significantly elevated. Serum corticosterone concentrations can be low, normal, or slightly elevated, while serum 18-hydroxycorticosterone and aldosterone concentrations will be low in the majority of cases. However, if the underlying genetic defect has selectively affected 18-hydroxylase activity, corticosterone concentrations will be substantially elevated. Conversely, if the deficit affects aldosterone synthase function primarily, 18-hydroxycorticosterone concentrations will be very high.

Expression of the *CYP11B2* gene is normally regulated by renin and not ACTH. In glucocorticoid-responsive hyperaldosteronism, the ACTH-responsive promoter of CYP11B1 exerts aberrant control over *CYP11B2* gene expression. Consequently, corticosterone, 18-hydroxycorticosterone, and aldosterone are significantly elevated in these patients and their levels follow a diurnal pattern, governed by the rhythm of ACTH secretion. In addition, the high levels of CYP11B2 lead to 18-hydroxylation of 11-deoxycortisol (an event that is ordinarily rare, as CYP11B1, which has much greater activity in 11-deoxycortisol conversion than CYP11B2, lacks 18-hydroxylation activity). Consequently, significant levels of 18-hydroxycortisol, which normally is only present in trace amounts, might be detected in these patients. Ultimate diagnostic confirmation comes from showing directly responsiveness of mineral corticoid production to ACTH1-24 injection. Normally, this has little, if any, effect on corticosterone, 18-hydroxycorticosterone, and aldosterone levels. This testing may then be further supplemented by showing that mineral corticoid levels fall after administration of dexamethasone.

Sex steroid levels are moderately to significantly elevated in CYP11B1 deficiency and much less, or minimally, pronounced, in CYP11B2 deficiency. Sex steroid levels in glucocorticoid-responsive hyperaldosteronism are usually normal.

Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1,000 ng/dL. For the few patients with levels in the range of greater than 630 ng/dL (upper limit of reference range for newborns) to 2,000 or 3,000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly to modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, in particular if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYP11B2 deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful in these cases. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires 11-hydroxylation of 17-hydroxyprogesterone.

Cautions

At birth the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis are activated and all adrenal steroids, including mineral corticoids and sex steroids and their precursors are high. In preterm infants, the elevations can be even more pronounced due to illness and stress. In doubtful cases, when the initial test was performed on a just-born baby, repeat testing a few days or weeks later is advised.

Adrenocorticotrophic hormone (ACTH)1-24 testing has a low, but definite risk of drug and allergic reactions and should, therefore, only be performed under the supervision of a physician in an environment that guarantees the patient's safety, typically an endocrine, or other centralized, testing center.

Interpretation of ACTH1-24 testing in the context of diagnosis of congenital adrenal hyperplasia (CAH) requires considerable experience, in particular for the less common variants of CAH, such as 11-hydroxylase deficiency, or 3-beta-hydroxysteroid dehydrogenase (3beta-HSD) deficiency, for which very few, if any, reliable normative data exist. For the even rarer enzyme defects, such as deficiencies of StAR (steroidogenic acute regulatory protein), 20,22 desmolase, 17a-hydroxylase/17-lyase, and 17-beta-hydroxysteroid dehydrogenase (17beta-HSD), there are only case reports. Expert opinion from a pediatric endocrinologist with experience in CAH should, therefore, be sought.

Clinical Reference

1. Von Schnakenburg K, Bidlingmaier F, Knorr D: 17-hydroxyprogesterone, androstenedione, and testosterone in normal children and in prepubertal patients with congenital adrenal hyperplasia. *Eur J Pediatr* 1980;133(3):259-267
2. Therrell BL: Newborn screening for congenital adrenal hyperplasia. *Endocrinol Metab Clin North Am* 2001;30(1):15-30
3. Collett-Solberg PF: Congenital adrenal hyperplasia: From genetics and biochemistry to clinical practice, part I. *Clin Pediatr* 2001;40:1-16
4. Forest MG: Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Hum Reprod Update* 2004;10:469-485
5. Tonetto-Fernandes V, Lemos-Marini SH, Kuperman H, et al: Serum 21-deoxycortisol, 17-hydroxyprogesterone, and 11-deoxycortisol in classic congenital adrenal hyperplasia: clinical and hormonal correlations and identification of patients with 11 beta-hydroxylase deficiency among a large group with alleged 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 2006;91:2179-2184

Performance

Method Description

The specimen and an internal standard are assayed by liquid chromatography-tandem mass spectrometry. The analyte is detected by multiple-reaction monitoring. (Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Tuesday; 10 a.m.

Analytic Time

3 days

Maximum Laboratory Time

9 days

Specimen Retention Time

14 days

Performing Laboratory Location

Rochester

Fees and Codes**Fees**

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact [Customer Service](#).

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

82528

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
CORTC	Corticosterone, S	2139-4

Result ID	Test Result Name	Result LOINC Value
88221	Corticosterone, S	2139-4