MAYO CLINIC LABORATORIES

Test Definition: DOCS

11-Deoxycorticosterone, Serum

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

Diagnosis of glucocorticoid-responsive hyperaldosteronism

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

Special Instructions

- Steroid Pathways

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Serum

Specimen Required

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Red top
Acceptable: Serum gel
Submission Container/Tube: Plastic vial
Specimen Volume: 0.5 mL
Collection Instructions:
1. Morning (8 a.m.) specimen is preferred.
2. Centrifuge and aliquot serum into a plastic vial.

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)	21 days	
	Ambient	7 days	
	Frozen	21 days	

Clinical & Interpretive

Clinical Information

The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineralocorticoids, 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).

11-Deoxycorticosterone represents the last intermediate in the mineral corticoid pathway that has negligible mineralocorticoid activity. It is converted by 11-beta-hydroxylase 2 (CYP11B2) or by 11-beta-hydroxylase 1 (CYP11B1) to the first mineralocorticoids with significant activity, corticosterone. Corticosterone is in turn converted to 18-hydroxycorticosterone and ultimately to aldosterone, the most active mineralocorticoid. Both reactions are catalyzed by CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and 18-methyloxidase activity.

The major diagnostic utility of measurement of steroid synthesis intermediates is in diagnosing disorders of steroid synthesis, particularly congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency except for 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, which accounts for >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, which accounts for <3% of cases), or the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies might also suffer mineralocorticoid 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, which accounts for <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 female patients or, in milder cases, in hirsutism, polycystic ovarian syndrome, or infertility, as well as in possible premature adrenarche and pubarche in both sexes.

Measurement of the various precursors of mature mineralocorticoids 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 11-deoxycorticosterone and its glucocorticoid pendant, 11-deoxycortisol (also known as compound S), is aimed at diagnosing:
-CYP11B1 deficiency (associated with cortisol deficiency)
-The rarer CYP11B2 deficiency (no cortisol deficiency)
-The yet less common glucocorticoid-responsive hyperaldosteronism (where expression of the gene *CYP11B2* is driven by the CYP11B1 promoter, thus making it responsive to corticotropin [previously adrenocorticotrophic hormone: ACTH] rather than renin)

For other forms of CAH, the following tests might be relevant:
21-Hydroxylase deficiency:
-OHPG / 17-Hydroxyprogesterone, Serum
-ANST / Androstenedione, Serum
-21DOC / 21-Deoxycortisol, Serum

11-Hydroxylase deficiency:
-DOCS / 11-Deoxycorticosterone, Serum
-CORTC / Corticosterone, Serum
-PRA / Renin Activity, Plasma
-ALDS / Aldosterone, Serum

3-Beta-steroid-dehydrogenase deficiency:
-17PRN / Pregnenolone and 17-Hydroxypregnenolone, Serum

17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities):
-17PRN / Pregnenolone and 17-Hydroxypregnenolone, Serum
-PGSN / Progesterone, Serum
-OHPG / 17-Hydroxyprogesterone, Serum
-DHEA_ / Dehydroepiandrosterone (DHEA), Serum
-ANST / Androstenedione, Serum

Cortisol should be measured in all cases of suspected CAH.

In the diagnosis of suspected 11-hydroxylase deficiency and glucocorticoid-responsive hyperaldosteronism, this test should be used in conjunction with measurements of 11-deoxycortisol, corticosterone, 18-hydroxycorticosterone, cortisol, renin, and aldosterone.

Reference Values

< or =18 years: <30 ng/dL
>18 years: <10 ng/dL

Interpretation

In 11-beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will be low (usually <7 mcg/dL for a morning collection). 11-Deoxycortisol and 11-deoxycorticosterone are elevated, usually to at least 2 to 3 times (more typically 20-300 times) the upper limit of the normal reference range for a morning blood collection. 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 mineralocorticoids (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 mineralocorticoid results in infants younger than 7 days; mineralocorticoid 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 corticotropin (previously 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 micrograms of ACTH1-24 will usually exceed 20 ng/mL or demonstrate 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 direct 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 mineralocorticoid 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 1000 ng/dL. For the few patients with levels in the range of higher than 630 ng/dL (upper limit of reference range for newborns) to 2000 or 3000 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, particularly if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYB11B2 deficiency should be considered and

interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylaion to be converted to cortisol but is usually not elevated in CYP11B1 deficiency since its synthesis requires via 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 are high, including mineralocorticoids and sex steroids and their precursors. In preterm infants, 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.

Corticotropin (previously 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, particularly 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

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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) Performed
Tuesday

Report Available
3 to 10 days

Specimen Retention Time
14 days

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
82633

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
DOCS	11-Deoxycorticosterone, S	1656-8

Result ID	Test Result Name	Result LOINC® Value
46922	11-Deoxycorticosterone, S	1656-8