REVIEW

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Interpretation of Neonatal Adrenal Function Results and Adrenal Function Results in Critical Illness

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Abstract

Adrenal insufficiency (AI) is a life-threatening disorder. Defects at any level of the hypothalamic-pituitary-adrenal axis can impair adrenal function. It is difficult to make a diagnosis of AI in the newborn because during the neonatal period clinical findings are not specific and range from insidious, nonspecific complaints to circulatorycollapse due to hypovolemic shock. Another condition when is difficult to make a diagnosis of AI is in critically ill patients. There is no consensus on which patients to test for AI, which tests to use and how to interpret them. In this evidence-based review we aim to provideinformation for the evaluation of adrenal function results and findings in both the neonatal period and critical illness in childhood and adolescence.
Keywords: Adrenal functions, neonatal, critical illness

Introduction

Interpretation of adrenal functions is especially important in the neonatal period and during episodes of critical illness. The diagnosis of adrenal insufficiency (AI) in newborns is challenging due to non-specific clinical signs and the fact that normal serum cortisol levels are much lower than in older children and adults (1).

Patients with sepsis, septic shock, acute respiratory distress syndrome, severe pneumonia, intoxication, severe diabetic ketoacidosis, and patients followed up in intensive care after major surgical operations are considered critical illnesses. In critical illness, activation of the hypothalamo-pituitary-adrenal axis (HPA) and increased cortisol secretion are essential for stress adaptation and cardiovascular stability. Although it is thought that stress-induced increase in adrenocorticotropin hormone (ACTH) secretion in critical illness will lead to significant increases in cortisol, insufficiency in glucocorticoid effect may be observed. This insufficiency in glucocorticoid effect may be due to decreased metabolic clearance of cortisol leading to suppression of ACTH, decreased number and affinity of glucocorticoid receptors, and decreased tissue sensitivity in response to cytokine secretion (1,2).

This evidence-based review with good practice points is developed by the 'Adrenal Working Group' of the 'Turkish Society for Pediatric Endocrinology and Diabetes' to providesuggestions for the evaluation of adrenal function in both the neonatal period and during critical illnesses in childhood and adolescence. The aim of the evidence-based reviewis to provide data to evaluate adrenal function assessments in these conditions and to recognize potential AI.

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1. Interpretation of Neonatal Adrenal Functions

Although the importance of the sample timing is negligible since the diurnal cortisol rhythm starts between 6-12 months and is completed by the age of three years, obtaining different samples (at least three) can be beneficial (2). For the diagnosis of mineralocorticoid deficiency, in addition to serum electrolytes, renin and aldosterone levels can be measured (1). If the ACTH level measured concurrently with a low serum cortisol level is more than double the upper limit of the reference range, the diagnosis of primary AI is definitive (3). In a patient with normal renal function, a Na/K ratio of <20 strongly suggests mineralocorticoid deficiency (2).

There are difficulties in measuring steroids, especially in the neonatal period. These include having low physiological steroid levels in serum and some endogenous compounds causing interference. Therefore, it is important to use reliable and sensitive methods (4,5).

Immunoassays and LC-MS/MS methods are widely used in steroid measurement. Immunoassaysare methods that do not require the personnel to have special skills and the reagents can be accessed more easily (6). Conventional radioimmunoassay (RIA) requires purification steps for analysis. Specificity is increased by removal of steroid-binding proteins and potentially interfering analytes. However, RIA is a cumbersome, time-consuming and expensive method. It requires a relatively large sample volume, especially when measuring low concentrations of steroids. There is also the possibility of crossreactivity with antibodies. Direct immunoassays (DIAs) are methods that have advantages over the RAI method, which came into use after the 1970s. In addition, DIAs may cause overestimation in the measurements of some analytes. Furthermore, DIAs may not be able to distinguish target analytes completely from some steroid binding globulins and the measurements may not be clear. Other disadvantages of DIAs are that it measures a single analyte at a time and there is a decrease in sensitivity in low level hormone measurements (7).

Mass spectrometry (MS) tests have replaced traditional RIAs and DIAs for steroid hormones in larger reference laboratories due to their high validity and throughput. The use of the liquid chromatography-tandem MS (LC-MS/MS) method in the measurement of steroids is increasing. With this method, many steroid hormones can be measured in a single analysis. It is also a method in which interference with other steroid molecules is minimized. It has optimal accuracy and specificity. In addition to having high analytical specificity and sensitivity, the extraction and pretreatment processes of the sample to be measured are minimized. Another feature of the LC-MS/MS method is that, in addition to measuring hormones with low serum levels, it enables the measurement of a large number of precursors at the same time and provides information about the precursor to product ratio (4,7).

Immunoassays can show cross reactivity with similar analytes or in the presence of various drugs. Measurement of cortisol by immunoassay may interfere with some drugs and cortisol precursors and steroid-binding proteins. With LC-MS/MS, cortisol, cortisone, prednisolone and prednisone can all be measured selectively (6). It has been shown that cortisol concentrations measured by immunoassay are significantly higher than those measured by the LC-MS/MS method. Thus, LC-MS/MS has been considered the preferred technique for clinical use due to its high analytical sensitivity even at low steroid concentrations and reduced interference from analytes commonly encountered in immunoassays (5,6). As the LC-MS/MS method can quantify multiple analytes simultaneously, it has the capacity to provide an integrated profile of adrenal steroidogenesis, even in a small sample size from infants (4).

With the LC-MS/MS method becoming more frequently used, interpreting steroid hormone measurements and making accurate clinical decisions require the development of reference ranges. In our country, recently, detailed reference ranges for 14 adrenal steroid hormones have been reported in healthy infants with a large number of cases using the LC-MS/MS technique (Table 1) (4). Neonatal screening programs aiming to reduce the morbidity and mortality associated with delayed CAH diagnosis are implemented in many countries. LC-MS/MS-based steroid panels and 21-deoxycortisol are increasingly used as second-line screening for neonatal CAH (4).

In infants suspected of classical 21-hydroxylase deficiency (21-OHD), a basal serum 17-hydroxyprogesterone (17-OHP) level greater than 100 ng/mL is diagnostic for 21-OHD. In normal neonates, the level is below 1 ng/mL. However, especially when the test is conducted on the first day following birth, even severe cases can exhibit normal values. 17-OHP level is normally high in cord blood, but falls to normal levels after about 24 hours, so that assessment of 17-OHP levels should not be made in the first day of life (1). Conversely, high 17-OHP levels can be detected in patients, particularly in sick, under severe stress, premature, or low birth weight infants, without CAH (8).

Preterm infants have a functional deficiency of several adrenal steroidogenic enzymes (9). This adrenal prematurity can cause false positive results. For example, in a Swedish screening program measuring 17-OHP with a cut-off level of 60 nmol/L in full-term infants, 350 nmol/L before 35

Table 1. Reference ranges for adrenal steroid hormones in healthy infants measured by LC-MS/MS

Metabolite (ng/mL)	Age	2.5%	Median	97.5%
	8-14 day	0.018	0.183	0.505
	15-28 day	0.027	0.229	0.737
	28-90 day	0.017	0.238	0.661
Corticosterone	3-7 day	0.041	0.534	0.871
	8-14 day	0.167	1.324	12.48
	15-28 day	0.108	0.760	11.82
	28-90 day	0.081	1.564	9.664
11-deoxycorticosterone	3-7 day	0.002	0.009	0.050
	8-14 day	0.005	0.021	0.577
	15-28 day	0.003	0.014	0.082
	28-90 day	0.003	0.036	0.164
Pregnenolone	3-7 day	0.049	0.191	2.523
	8-14 day	0.126	0.478	8.262
	15-28 day	0.124	0.358	4.228
	28-90 day	0.153	0.504	2.854
17-OH-pregnenolone	3-7 day	0.049	0.237	1.184
	8-14 day	0.102	0.741	4.920
	15-28 day	0.059	0.591	5.349
	28-90 day	0.048	0.774	3.588
Progesterone	3-7 day	0.004	0.019	1.210
	8-14 day	0.015	0.088	0.369
	15-28 day	0.003	0.051	0.246
	28-90 day	0.002	0.013	0.121
17-OH-progesterone	3-7 day	0.001	0.005	0.769
	8-14 day	0.180	0.542	1.621
	15-28 day	0.001	0.407	1.687
	28-90 day	0.001	0.003	0.785
21-deoxycortisol	3-7 day	0.008	0.066	0.411
	8-14 day	0.026	0.083	0.323
	15-28 day	0.007	0.058	0.240
	28-90 day	0.007	0.044	0.409
11-deoxycortisol	3-7 day	0.102	0.228	0.872
	8-14 day	0.083	0.227	0.724
	15-28 day	0.101	0.290	0.554
	28-90 day	0.054	0.243	0.594
Cortisol	3-7 day	2.989	20.91	112.1
	8-14 day	3.440	29.35	129.9
	15-28 day	2.724	17.22	93.77
	28-90 day	3.666	18.07	150.4
Cortisone	3-7 day	8.011	31.66	102.0
	8-14 day	10.76	40.07	139.4
	15-28 day	10.74	31.08	94.09
	28-90 day	5.486	31.66	73.78
DHEA	3-7 day	0.027	0.254	8.545
	8-14 day	0.024	1.293	15.03
	15-28 day	0.024	1.202	11.32
	28-90 day	0.159	0.744	7.180
DHEA-S	3-7 day	30.95	113.1	659.8
	8-14 day	44.57	249.8	836.7
	15-28 day	28.83	204.4	734.2
	28-90 day	23.27	141.1	484.9

Table 1. Reference ranges for adrenal steroid hormones in healthy infants measured by LC-MS/MS

Metabolite (ng/mL)	Age	2.5%	Median	97.5%
Androstenedione	3-7 day	0.003	0.070	0.698
	8-14 day	0.049	0.223	0.598
	15-28 day	0.008	0.112	0.633
	28-90 day	0.003	0.031	0.481
Androsterone	3-7 day	0.039	0.266	14.16
	8-14 day	0.148	1.097	6.134
	15-28 day	0.101	0.787	2.498
	28-90 day	0.141	0.448	2.979
(17-OH-progesterone + 21- deoxycortisol)/cortisol	3-7 day	0.001	0.008	0.158
	8-14 day	0.005	0.023	0.235
	15-28 day	0.000	0.013	0.218
	28-90 day	0.000	0.003	0.114
11-deoxycortisol/cortisol	3-7 day	0.001	0.015	0.114
	8-14 day	0.001	0.010	0.116
	15-28 day	0.002	0.016	0.117
	28-90 day	0.002	0.009	0.056
(17-OH-progesterone + 21- deoxycortisol)/cortisol	3-7 day	0.005	0.060	0.487
	8-14 day	0.022	0.135	0.632
	15-28 day	0.012	0.175	0.822
	28-90 day	0.012	0.110	0.551
Cortisol/cortisone	3-7 day	0.102	0.645	4.250
	8-14 day	0.066	0.646	5.415
	15-28 day	0.097	0.451	3.626
	28-90 day	0.153	0.769	3.921

LC-MS/MS: liquid chromatography-tandem mass spectrometry, 17-OH: 17-hydroxy, DHEA-S: dehydroepiandrosterone sulfate

weeks of gestation and to 100 nmol/L for 35 and 36 weeks, the positive predictive value for full-term infants was 25%, whereas it was only 1.4% for preterm infants, and the 17-OHP level correlated very strongly with gestational age (10).

There are no universally accepted standards for stratifying infants. Most labotarories use birth weight-adjusted cut-offs. In one study, the threshold for 17-OHP levels in babies weighing less than 1300 grams was set at 165 ng/mL, and for those weighing more than 2200 grams, at 40 ng/mL (11). Another study set the threshold at 65 ng/mL for infants weighing less than 2500 grams and 40 ng/mL for those weighing more (12).

However, actual gestational age, or both gestational age and birth weight-adjusted cut-offs might be preferable, because gestational age correlates much better with 17-OHP levels (13). Also, sceening a second sample several days later improves both sensitivity and positive predictive value (12,14).

In preterm infants (≤36 weeks), the first blood sample should be taken between days 3-5, and before transfusion. However, if dexamethasone is administered to the mother and baby, false negativity should be kept in mind. In cases of fluid imbalance in the infant or hyperbilirubinemia, false positive results can be obtained due to dehydration or interaction in the test (15). Neonatal CAH screening is explained in detail in Part 4 of this supplement (65).

Good practice points:

1. Serum cortisol levels should be measured by LC-MS/MS method (2⊕⊕OO).

2. In CAH due to 21-OHD, 17-OHP levels are elevated. Since high 17-OHP levels can be found in patients who are premature or have low birth weight without having CAH, the test should be repeated in suspicious cases, and if necessary, an ACTH stimulation test should be conducted (1⊕⊕⊕O).

ACTH Stimulation Test in Neonates

ACTH stimulation testing has become the preferred method for diagnosing AI in newborns. Low-dose ACTH stimulation testing is typically used to investigate central causes of AI in newborns, while the "standard" dose stimulation test is typically used to investigate primary AI (16). There is not enough data regarding normal response and peak cortisol

time in the neonatal period. In addition, the response may be difficult to interpret in premature or sick newborns. It was suggested that the low-dose ACTH test may be more disciminatory than the standard-dose test among babies under stress (17). I significant in a study conducted with 49 newborns, with a median gestational age of 36.1 weeks, reported that the majority of cortisol peaks during neonatal low-dose ACTH stimulation testing occurred at the 60-minute sampling time. Moreover, the inclusion of an additional 30-minute sample provided substantial benefits (18). In a meta-analysis including 228 children, low- and high-dose ACTH stimulation tests had the same diagnostic accuracy. However, different peak serum cortisol cutoff values are used in adults and children. According to this meta-analysis, although both tests have high specificity, their sensitivity is generally low. The data were only used to estimate the sensitivity of the high-dose ACTH stimulation test (92%) because there were an insufficient number of articles to evaluate this for primary AI (16). In general, in children, an increase in cortisol response by 7 µg/dL (190 nmol/L) compared to baseline at 60 minutes or a peak response of >18 µg/dL (500 nmol/L) is considered normal (19). A study has reported that in 18 infants in the neonatal intensive care unit, a lower limit of 13 µg/dL (360 nmol/L) can be considered acceptable (20).

2. Adrenal Functions in Critical Illness

Many critically ill patients with sepsis, septic shock, major trauma, burns, and acute respiratory distress syndrom develop secretory failure of the adrenal gland and undiagnosed absolute primary or secondary AI may become apparent. Some patients infrequently may have structural damage to the adrenal gland from either hemorrhage or infarction (21,22,23).

In severe illness, requiring intensive care, the American Critical Illness Care Association recommended in 2008 that the definition of "relative AI", which means an increased but inadequate cortisol response of the adrenal gland, which is functionally normal under normal conditions, in case of stress, should be changed to "corticosteroid insufficiency associated with a critical illness (CIACI)" (24).

The presence of AI may be a factor that may lead to organ dysfunction and worsen the prognosis. In case of hypotension unresponsive to vasopressor and fluid treatment, shock, prolonged mechanical ventilation, and sudden worsening of hemodynamic parameters, CIACI should be considered (24). There is no consensus for a gold standard test and cortisol threshold value for diagnosis and treatment management in childhood. There have been studies conducted to assess concentration of serum total and free cortisol to assess adequacy of glucocorticoid response in critically ill patients (21,25,26,27).

Pathophysiology of Adrenal Insufficiency in Critical Illness

Several mechanisms affect cortisol levels and function in critical illness, including HPA activation (resulting in increased circulating cortisol levels), HPA dysregulation causing adrenocortical hypersensitivity, and glucocorticoid resistance:

Activation of the HPA axis: Normal serum cortisol levels show significant variability depending on the time of day (28). In critically ill patients, diurnal variation disappears, and serum cortisol levels may increase to 40 to 50 mcg/dL (28,29). HPA activation has been reported to be associated with decreased cortisol clearance (enzymes metabolizing cortisol are reduced, cortisol degradation is reduced by 40%, and half-life is prolonged 5-fold) (29), decreased binding of cortisol to cortisol-binding globulin, and albumin (30,31), increased glucocorticoid receptor affinity for cortisol and increased peripheral conversion of precursors to cortisol (32,33). Other factors that stimulate cortisol synthesis, independent of ACTH, are inflammatory cytokines, including interleukin (IL)-1, IL-6, tumor necrosis factor-α, vasopressin, adipokines, bacterial pathogens, and endothelial cells (22,24).

Disruption of the HPA axis: Several factors are known to disrupt the HPA axis in critically ill patients, including head trauma, central nervous system depressants, pituitary apoplexy, pituitary ischemia, adrenal hemorrhage, ischemia or apoptosis, infections, malignancy, previous glucocorticoid treatment, and medications such as phenytoin, etomidate, and ketoconazole (34,35).

Glucocorticoid resistance: When critical illness or intensive care unit hospitalization lasts longer than 3-7 days, the HPA axis stress response and the response of tissues change in response to prolonged stress. ACTH is suppressed with high cortisol levels, ACTH pulsatility is lost, resistance develops at the receptor level, and cortisol response decreases. Tissue response is also impaired. Cortisol resistance occurs in peripheral tissues. It has been reported that the beta-isoform of the glucocorticoid receptor, an isoform associated with steroid resistance, shows higher expression levels (36).

Absolute and Partial Adrenal Insufficiency

Absolute AI is rare in critically ill patients, and the incidence is estimated to be ≤3% (37). However, no consensus exists

on the diagnostic criteria for CIACI. In addition, there is uncertainty about which cortisol level is "normal" or "appropriate" in septic shock, what constitutes an adequate response to ACTH, and what dose of synthetic ACTH should be used for stimulation testing. It is believed that the diagnosis of "relative AI" is uncertain because there is no clear definition, and cortisol tests available in most clinical laboratories are not reliable in critically ill patients (38).

Clinical Findings

The most common clinical finding is hypotension, which was first described in adults with sepsis and later reported in children (38,39). It is characterized by an exaggerated and prolonged proinflammatory response, especially in septic shock and early severe acute respiratory distress syndrome. Prolonged mechanical ventilation, sudden deterioration of hemodynamic parametersand hypotension unresponsive to vasopressor and fluid treatment are observed. It is important to carefully evaluate the HPA axis in the presence of drug use that may suppress the HPA axis, hypothalamic-pituitary disease, radiotherapy, and autoimmune disease. The presence of eosinophilia, hyponatremia, hyperkalemia, hypoglycemia, andhigh ACTH levels in laboratory tests suggests AI (40).

Diagnosis

AI is frequently defined in the critically ill pediatric population by an inadequate response to an ACTH stimulation test (< 9 mcg/dL change in cortisol from baseline one hour after IV cosyntropin administration). A multicenter study using this definition showed that 30% of 381 critically ill children met the criteria for AI on the first day of intensive care, with a frequency similar to that seen in 59 patients with sepsis (23). It has been reported that the rate of AI was higher (43%) in patients receiving catecholamines (23).

In general, most clinicians do not require laboratory tests to select glucocorticoid replacement therapy in patients with septic shock because laboratory analyses of plasma cortisol concentration and response to ACTH stimulation are unreliable in critically ill patients. In addition, in major randomized trials, baseline cortisol levels and ACTH stimulation testing have been reported to be unable to identify patients with septic shock who benefit from glucocorticoid use.

Keeping this caveat in mind, for clinicians who wish to assess adrenal reserve in critically illpatients, the international guidelines of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine have reported an increase in serum cortisol levels of ≤9 μg/dL after administration of cosyntropin (250 mcg; high-dose ACTH stimulation) and a random plasma cortisol value < 10μg/dL as indicators of possible AI in critically illpatients (23).

Studies have described these tests' diagnostic and prognostic performance in critically ill patients. Total serum cortisol levels vary significantly in patients with septic shock (41,42). Changes in the production and transport of cortisol, increase in free cortisol, cortisol resistance, and etomidate used for intubation decrease the reliability of the test. Due to intraday variations, a single measurement for cortisol is not sufficient. Although used in somestudies, high or low serum cortisol levels are not associated with mortality and morbidity in patients with septic shock (43,44,45,46,47,48). A prospective study including 101 patients with sepsis reported that the best predictor of AI was a baseline random cortisol level of ≤10 μg/dL or an increase in cortisol of < 9 μg/dL after ACTH stimulation (44).

Some studies have shown that elevated basal cortisol levels positively correlate with the 'Pediatric Risk of Mortality III' (PRISM III) score (49,50,51).

Ninety per cent of serum total cortisol is bound to proteins (corticosteroid-binding protein and albumin). Hypoproteinemia due to malnutrition, haemodilution, and systemic inflammatory response syndrome in critically ill patients may lead to misevaluation (26). In addition, there is a transition from protein-bound inactive cortisol to physiologically active free cortisol in critically ill patients. It has been suggested that free cortisol more accurately reflects HPA axis activation in critically ill patients (26,27,38). However, standard tests for plasma cortisol measurement, including total (free and bound) plasma cortisol and free cortisol tests, are unavailable in most clinical centers (39).

Some studies support free cortisol measurement as a more accurate measure of AI in critically ill patients. In one prospective study, critically ill patients were reported as having 7 to 10 times higher free cortisol levels than healthy volunteers, compared with total serum cortisol concentrations of only two to three times higher (38). In another prospective study, baseline free cortisol levels reflected the severity of the disease better than total cortisol levels (40). While free cortisol levels were 186 nmol/L in patients with septic shock, 29 nmol/L in patients with sepsis, and 13 nmol/L in healthy controls, total cortisol levels were reported as 880 nmol/L in patients with septic shock, 417 nmol/L in patients with sepsis and 352 nmol/L in healthy controls (40).

No threshold "salivary cortisol value" for AI exists. In addition, sample collection is difficult due to reasons such as intubation, intra oral bleeding due to coagulation disorders, candidiasis, and disinfectant use. Therefore, salivary cortisol measurement is not reliable in the diagnosis of critically ill children with AI. Studies also report only a moderate correlation between stress and salivary cortisol (52). In a cohort study conducted in children, it was suggested that salivary cortisol level had a significant positive correlation with cortisol levels at basal and after 250 mcg ACTH test in critical illness, and a salivary cortisol level < 8.2 µg/dL after ACTH had 79% sensitivity and 62% specificity in detecting the need for vasoactive and inotropic support (21).

ACTH Stimulation Tests in Critical Illness

It has been suggested that spontaneous increases of ≥9 µg/dL in serum cortisol levels occur even without cosyntropin stimulation in some critically ill individuals. Therefore, this threshold value may not be clinically helpful (21,53).

In an adult study in which hydrocortisone treatment and good response to treatment were evaluated in patients who did not respond to the ACTH test and had adequate cortisol response, it was reported that it was not appropriate to make a treatment decision according to the ACTH test result (54,55). ACTH stimulation tests may give inconsistent results in thesame individuals when performed on more than one occasion (43).

Etomidate, which suppresses the HPA axis (35), has been reported to affect the results of ACTH stimulation when used to intubate patients with septic shock.

Studies using a high-dose ACTH stimulation test (250 mcg cosyntropin) have yielded variable septic shock results (41,43,54). Forexample, in a prospective cohort study including 189 patients with septic shock, it was reported that a baseline serum cortisol level > 34 mcg/dL and a maximum increase in cortisol ≤9 mcg/dL were defined as risk factors for death (54). Similarly, in another retrospective cohort study including 477 patients with severe sepsis or septic shock, survivors were reported to have a higher baseline cortisol level (30 vs. 24 mcg/dL) and a minor cortisol increase (6 vs. 11 mcg/dL), indicating that lower cortisol levels were associated with higher mortality, longer shock duration or shorter survival time (55).

Few clinical studies have assessed the low dose (1 mcg) ACTH stimulation test. It was compared with a high-dose ACTH stimulation test in patients with septic shock. An increase of ≤9 µg/dL in serum cortisol values after stimulation supports the diagnosis of CIACI (56,57). In a prospective cohort study of 59 patients with septic shock, AI (defined as post-cosyntropin serum cortisol < 18 mcg/dL) was detected in more patients with low-dose ACTH stimulation test than with high-dose ACTH stimulation test (22% vs. 8%) (58). The low-dose ACTH stimulation test was superior to the high-dose ACTH stimulation test in differentiating steroid-responsive patients (i.e., patients who could maintain a mean arterial blood pressure > 65 mmHg without norepinephrine infusion within 24 hours) from non-responders (58). In another retrospective study, the survival rate of non-responders to the low-dose ACTH stimulation test was lower than that of responders to both tests (27% vs. 47%) (49). In studies performed in the neonatal period, it has been reported that low-dose stimulation tests are clinically more significant compared with high-dose stimulation tests (47,59,60). A low-dose ACTH stimulation test identifies a subgroup of patients within adequate adrenal reserve in septic shock, and they may be overlooked because of cortisol increase due to supraphysiological stimulation with a high-dose stimulation test (56,58,59,60). Although these studies suggest that low-dose ACTH stimulation tests may predict mortality, more studies are needed to confirm the findings (56,58,59,60).

Patients with central AI have been shown to have low mean serum dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S) levels at baseline and after low-dose ACTH stimulation. Regular DHEA and DHEA-S levels are strong indicators of normal ACTH secretion and adequate adrenal cortical function. In adult studies, significantly lower serum DHEA-S levels have been reported in both septic shock and trauma patients compared to healthy controls (61,62,63). However, despite low circulating DHEA-S, it has been reported that DHEA levels are significantly increased in septic patients. This may be due to sepsis-related suppression of SULT2A1, which converts DHEA to DHEA-S (63). Thus, if SULT2A1 activity is impaired, circulating DHEA-S levels may not appropriately reflect the circulating DHEA pool, which is considered biologically active and may not be a reliable marker of adrenal androgen output (61,62).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (64).

Good practice points:

1. Adrenal reserve should be assessed in critically ill patients, especially in cases of prolonged mechanical ventilation, sudden deterioration of hemodynamic parameters, and hypotension unresponsive to vasopressor and fluid therapy (1⊕⊕⊕O).

2. Interpretation of adrenal function tests (serum cortisol level, free cortisol level salivary-free cortisol measurement, ACTH stimulation test) is special in critical illnesses. Salivary cortisol measurement is not recommended for the diagnosis of AI (2⊕⊕OO).

3. Measurement of serum ACTH level has no place in the diagnosis of CIACI. The diagnosis of AI is made by ACTH stimulation test. Although the ACTH stimulation tests are unreliable for critically ill patients, an increase of ≤9 µg/dL in serum cortisol levels after ACTH stimulation in critically ill patients indicates possible AI (2⊕⊕OO).

Footnotes

Authorship Contributions

Concept - Design - Data Collection and Processing - Analysis or Interpretation - Literature Search - Writing: Nesibe Akyürek, Beray Selver Eklioğlu, Çiğdem Binay.

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