REVIEW

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Central Adrenal Insufficiency: Etiology and Diagnostic Approach

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Abstract

Central adrenal insufficiency (CAI) occurs due to a pituitary gland disorder (secondary AI) or hypothalamic dysfunction (tertiary AI). It is a potentially life-threatening condition that has many congenital and acquired causes. Adrenocorticotropic hormone deficiency may be isolated or more commonly it can be accompanied by other pituitary hormone deficiencies or midline defects. The signs and symptoms of CAI are associated with glucocorticoid deficiency. A three-step diagnostic approach including dynamic stimulation tests is recommended in the evaluation of patients with suspected CAI. Here, members of the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes' present an evidence-based review with good practice points and recommendations for etiology and diagnostic approach in children and adolescents with CAI.

Keywords: Central adrenal insufficiency, secondary, ACTH, guideline, children

Introduction

Central adrenal insufficiency (CAI) occurs due to impaired production of adrenocorticotropic hormone (ACTH) caused by a pituitary gland disorder (secondary AI), or inadequate production of corticotropin-releasing hormone (CRH) as a result of hypothalamic dysfunction or long-term exogenous glucocorticoid administration exceeding physiological replacement doses (tertiary AI). It is a potentially life-threatening condition that has many congenital and acquired causes (1,2). Although mild hyponatremia may be present at diagnosis, electrolyte levels are generally normal since mineralocorticoid synthesis is mainly controlled by the renin-angiotensin system. ACTH deficiency may be isolated or, more commonly, it can be accompanied by other pituitary hormone deficiencies or midline defects.

This evidence-based review with good practice points is developed by 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes'. We developed this evidence-based review for "Central Adrenal Insufficiency: Etiology and Diagnostic Approach" in children and adolescents. The overall purpose of this evidence-based review is to provide good practice points, with focus on recommendations for daily management.

Causes of Central Adrenal Insufficiency

There are various genetic causes that may lead to ACTH deficiency.

TBX19 (TPIT): Isolated ACTH deficiency is rare and mostly caused by recessive mutations (homozygous or compound heterozygous) in the *TBX19* gene, which codes for a transcription factor. These patients may present with severe hypoglycemia and/or cholestatic jaundice in the neonatal period. In a case series of 27 patients with isolated ACTH deficiency, 10 different *TBX19* mutations were identified in approximately two-thirds of the patients (3). In another series, *TBX19* mutations were detected in 65% of the patients with neonatal-onset, severe, isolated ACTH deficiency (4). *TBX19* mutations are the principal molecular cause of neonatal-onset, congenital, isolated

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ACTH deficiency. However, they are not detected in partial or late-onset isolated ACTH deficiency (4).

Proopiomelanocortin (*POMC*) deficiency: Recessively inherited deletions or mutations in the *POMC* gene are associated with ACTH deficiency, and characterized by red hair, pale skin, and severe, early-onset obesity due to hyperphagia. *POMC* deficiency is extremely rare, and less than 50 patients have been reported at the time of writing (5). It may be associated with central hypothyroidism (6,7). Recent data support the use of setmelanotide, a melanocortin-4 receptor (MC4R) agonist, to suppress appetite and achieve weight loss in *POMC* deficiency (8).

Prohormone convertase 1 (*PC1*) deficiency: *PC1* deficiency, which is an even rarer cause of ACTH deficiency, may have a phenotype including glucose metabolism disorders (often postprandial hypoglycemia), early-onset obesity, hypogonadotropic hypogonadism, and neonatal-onset persistent diarrhea (9).

***NFKB2* deficiency:** Isolated ACTH deficiency may be associated with common variable immune deficiency due to heterozygous mutations in the *NFKB2* gene (DAVID syndrome). ACTH deficiency is observed in only around two-thirds of the patients with *NFKB2* mutations. In the literature, it has been associated with growth hormone (GH) deficiency and thyroid-stimulating hormone (TSH) deficiency in only one patient (10).

The development of the hypothalamic-pituitary axis depends on the expression of various transcription factors and signaling molecules. Genetic mutations in any of these factors may lead to isolated or multiple pituitary hormone deficiency (MPHD). ACTH deficiency may occur as a part of MPHD. Although there are many genetic causes, its etiology has not yet been elucidated in most patients. Cases may have various phenotypic features including a wide spectrum of craniofacial anomalies and midline defects, such as septo-optic dysplasia and holoprosencephaly. Rathke cleft cyst and more complex syndromes such as Pallister-Hall syndrome, Webb-Dattani syndrome, Prader-Willi syndrome, CHARGE syndrome, or Williams-Beuren syndrome are among the congenital causes of CAI. ACTH deficiency can occur at any time in children or adults with childhood-onset GH deficiency, especially in the presence of structural hypothalamus-pituitary abnormalities or TSH deficiency (11,12). Even in patients with autosomal dominant mutations in the *GH1* gene, which is associated with isolated GH deficiency, additional hormone deficiencies, including ACTH deficiency, may be observed (13,14). Therefore, in patients with other pituitary hormone deficiencies, careful monitoring and long-term follow-up are required in terms of ACTH production. A genetic diagnosis is beneficial in the follow-up. All known genes responsible for CAI, their inheritance patterns, and accompanying phenotypic and structural findings are presented in Table 1 (15).

Acquired causes: Acquired ACTH deficiency may occur as a component of MPHD due to tumors arising in and around the sella turcica (such as craniopharyngioma), trauma, surgery, or as a complication of high-dose cranial radiotherapy. Inflammation, infection, or infiltrative diseases (such as Langerhans cell histiocytosis and hemochromatosis) are also among acquired causes.

Good practice points:

1. Newborns examined for severe hypoglycemia and/or cholestatic jaundice and diagnosed with isolated complete ACTH deficiency in neonatal period should primarily be investigated for pathogenic *TBX19* variants (1⊕⊕⊕O).

2. In patients with isolated or multiple other pituitary hormone deficiencies, ACTH deficiency may appear at any time in children or adults. Therefore, careful monitoring and long-term follow-up are required (1⊕⊕⊕O).

Clinical Findings

The signs and symptoms of CAI are associated with glucocorticoid deficiency. It manifests as severe hypoglycemia, seizures, cholestatic jaundice and developmental delay in newborns (3,4). It may take 6-10 weeks for cholestasis to resolve after the initiation of treatment (16). Since aldosterone production is preserved, serum electrolyte levels are usually normal and adrenal crisis is rare. However, because cortisol contributes to the regulation of free water clearance, patients with CAI are at risk for dilutional hyponatremia with normal serum potassium levels (17). Glucocorticoid deficiency may present with severe hypoglycemia, frequent infections, weakness, fatigue, nausea, headache, myalgia and arthralgia in children and adolescents. However, in the presence of partial ACTH deficiency, patients may be asymptomatic, and adrenal crisis may occur in case of acute stress or illness. Since adrenal androgen secretion is controlled by ACTH, girls with ACTH deficiency may have inadequate genital hair growth. Unlike in primary adrenal insufficiency, hyperpigmentation is not present in patients with CAI (15).

CAI findings may be accompanied by symptoms caused by an underlying central nervous system disease and/or other pituitary hormone deficiencies. Clinical findings strongly

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Table 1. Genetic causes of central adrenal insufficiency and accompanying findings (modified from reference 15)

Gene	Chromosome	Inheritance pattern	Hormone deficiencies	Additional findings
TBX19 (TPIT)	1q24.2	AR	ACTH	Neonatal-onset congenital isolated ACTH deficiency
POMC	2p23.3	AR	ACTH, TSH	Early-onset obesity, red hair
PC1 (PCSK1)	5q15	AR	ACTH, FSH, LH	Obesity, glucose metabolism disorders, enteropathy
NFKB2	10q24.32	AD	ACTH, GH, TSH	DAVID syndrome
PROP1	5q35.3	AR	MPHD	
LHX3	9q34.3	AR	MPHD	Short cervical spine with limited neck rotation, scoliosis, sensorineural hearing loss
LHX4	1q25.2	AD	MPHD	Chiari malformations, cerebellar anomalies
HESX1	3p14.3	AR, AD	MPHD	Septo-optic dysplasia
SOX2	3q26.33	AD	MPHD	Microphthalmia, central nervous system anomalies
SOX3	Xq27.1	X-linked	MPHD	Mental retardation, midline defects
OTX2	14q22.3	AD	Isolated GH deficiency or MPHD	Anophthalmia or microphthalmia, coloboma, developmental delay
FGFR1	8p11.23	AD	FSH, LH, ACTH	Septo-optic dysplasia, Kallmann syndrome
PROKR2	20p12.3	AD	FSH, LH, ACTH	Kallmann syndrome
FGF8	10q24.32	AD	FSH, LH, ACTH, TSH, PRL	Septo-optic dysplasia, Kallmann syndrome, holoprosencephaly, diabetes insipidus
FOXA2	20p11.21	AD	MPHD	Hyperinsulinism, endoderm-derived organ abnormalities
GLI2	2q14.2	AD	MPHD	Holoprosencephaly, craniofacial anomalies, polydactyly
CDON	11q24.2	AD	MPHD	Holoprosencephaly, pituitary stalk interruption syndrome
ROBO1	3p12.3	AD	MPHD	Pituitary stalk interruption syndrome
GLI3	7p14.1	AD	MPHD	Pallister-Hall syndrome
ARNT2	15q25.1	AR	MPHD	Webb-Dattani syndrome
NDN, SNRPN	15q11.2		MPHD	Prader-Willi syndrome
PGM1	1p31.3	AR	GH, FSH, LH, ACTH	Congenital disorders of glycosylation
CHD7	8q12.2	AD	MPHD	CHARGE syndrome
	7q11.23	AD	MPHD	Williams-Beuren syndrome
EIF2B5	3q27.1	AR	TSH, ACTH	Leukoencephalopathy with vanishing white matter
GH1	17q23.3	AD	GH, ACTH, TSH	Isolated GH deficiency type 2

AR: autosomal recessive, AD: autosomal dominant, MPHD: multiple pituitary hormone deficiency, FSH: follicle-stimulating hormone, GH: growth hormone, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, PRL: prolactin, LH: luteinizing hormone

depend on the number and severity of hormone deficiencies. Newborns with panhypopituitarism may present with non-specific symptoms such as hypoglycemia, lethargy, apnea, poor feeding, jitteriness, seizures, hyponatremia without hyperkalemia, impaired thermoregulation, sepsis, and poor weight gain. Male infants with hypogonadism may have undescended testicles and micropenis. Nystagmus may be observed in infants with optic nerve hypoplasia or agenesis of the corpus callosum. Symptoms such as headache, vomiting, visual field defects or seizures may be observed in patients with an underlying pituitary or hypothalamic tumor (15).

Diagnostic Tests for Central Adrenal Insufficiency

Baseline cortisol: Both cortisol and ACTH levels are low in CAI. Since cortisol is secreted with a diurnal pattern, baseline cortisol and ACTH levels are measured at 08:00 am in the morning, in patients older than 6 months. A morning cortisol level of <3 µg/dL (83 nmol/L) indicates adrenal insufficiency, and a level of >13 µg/dL (365 nmol/L) indicates that the hypothalamic-pituitary-adrenal (HPA) axis is functioning normally (18,19). If cortisol levels are between these limits (3-13 µg/dL), additional dynamic stimulation tests are required. Dynamic tests used in the evaluation of the HPA axis are presented in Table 2 (15).

Corticotropin stimulation tests: The most commonly used test is the corticotropin (synthetic ACTH) stimulation test. The test is based on the fact that chronic endogenous ACTH deficiency causes a diminished response of the adrenal zona fasciculata to ACTH stimulation. If ACTH deficiency is severe and prolonged, an inadequate response is obtained due to secondary adrenal atrophy. However, in moderate or

Table 2. Dynamic diagnostic testing to evaluate hypothalamic-pituitary-adrenal axis (modified from references 15 and 19)

Test	Dose	Timing (minute)	Normal results	Advantages	Disadvantages
ITT	Regular insulin 0.1 U/kg, IV	0-30-60-90-120	Cortisol > 20 µg/dL (550 nmol/L)	Gold standard	Hypoglycemic convulsions
Metyrapone test	Metyrapone 30 mg/kg, at 11:00 pm, oral	At 08:00 am in the following morning	11-deoxycortisol > 7 µg/dL (200 nmol/L)	High sensitivity	Rarely used. Risk of adrenal crisis. 11-deoxycortisol measurement is not routinely available.
Standard dose short ACTH test	Synacthen 250 µg/m^2, IV (max 250 µg)	0-30-60	Cortisol > 39 µg/dL (1076 nmol/L) in children Cortisol > 30 µg/dL (833 nmol/L) in adults	Easy, safe	Low sensitivity
Low dose short ACTH test	Synacthen 1 µg (23) or 0.5 µg/m^2 (24) or 1 µg/m^2 (25) IV	0-30	Cortisol > 22 µg/dL (600 nmol/L)	Easy, safe More sensitive than standard dose short ACTH test	The process of dilution is challenging. The false negative test rate is high in patients with partial or recently emerged ACTH deficiency
Glucagon test	≥6 years: 1 mg, < 6 years: 30 µg/kg, IM	0-30-60-90-120-150-180	Cortisol > 14.6 µg/dL (402 nmol/L)	Cortisol and GH production can be evaluated simultaneously	Vomiting
CRH test	CRH 1 µg/kg (max 100 µg), IV	0-30-60	Cortisol > 18 µg/dL (500 nmol/L)	Differentiates hypothalamic disease from pituitary disease	Rarely used. Fascial flushing. Cut-off values are not well-defined.

ITT: insulin tolerance test, ACTH: adrenocorticotropic hormone, CRH: corticotropin-releasing hormone, GH: growth hormone, max: maximum

recently emerged ACTH deficiency, the sensitivity of the test is low since adrenal atrophy has not developed or is mild (20).

- Standard dose short ACTH test: Synacthen 250 µg ampoules are used. A peak cortisol response of < 16 µg/dL (440 nmol/L) most likely indicates CAI. To exclude CAI, the peak cortisol value should be > 30 µg/dL (833 nmol/L) in adults, and > 39 µg/dL (1076 nmol/L) in children (21,22). However, false negative results have been reported in patients with clinical signs of CAI. In order to increase the sensitivity of the standard dose short ACTH test, the low dose short ACTH test has been used (22).

- Low dose short ACTH test: The lowest ACTH dose that can produce a maximal cortisol response in healthy children and adults is 500 ng/1.73 m^2. Since the administration of 250 µg ACTH corresponds to supraphysiological doses, it has been suggested that the low dose short ACTH test using 1 µg ACTH is a more sensitive test for the diagnosis of CAI. Although various dosing recommendations for children have been reported in different studies, such as 1 µg (23), 0.5 µg/m^2 (24) and 1 µg/m^2 (25), administration of 1 µg ACTH is preferred. Children older than three years of age with a mature HPA axis can achieve the total daily ACTH production rates of 250 µg. Therefore, considering the technical difficulties in diluting and administering available corticotropin formulations in doses lower than 1 µg, the use of 1 µg of corticotropin analogue without body surface adjustment is rational and practical in children older than three years of age and in adults (23). To prepare a 1 µg dose, a Synacthen 250 µg ampoule is diluted with 250 mL normal saline and 1 mL of mixture is used for the test. Serum cortisol should be measured at baseline and 30 minutes after injection. The timing of cortisol sampling is very important because samples taken after more than 30 minutes may lead to false positive results. In children, a cortisol response of < 16 µg/dL (440 nmol/L) is highly suggestive of CAI, whereas a cortisol response of > 22 µg/dL (600 nmol/L) excludes CAI (19). The test is easier to perform than the insulin tolerance test (ITT) and carries a very low risk of side effects. However, it has not been validated in patients with acute illness, abnormal sleep-wake cycles, acute hypothalamic-pituitary disorders, patients who underwent pituitary surgery or received radiotherapy, and the impact of eating and drinking on the test results is unclear. In addition, its performance in children younger than three years of age has not been well studied. False negative results may be observed in recently emerged or partial ACTH deficiency. Therefore, ITT or metyrapone test is preferred in patients with normal biochemistry but ACTH deficiency is clinically suspected (19,20,26).

Low dose short ACTH test has been successfully used to monitor the recovery of adrenal function after discontinuation of oral glucocorticoids and to detect mild impairment in adrenal reserve during inhaled steroid

therapy (19). In a large meta-analysis, 13 studies conducted in adults were evaluated and it was concluded that the low dose test (with sampling 30 minutes after stimulation) had higher sensitivity than the standard dose test (26). In a later study, it was reported that the sensitivity of the low dose test was higher in children (19). Adrenal function is considered normal if the cortisol response to low dose (1 µg) or standard dose (250 µg) ACTH stimulation is >22 µg/dL (600 nmol/L). In a recently conducted meta-analysis, the diagnostic values of low dose and standard dose ACTH tests were found to be similar (27).

Insulin tolerance test: Since hypoglycemia is a strong stressor that causes rapid activation of the HPA axis, ITT is considered as the gold standard test for the diagnosis of secondary AI. Adequate increase in cortisol to insulin-induced hypoglycemia proves normal functioning of the axis. Glucose and cortisol levels are measured in the blood sample taken at 0, 30, 60, 90, 120 minutes after administering 0.1 U/kg regular insulin intravenously. To evaluate cortisol response, the serum glucose levels must decrease below 45 mg/dL or decrease by at least 50% compared to basal value. A peak serum cortisol level above 20 µg/dL (550 nmol/L) indicates normal ACTH reserve. Due to the risk of hypoglycemic convulsions, it should be performed in the hospital with caution. Particularly in young children, an alternative ACTH test is usually preferred. ITT is contraindicated in patients with cardiovascular diseases or a history of convulsions (19,20).

Metyrapone test: A single dose of 30 mg/kg metyrapone is orally administered at night, and the plasma 11-deoxycortisol levels are measured at 08:00 am in the following morning. The effect of metyrapone is to reduce cortisol and corticosterone production by blocking 11-beta-hydroxylation and therefore to increase the 11-deoxycortisol (compound S) and 11-deoxycorticosterone levels due to the increased ACTH effect as a result of the decreased negative feedback effect on the HPA axis. Detection of plasma 11-deoxycortisol levels above 7 µg/dL (200 mmol/L) in the morning indicates that the HPA axis is functioning normally. The stimulating effect of metyrapone on ACTH is not as strong as the effect of hypoglycemia (26).

Glucagon test: In young children, evaluation with the glucagon stimulation test is preferred to ITT because of safety. Cortisol and GH levels are measured simultaneously. Glucagon elevates blood glucose levels, then the glucose levels decrease with the secretion of endogenous insulin and in parallel with this, cortisol and GH levels increase. For the diagnosis of CAI in children with GH deficiency below six years, the results of glucagon test have been found to be consistent with the results of ITT (28). A cortisol response of <14.6 µg/dL (402 nmol/L) to glucagon strongly supports CAI in young children with GH deficiency. It has been suggested that the glucagon test is easy to perform and also sensitive in terms of reflecting the functioning of the HPA axis (28).

Corticotropin-releasing hormone test: This has been used to differentiate the disorders of the hypothalamus from those of the pituitary. Since normal response values in children are not well defined and the cortisol response to CRH is highly variable, it is not widely used in children (20).

Dehydroepiandrosterone sulfate: Measuring the dehydroepiandrosterone sulfate (DHEAS) levels may be useful in evaluating the HPA axis. In the presence of normal DHEAS levels, the probability of CAI decreases (29).

Good practice points:

1. If there is a suspicion of CAI, the first step test should be a baseline morning cortisol measurement at 08:00 am. In infants older than six months and children, a morning cortisol level of <3 µg/dL (83 nmol/L) indicates adrenal insufficiency, and a level of >13 µg/dL (365 nmol/L) indicates normal functioning of the HPA axis (1⊕⊕⊕O).

2. Low-dose (1 µg) short ACTH test is recommended as a safer and more sensitive test for the diagnosis of CAI. In children, a cortisol response of <16 µg/dL (440 nmol/L) is highly suggestive of CAI, whereas a cortisol response of >22 µg/dL (600 nmol/L) excludes CAI (1⊕⊕⊕O).

Diagnostic Approach

The first step of the diagnostic approach is measuring the morning basal cortisol level. If the basal cortisol level is between 3-13 µg/dL, the low dose short ACTH test should be performed as the second step. If there is any uncertainty in the results and there are no contraindications, the ITT or metyrapone test should be performed. None of the tests, including ITT, are 100% accurate and false positive or false negative results may be observed. Therefore, clinical evaluation is crucial to decide which patients should be re-evaluated in terms of adrenal function. The diagnostic approach in patients with suspected CAI is summarized in Figure 1 (15,19).

Evaluation of adrenal function in hypothalamic-pituitary disorders: In all hypothalamic-pituitary disorders, such as tumors, pituitary apoplexy, infiltrative or inflammatory diseases, severe cranial trauma, and craniospinal

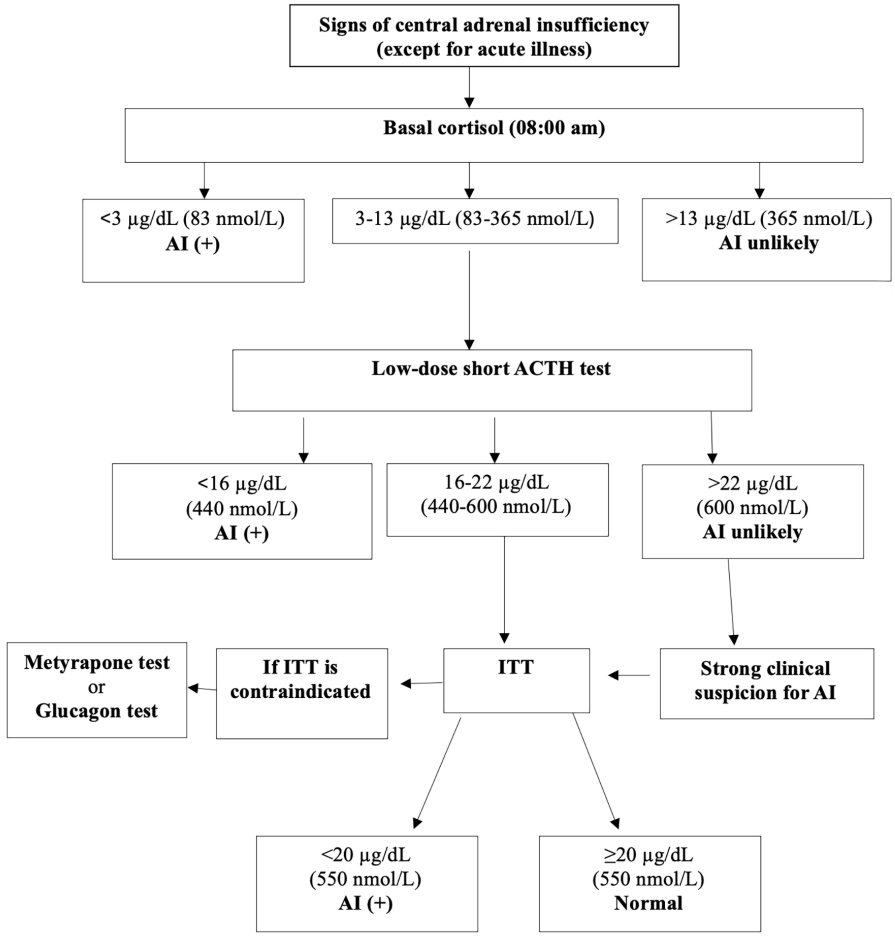

Figure 1. Diagnostic approach in patients with suspected central adrenal insufficiency (modified from references 15 and 19)

AI: adrenal insufficiency, ITT: insulin tolerance test, ACTH: adrenocorticotropic hormone

radiotherapy (including patients treated with low-dose radiotherapy < 40 Gy), patients are at risk for complete or partial ACTH deficiency. Even if these patients are clinically asymptomatic, the HPA axis may not show an adequate stress response. Therefore, it is necessary to evaluate the patients in terms of CAI. However, a normal cortisol response does not exclude the possibility of CAI in the future, and lifelong follow-up is recommended for these patients (23).

Central adrenal insufficiency after pituitary surgery: Since adrenal atrophy may develop gradually from the onset of ACTH deficiency, screening should be performed with low dose ACTH test at least 4-6 weeks after pituitary surgery. Until then, hydrocortisone replacement should be initiated in patients whose morning basal cortisol levels are < 16 µg/dL (450 nmol/L) three days after surgery and < 12 µg/dL (350 nmol/L) seven days after surgery, in whom CAI could not be excluded. If the patient is stable, low dose ACTH test can be performed after 12-24 hours discontinuation of hydrocortisone (30).

Central adrenal insufficiency in critically ill patients: Partial CAI may not be recognized in critically ill patients. Catecholamine-dependent hypodynamic shock, which generally responds to hydrocortisone therapy, is observed in these patients (31). In critically ill patients with suspected AI, sampling for random serum cortisol and plasma ACTH is recommended, followed by immediate initiation of hydrocortisone. Etomidate, a widely used strong hypnotic agent, can inhibit cortisol production. Therefore, the use of etomidate should be questioned, especially in critically ill patients (32).

Central adrenal insufficiency after corticosteroid therapy: Suppression of the HPA axis by exogenous glucocorticoid therapy is the most common cause of impaired adrenal response. This topic is discussed in Part 11 (33).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (34).

Good practice points:

1. A three-step approach should be taken in the evaluation of patients with suspected CAI. The first step should be measuring the morning basal cortisol level, the second step should be performing the low dose short ACTH test, and if there is any uncertainty in the results and there are no contraindications, the third step should be performing the ITT or metyrapone test (1⊕⊕⊕O).

2. In all hypothalamic-pituitary abnormalities, such as tumors, pituitary apoplexy, infiltrative or inflammatory diseases, severe cranial trauma, craniospinal radiotherapy and pituitary surgery, patients should be evaluated for CAI, and lifelong follow-up is required (1⊕⊕⊕O).

3. In critically ill patients with suspected AI, sampling for random serum cortisol and plasma ACTH is recommended, followed by immediate initiation of hydrocortisone (1⊕⊕⊕O).

Footnotes

Authorship Contributions

Concept: Firdevs Baş, Design: Firdevs Baş, Analysis or Interpretation: Melek Yıldız, Literature Search: Melek Yıldız, Ruken Yıldırım, Writing: Melek Yıldız, Ruken Yıldırım, Firdevs Baş.

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