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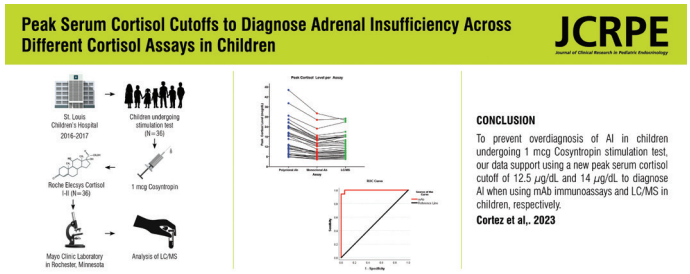

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EDITORIAL

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J Clin Res Pediatr Endocrinol 2025;17(Suppl 1):1-2

Congenital Adrenal Hyperplasia and Adrenal Insufficiency in Children: An Evidence-based Review with Good Practice Points by Adrenal Working Group of The Turkish Society for Pediatric Endocrinology and Diabetes

Zeynep Şıklar

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Keywords: Congenital adrenal hyperplasia, adrenal insufficiency, children, childhood, neonatal, CAH screening, genetics, antenatal, quality of life, adrenal crisis

Adrenal gland diseases in pediatric cases constitute a heterogeneous group of diseases. Within this group, congenital adrenal hyperplasia (CAH) and adrenal insufficiencies are important endocrine problems that require accurate diagnosis and urgent treatment. Recent developments, the development of genetic diagnostic methods, the widespread use of screening programs and innovations in the field of treatment have caused more attention in this diagnostic group.

Fifteen years ago, various working groups according to endocrine disease groups were established within the Turkish Society for Pediatric Endocrinology and Diabetes. 'Adrenal Working Group' is one of these groups with the aim of improving the care of children with pediatric adrenal diseases. This working group plans and continues educational activities such as preparing diagnosis and treatment recommendations for pediatric adrenal diseases, preparing materials (videos, brochures) to inform pediatricians and pediatric endocrinologists, and organizing seminars and conferences.

Classical CAH is the most common form of primary adrenal insufficiency in childhood and is a potentially life-threatening condition. In our country, a pilot study found that the incidence of classical 21-hydroxylase deficiency in the screened population was 1:7,787; subsequently, the initiation of the newborn CAH screening program was a significant diagnostic step (1).

Moreover, since most diseases of the adrenal gland are hereditary, their incidence is higher in societies where consanguineous marriages are common than in other societies. Studies reported from our country draw attention to the importance of adrenal problems (2,3,4,5,6). In addition to common diseases of the adrenal gland, sharing experiences with rare adrenal gland problems will also be useful for the management of these diseases.

One of the rare causes of CAH is 17-hydroxylase deficiency. A publication from our country that included the largest pediatric endocrine case series, analyzed data from a total of 97 cases from 78 families. In addition to important clinical and genetic data specific to 17-hydroxylase deficiency, data

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from a significant number of patients regarding the final height of the cases were presented (7).

New medications are being introduced for adrenal gland diseases, especially for CAH. Children with classic CAH require treatment with glucocorticoids, usually at supraphysiologic doses, to address cortisol insufficiency and reduce excess adrenal androgens. However, such treatment confers a predisposition to glucocorticoid-related complications. For this reason, there are new treatment interventions such as corticotropin-releasing factor type 1 receptor antagonist, modified release hydrocortisone etc. (8,9).

Despite all the developments and advances, the diagnosis and treatment of adrenal insufficiency remains a challenge for both patients and healtcare providers. Some problems are occasionally encountered in those cases. It is known that, patients with adrenal insufficiency have increased morbidity, mortality and impaired quality of life (1). Understanding the issues that may arise during long-term follow-up is another important aspect of managing these patients.

It is very valuable for physicians working in the field of pediatric endocrinology, as well as pediatricians who first encounter patients, to have access to adequate information about CAH and adrenal insufficiency, especially in managing patients during emergencies.

It has been acknowledged by the 'Adrenal Working Group' that there is a need to prevent these difficulties, raise awareness about CAH and adrenal insufficiency, and create an easily accessible and holistic resource in diagnosis and treatment. This evidence-based review with good practice points developed by 'Adrenal Working Group of 'The Turkish Society for Pediatric Endocrinology and Diabetes' to provide good practice points, with focus on recommendations for daily management of adrenal diseases including CAH and adrenal insufficiencies.

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REVIEW

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Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency

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Abstract

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease caused by the deficiency of one of the enzymes involved in cortisol synthesis. Between 90% and 99% of cases of CAH are caused by 21-hydroxylase deficiency (21-OHD) caused by mutations in *CYP21A2*. Although 21-OHD has been historically divided into classical and non-classical forms, it is now thought to show a continuous phenotype. In the classical form, the external genitalia in females becomes virilized to varying degrees. If the disease is not recognized, salt wasting crises in the classical form may threaten life in neonates. Children experience accelerated somatic growth, increased bone age, and premature pubic hair in the simple virilizing form of classical 21-OHD. Female adolescents may present with severe acne, hirsutism, androgenic alopecia, menstrual irregularity or primary amenorrhea in the non-classical form. Diagnosis of CAH is made by clinical, biochemical and molecular genetic evaluation. In cases of 21-OHD, the diagnosis is based on the 17-hydroxyprogesterone (17-OHP) level being above 1000 ng/dL, measured early in the morning. In cases with borderline 17-OHP levels (200-1000 ng/dL), it is recommended to perform an adrenocorticotropic hormone (ACTH) stimulation test. Genotyping in cases with CAH should be performed if the adrenocortical profile is suspicious or if the ACTH stimulation test cannot be performed completely. After diagnosis, determining the carrier status of the parents and determining which parent the mutation was passed on from will help in interpreting the genetic results and determining the risk of recurrence in subsequent pregnancies.

Keywords: Congenital adrenal hyperplasia, 21-hydroxylase deficiency, children, adolescent, diagnosis

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease caused by the deficiency of one of the enzymes involved in cortisol synthesis. Between 90% and 99% of cases are caused by 21-hydroxylase deficiency (21-OHD) due to mutations in the *CYP21A2* gene (1,2). Although 21-OHD has been historically divided into classical and non-classical forms, it is now thought to show a continuous phenotype. The classical form is accompanied by absence or severe deficiency in enzyme activity. The most serious form is the classical form of CAH with salt loss and is characterized by adrenal insufficiency with cortisol and aldosterone deficiency and excessive androgen production (2). If this form is not recognized, salt wasting crises (hyponatremia, hyperkalemia, acidosis, hypovolemia and shock) develop in 75% of cases in the first three weeks of life (3).

In the simple virilizing form, enzyme activity is at the level of 1-5%. Cortisol deficiency and androgen excess are prominent (2). Affected children are identified later in

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childhood because of early pubic hair development and virilization (3).

Milder forms of the disease are defined as 'late-onset' or 'non-classical' CAH (NCCAH), and partial enzyme deficiencies are compensated by elevations in adrenocorticotropic hormone (ACTH) (1). In NCCAH, mild subclinical impairment in cortisol synthesis does not usually lead to adrenal crisis.

The purpose of this review is to provide practical clinical points for the diagnosis of 21-OHD in children and adolescents. This evidence-based review with good practice points was developed by the 'Adrenal Working Group' of the 'Turkish Society for Pediatric Endocrinology and Diabetes'. The Adrenal Working Group held meetings online between 2022-2024, at least four times annually. First of all, two subgroup topics (subgroup 1: CAH and other adrenal deficiencies in childhood and adolescence; subgroup 2: Adrenal tumors and Cushing syndrome) were created. A total of 41 researchers, 28 in the first subgroup, 13 in the second subgroup, also organized meetings among themselves. Evidence-based review with good practice points was guided by systematic reviews of evidence and discussion. During the meetings, all comments and suggestions were discussed and implemented as appropriate by the working group.

Good practice points are graded according to the Grading of Recommendations, Assessment, Development, and Evaluation system. When grading, first the strength of recommendation and then the quality of evidence are stated. The recommendations are categorized as 1 (strong recommendation) or 2 (weak recommendation). The quality of evidence behind the recommendations is classified as very low (⊕OOO), low (⊕⊕OO), moderate (⊕⊕⊕O) and strong (⊕⊕⊕⊕) (4).

Epidemiology

Based on newborn screening and national case registries, the frequency of classic CAH has been shown to be 1/14,000-18,000 worldwide (5). In the extended neonatal screening programme for CAH in Turkey, the incidence of classical 21-OHD was determined to be 1:15,067. Of these patients, 75% had salt wasting and 25% had simple virilizing 21-OHD CAH (6). Based on haplotype association studies, the prevalence of NCCAH forms in the white population is estimated to be between 1:500 and 1:1,000, but may be as high as 1:50 to 1:100 in populations with a high rate of consanguineous marriages (5). It has also been reported that the frequency is higher among Ashkenazi Jews, Hispanics, those of Mediterranean origin, those from the Middle East and Inuits (7). In a more recent study, it has been shown that the frequency of NCCAH in the United States population is 1:200 as a result of *CYP21A2* genotype analysis (8). In another study, the frequency of NCCAH was found to be approximately 4% among women presenting with androgen excess symptoms (9).

Clinical Findings

In the classical salt wasting form, affected infants usually present within the first three weeks after birth with poor weight gain, recurrent vomiting, dehydration, hypotension, acidosis, hyponatremia, hyperkalemia, hypoglycemia and shock. With the increase in prenatal androgen production, the external genitalia in females becomes virilized to varying degrees (cliteromegaly, labial fusion, hyperpigmentation, or various degrees of virilization similar to male external genitalia). In the presence of atypical genitalia or bilateral nonpalpable testicles, pelvic ultrasonography may be necessary to determine presence or absence of uterus in females (2,3). External genitalia of male infants with the classical form may present with hyperpigmentation and macrogenitalia (2).

In the mild form of classical CAH (simple virilizing CAH) affected children are identified later in childhood because of early pubic hair development, clitoromegaly, urogenital sinus that was not noticed earlier in life, or both, in females, and with early development of pubic hair, phallic enlargement, or both, in males (3). With androgen excess, these children experience accelerated somatic growth and increased bone age (2,3).

As a result of high androgens and poor hormonal control, central precocious puberty, menstrual irregularities, acne, hirsutism, male pattern hair loss, and masculine body structure in young girls, and decreased fertility are observed. In cases that do not receive appropriate treatment, adult height remains short due to the effect of high androgens (2). Another reason why adult height remains short is the suppression of growth by inappropriate use of high dose steroids for a long time (3). A summary of the clinical findings seen in patients with CAH is shown in Figure 1.

In the non-classical form, the spectrum of symptoms at diagnosis is mostly age-related. While premature adrenarche is the most common complaint (87%) in children under the age of 10 years, female adolescents have been reported to present with severe acne, hirsutism, androgenic alopecia, clitoromegaly (11%), menstrual irregularity (56%) and even with primary amenorrhea (9%) (9,10).

Girls with NCCAH often present during adolescence and young adulthood with acne, hirsutism, menstrual

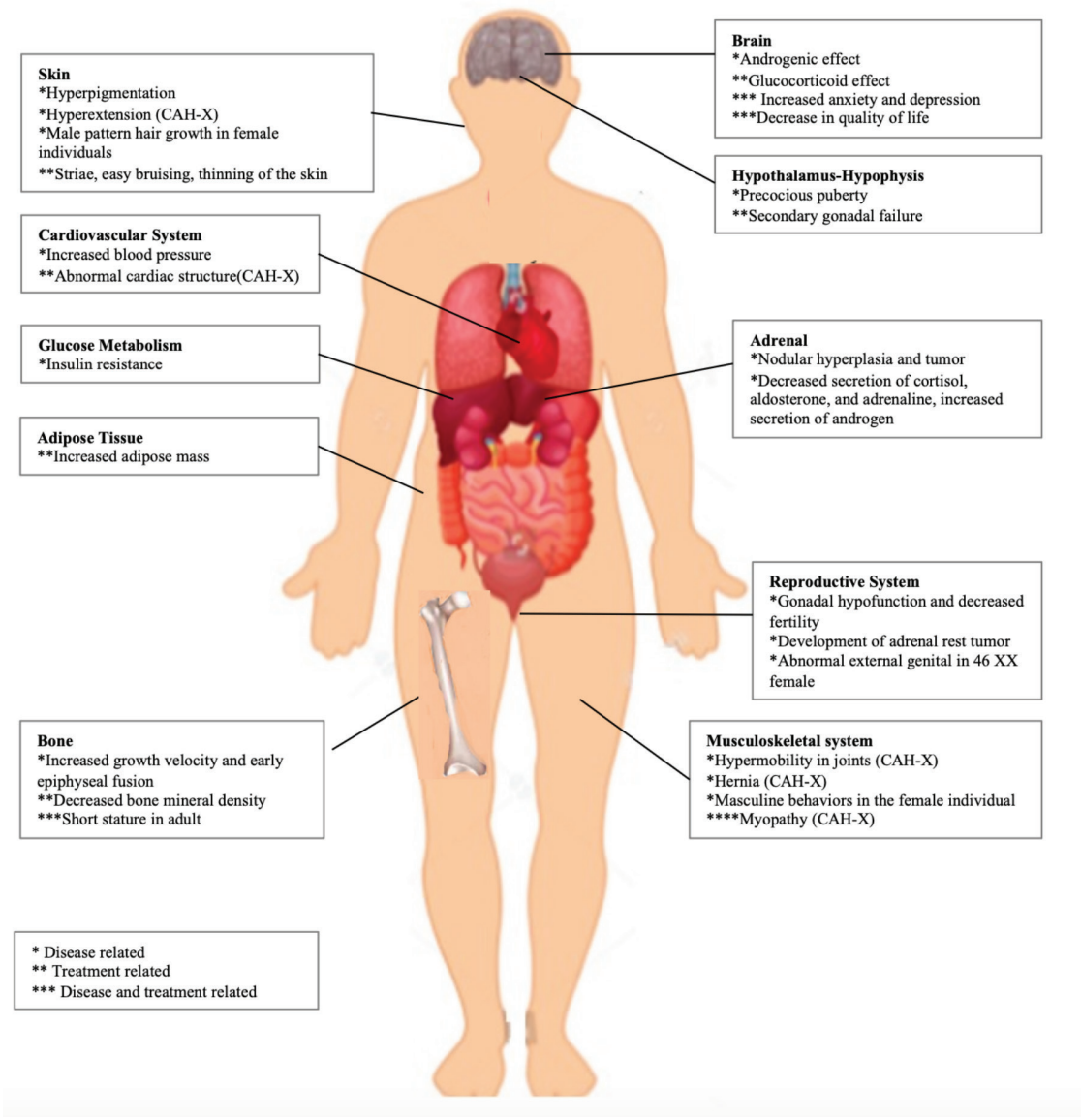

Figure 1. Clinical findings and complications in patients with CAH

CAH: congenital adrenal hyperplasia

abnormalities, or infertility; all of which largely overlaps with polycystic ovary syndrome (PCOS). Male patients with NCCAH are less likely to be admitted to hospital due to symptoms of androgen excess and because of this, they are diagnosed less frequently than girls. Males are mostly diagnosed during genetic screening for pre-pregnancy counseling (9,11). Studies on male patients with NCCAH are thus quite limited. In a study of 45 male cases, it was reported that 29% of the cases presented with premature pubarche (12).

During childhood androgen excess in NCCAH does not cause virilization of the external genitalia in 46, XX fetuses during the prenatal period. The most common findings in patients presenting during childhood may be listed as oily skin, acne or adult-type body odor, and premature pubarche. It has been shown that 20% of children under the age of 10 years have clitoromegaly and acne (10). Increased androgen levels can lead to accelerated growth. However, since androgen excess in the early period does not affect the growth rate, no acceleration in growth is observed before the age of 1-2 years (13,14). In patients with NCCAH, increased 17-OHP and adrenal androgens may convert to estrogens and cause advanced bone age. Although previous studies have reported that the final height of most children with NCCAH reaches the target height range, it is nevertheless suggested that accelerated bone age may negatively affect final height

over time (9,15). In a study conducted among females over the age of 10 years, the most common complaints were: hirsutism (59%); oligomenorrhea (54%); acne (33%); infertility (13%); clitoromegaly (10%); alopecia (8%); primary amenorrhea (4%); and premature pubarche (4%) (10).

Good practice points:

1. CAH is a problem that most commonly occurs as a result of 21-OHD, and in its classical form, cortisol and aldosterone deficiency and androgen excess are observed (1⊕⊕⊕O).

2. Diagnosis is made by clinical, biochemical and genetic evaluation (1⊕⊕⊕O).

Biochemical Diagnosis

To reiterate, 21-OHD should be kept in mind in an infant with symptoms of dehydration, acidosis, hyponatremia, hyperkalemia, hypoglycemia or shock. There is relative renal tubular resistance to aldosterone in the early period of the disease (2).

Analysis of steroid hormones is based either on immunoassay principles or chromatographic methods combined with mass spectrometry (MS). In the immunoassay method, the antibody used must be specific to prevent cross-reactivity with other metabolites. Moreover, organic extraction will ensure the removal of cross-reacting substances, such as steroid sulfates (2).

Today, MS is the method that provides the most accurate and versatile results in steroid measurement. Applying liquid chromatography (LC) or gas chromatography (GC) initially increases specificity. A significant portion of the steroids is excreted in the urine. Thus urinary steroid analysis is one of the methods with high diagnostic value. LC-MS is a newer technique than GC-MS, and extra filtering by tandem MS (MS/MS) further improves the separation ability of LC. Today, measurement of steroid hormones in plasma or serum by LC-MS/MS is the most appropriate method (2).

In cases of 21-OHD, the diagnosis is based on the 17-OHP level being above 1000 ng/dL (30 nmol/L). However, in most infants the level is above 5000 ng/dL (150 nmol/L). Although random measurements are informative for diagnosis, corticotropin stimulation testing is necessary to confirm the diagnosis and exclude other rare disorders of steroidogenesis. High 17-OHP levels can be seen in 11β-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency and P450 oxyreductase deficiencies (3). Since the 17-OHP level is closely related to the circadian rhythm of ACTH, incidentally measured 17-OHP levels must be checked early in the morning (before 08:00) (1). For menstruating women, steroid measurements should be made during the follicular phase, as fluctuations in 17-OHP levels occur during the luteal phase of the menstrual cycle. Sometimes it may be difficult to distinguish between classical and non-classical forms of CAH that do not cause salt loss (1,5).

The pharmacological dose currently used for testing is 0.25 mg cosytropin intravenously (iv), which maximally stimulates the adrenal cortex (in very low birth weight infants, the dose may be reduced to 0.125 mg). Blood samples should be taken at baseline and 60 minutes after iv cosyntropin administration (5). There are studies showing that the intramuscular cosyntropin test is safe and effective in the diagnosis of adrenal insufficiency and CAH if the iv form is not available (16,17,18).

For the test to be informative at least cortisol and 17-OHP should be measured. In order to evaluate all enzyme defects that may cause CAH, it is appropriate to measure 17-OHP, cortisol, 11-deoxycorticosterone, 11-deoxycortisol, 17-OH-pregnenolone, dehydroepiandrosterone and androstenedione in blood samples by LC-MS/MS after the stimulation test (5).

It is reported that in a case with suspected CAH, if the 17-OHP level is found to be lower than 80 ng/dL (2.5 nmol/L) in children and 200 ng/dL (6.0 nmol/L) in adults, the diagnosis of CAH should be excluded (19,20,21,22). It has been suggested that only 10% of patients with NCCAH due to 21-OHD had basal 17-OHP levels lower than 200 ng/dL (6 nmol/L) (23). A 17-OHP measurement for 21-OHD deficiency being greater than 200 ng/dL (6 nmol/L) suggests the diagnosis of NCCAH. Typically, this value is greater than 10,000 ng/dL (300 nmol/L) in patients with classical 21-OHD. Patients with moderately high 17-OHP levels (6-30 nmol/L or 200-1,000 ng/dL) should undergo an ACTH (cosyntropin) stimulation test. If the stimulated 17-OHP result is <1000 ng/mL (<30 nmol/L), 21-OHD will be excluded (Figure 2) (5).

The threshold value for the 17-OHP level needs to be evaluated according to the test methodology. When the threshold value of 17-OHP is accepted as >200 ng/dL (>6 nmol/L), the diagnosis may be missed in some patients with NCCAH (24). Therefore lower threshold values have been recommended, especially when using the MS method (2). False-positive 17-OHP screening results are even more common, especially when immunoassay methods are used and blood samples are taken in the luteal phase.

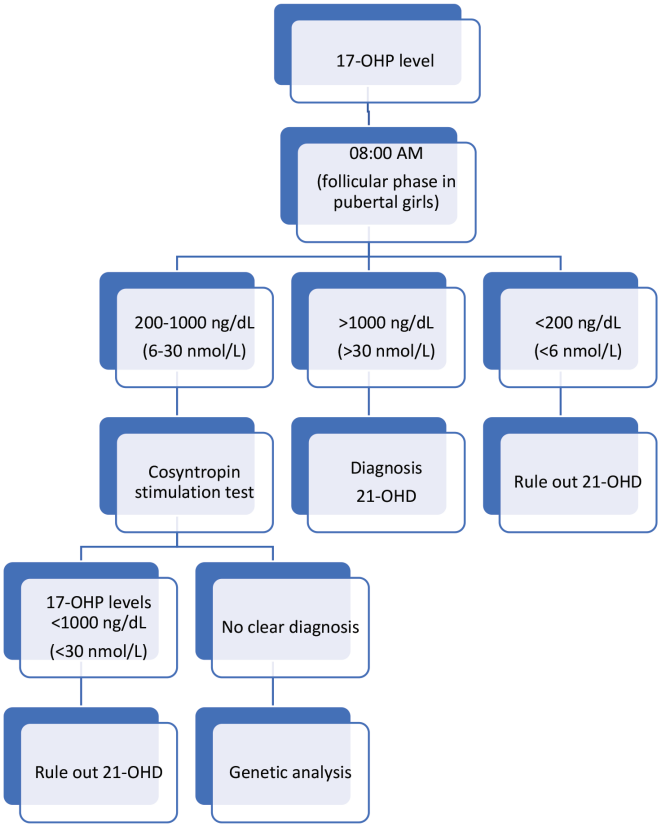

Figure 2. 17-OHP levels for 21-OHD diagnosis

17-OHP: 17-hydroxyprogesterone, 21-OHD: 21-hydroxylase deficiency

NCCAH and PCOS may have similar clinical appearance. Moderate elevation of 17-OHP has been reported in 25% of women with PCOS (25,26). Furthermore, some individuals with adrenal incidentalomas may have 17-OHP levels above >1000 ng/mL (30 nmol/L) without a genetically confirmed carrier state or NCCAH (27). Most patients with NCCAH have normal ACTH levels. In cases with 21-OHD, it results in an increase in 17-OHP levels, independent of the increase in ACTH, due to the kinetics of the enzymatic steps. Increased 17-OHP levels results in overproduction of adrenal androgens and their precursors. These androgens include testosterone (T) and androstenedione, as well as metabolites called 11-oxyandrogens (28). Usually, a high androstenedione/T ratio suggests adrenal androgen excess. However, while women with CAH often develop PCOS, the production of adrenal androgens is also increased in the majority of patients with PCOS. This makes the situation more complicated (1).

The most common symptom of NCCAH in childhood is premature adenarche. In a study including 59 cases diagnosed with premature adrenarche, basal and ACTH stimulated 17-OHP levels were examined. In addition, DNA sequencing and multiplex ligation-dependent probe amplification (MLPA) analysis were performed to identify mutations in *CYP21A2*. In this study, twelve girls were diagnosed with NCCAH (29). In a study with 238 patients with premature pubarche, the frequency of NCCAH was 4% with ACTH stimulation test (20). In another study including 111 patients, six cases were diagnosed with NCCAH and the investigators also concluded that a basal 17-OHP level of >200 ng/dL (>6 nmol/L) was a useful screening test (30).

A total of 126 patients with premature pubarche, hirsutism, or PCOS were studied by Binay et al. (31). Among them, six patients (4.7%) were diagnosed with NCCAH based on mutational analysis. NCCAH was diagnosed in 4.2% of cases with premature pubarche and in 3.8% of cases with PCOS.

Good practice points:

1. LC-MS/MS method should preferably be used in adrenal steroid measurement. However, if LC-MS/MS is not available, immunoassay methods using specific antibodies are used (1⊕⊕⊕O).

2. In symptomatic cases after infancy, screening is performed in the early morning hours (before 08:00) with the basal 17-OHP level measured by the LC-MS/MS method (1⊕⊕OO).

3. In cases with borderline 17-OHP levels (6-30 nmol/L or 200-1000 ng/dL), it would be appropriate to perform an ACTH stimulation test and check a complete adrenocortical hormonal profile to distinguish 21-OHD from other enzyme defects (1⊕⊕OO).

4. NCCAH should be considered in the differential diagnosis in all adolescent girls with a PCOS-like phenotype. In addition, NCCAH should be excluded in all pediatric cases presenting with premature adrenarche (2⊕⊕OO).

Molecular Genetic Diagnosis

In suspected cases, the diagnosis should be confirmed with genetic tests and genetic counseling should be provided with a treatment decision accordingly (10). Interpretation of the steroid profile may be difficult in some cases; slight elevations of 17-OHP may be observed in some cases with heterozygous mutation. In some cases with homozygous mutations, the same mutation (such as c.293-13C>G) may result in simple virilization in some patients or salt wasting in others. Genetic analysis may be necessary to provide genetic counseling and make a definitive diagnosis (5). In addition, an accurate and reliable genotype-phenotype association

in 21-OHD will help in therapeutic management. In fact, genetic mutation analyzes of *CYP21A2* are recommended by some authors as one of the first options, as the use of genetic techniques is increasing, they are becoming cheaper, and the time to get results is shortening. It is considered a practical and economical diagnostic modality by some authors (32).

It is currently reported that in 21-OHD cases, *CYP21A2* genotyping with next-generation sequencing and MLPA as a genetic diagnosis method can accurately and reliably confirm the diagnosis (32). Today, the Southern blot analysis method is no longer considered the gold standard method because it requires a large amount of high-quality DNA, is time-consuming, has excessive workload, and is insufficient to detect deletions/duplications. The most commonly used method for determining gene dosage (deletion, duplication, rearrangement, fusion) is MLPA. It is appropriate to use *CYP21A1*-specific primers to prevent pseudogene amplification and allele loss of non-amplified PCR fragments (2). Within the scope of 21-OHD genetic testing, copy number variation (CNV) evaluation is required. Since individuals carrying the p.Gln319Ter variant usually have a duplication in *CYP21A2*, CNV evaluation is always recommended in cases where this mutation is detected (33).

Targeted molecular genetic strategies for frequent mutations are implemented in some laboratories. However, direct sequencing of amplified PCR products and their combination with methods that detect gene deletions/chimeric genes can detect almost all of the mutations (2). In a study using the next-generation sequencing method, 222 of 226 alleles were detected in cases with 21-OHD. Therefore, its diagnostic sensitivity was 98.2% (32).

The gene encoding 21-hydroxylase, *CYP21A2*, is located in the human leukocyte antigen (HLA) class 3 region on chromosome 6 at the 6p21.3 position, with 98% homology to the active gene, but together with the inactive *CYP21A1P* pseudogene. Four genes [serine/threonine kinase 19, complement C4, steroid 21-hydroxylase CYP21, and tenascin X (TNX)] are organized in this region, forming an RCCX module. Mutations that cause 21-OHD mostly occur as a result of intergenic recombinations, microconversion events, gene deletions, chimerism and gene duplications (11,34).

Intergenic recombinations are responsible for 70% of mutations related to 21-OHD. Among intergenic recombinations, approximately 75% occur when mutations in the *CYP21A1P* pseudogene are transferred to the functional *CYP21A2* as a result of microconversion (3,33).

To date, nine different chimeric *CYP21A1P/CYP21A2* genes have been identified. Seven chimeras carry the pseudogene specific mutation c.293-13C>G in intron 2 and this is associated with severe salt-wasting CAH; this chimerism is called classical or general chimerism. If the junction site occurs upstream of the c.293-13C>G variant, 21-hydroxylase activity is less affected and a milder clinical phenotype occurs, termed attenuated chimerism (33).

Clinical severity is determined by the extent of the residual enzyme activity in one or both variant alleles. Mutations that lead to the salt-wasting CAH phenotype that completely abolish 21-hydroxylase enzyme activity are associated with both lack of glucocorticoid and mineralocorticoid production that leads to salt loss. Milder phenotypes are caused by *CYP21A2* variants that result in lesser degrees of enzymic dysfunction/loss. The simple virilizing CAH-associated variants have 2-10% residual function while the enzymatic activity of the milder NCCAH phenotypes has a wide range, between 10% and 75% (11,34,35,36).

The correlation of clinical phenotype with genotype was strong, particularly in salt-wasting and NCCAH disease (37). Variants on *CYP21A2* are classified into four groups, Group 0, A, B and C, according to residual 21-hydroxylase activity. Group 0 and A are associated with the salt-wasting form and the Group 0 (null variants) have 0% enzyme activity. Group A variants carry a minimal (<1%) residual activity, Group B has almost 2% residual enzymatic activity, and Group C variants have 20-50% enzyme activity (32,38).

Group A and included patients who carry homozygous null mutations result in completely inactive enzymes, including gene deletions such as 8bp del, large gene conversion, E6 cluster, p.Arg357Trp, p.Gln319Ter, p.L308Ffs*6, p.Gly111Valfs*21, novel frameshift mutation, and multiple mutations alleles with any of these mutations. Group A variants include those homozygous for the IVS2-13A/C>G mutation or compound heterozygosity with the null variants. Group B include most frequently the mutation p.Ile173Asn and the promoter conversion + Pro31Leu, homozygous or compound heterozygous with a null or Group A mutation. Group C variants include homozygous p.Pro30Leu, p.Pro453Ser, p.Val281Leu mutations (20-50%) or in compound heterozygosis with the former (null, A, or B) mutations. Group B and C variants are related to the simple virilizing and NCCAH form of the 21-OHD, respectively (30,31,32,34,35,36,37,38,39,40). In addition, Group D and Group E genetic variants have been identified. Group D consist of patients with novel mutations or variants whose enzymatic activity impairment had not been assessed, and Group E consist of patients with at least one allele without mutations (38).

In a study of 113 cases, genotype-phenotype correlation was analyzed to determine predictive properties of variant groups of *CYP21A2*. Genotype-phenotype correlation was reported to be 91.5%. A complete genotype-phenotype match was observed in Group 0. It was also proposed that Group A be divided into two subgroups, A1 and A2, and the positive prediction of subgroup A1 was higher than Group A and subgroup A2. Genotypes correctly predicted phenotypes in 79.5% of patients in Group A; 100% in subgroup A1 and 75% in subgroup A2 (32).

In the case of compound heterozygosity, the mutation with the mildest effect on enzymatic activity determines the predicted phenotype. However, in alleles containing multiple mutations, the most deleterious mutation determines the genotype groups (41).

The c.293-13C>G mutation is more deleterious than homozygous genotype when trans with null mutations. While the c.293-13C>G mutation mostly causes salt-wasting CAH, it is also seen in approximately 20% of simple virilizing cases. NCCAH is observed in the majority of cases carrying the p.Pro30Leu mutation, while the classical CAH phenotype can be seen in >30%. While the p.Ile173Asn mutation usually causes a simple virilizing phenotype, it is also detected in 23% of salt-wasting CAH cases (32,34,40).

In different studies from Turkey, c.293-13C>G, large deletions/conversions, p.Arg357Trp and p.Gln319Ter were found to be the most common genetic mutations in the salt-wasting form; c.293-13C>G and p.Ile173Asn were found to be the most common genetic mutations in the simple virilizing form and c.293-13C>G, p.Ile173Asn, p.Pro30Leu, and p.Gln319Ter were found to be the most common genetic mutations in the non-classical form (23,32,42,43,44,45).

In two studies in which children born to women with NCCAH were retrospectively analyzed, the risk of having a child with classical 21-OHD was found to be 1.5-2.5% (46,47). In terms of risk identification, *CYP21A2* genotyping is recommended before planning pregnancy (5).

As a result of complete deletion of *CYP21A2*, the recessive form of Ehler-Danlos syndrome associated with tenascin-X-deficiency occurs. Joint hypermobility, arthralgia, joint dislocation, hernias and midline defects are observed in these cases (2,3,9,33).

Genetic screening of carriers: If possible, determining the carrier status of the parents and determining which parent the mutation was passed on from (especially in case of combined heterozygosity) will help in interpreting the genetic results and determining the risk of recurrence in subsequent pregnancies (2).

Good practice point:

1. Genotyping in cases with CAH is recommended for diagnosis and management in cases where 21-OHD is considered. If the patient has a steroid profile and ACTH stimulation test result that suggests the diagnosis of CAH, or baseline steroid levels may not be readily available, genotyping should be performed (2⊕⊕OO).

Footnotes

Authorship Contributions

Concept: Zeynep Şıklar, Design: Zeynep Şıklar, Data Collection or Processing: Zeynep Şıklar, Analysis or Interpretation: Havva Nur Peltek Kendirci, Zeynep Şıklar, Literature Search: Sevinç Odabaşı Güneş, Havva Nur Peltek Kendirci, Edip Ünal, Ayşe Derya Buluş, İsmail Dündar, Zeynep Şıklar, Writing: Sevinç Odabaşı Güneş, Havva Nur Peltek Kendirci, Edip Ünal, Ayşe Derya Buluş, İsmail Dündar, Zeynep Şıklar.

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REVIEW

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Treatment and Follow-up of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency in Childhood and Adolescence

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Abstract

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease caused by the deficiency of one of the enzymes involved in cortisol synthesis. More than 95% of the cases occur as a result of defects in the gene encoding 21-hydroxylase (*CYP21A2*). 21-hydroxylase deficiency has been divided into classical and non-classical forms. In the treatment of classical CAH, it is necessary to replace both glucocorticoid (GC) and mineralocorticoid hormones to prevent salt wasting crisis and reduce excessive corticotropin. In addition to biochemical measurements to evaluate the adequacy of GC and mineralocorticoid treatment; growth rate, body weight, blood pressure and physical examination should be evaluated regularly. There is insufficient data regarding the use of continuous slow-release or modified-release hydrocortisone (HC) preparations and continuous subcutaneous HC infusion, additional/alternative treatment approaches, and cell-based therapies and gene editing technology in children with CAH. GC therapy is recommended in children with inappropriately early onset and rapidly progressing pubarche or accelerated bone age progression, and in adolescents with non-classical CAH (NCCAH) who have overt virilization. In patients with NCCAH, stress doses of HC is recommended for major surgery, trauma, or childbirth but only if the patient has a suboptimal cortisol response to the adrenocorticotropic hormone test. 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 optimize treatment, and follow-up of children with CAH due to 21-hydroxylase deficiency in the light of the most recent evidence.

Keywords: Congenital adrenal hyperplasia, children, adolescent, 21-hydroxylase deficiency, non-classic congenital adrenal hyperplasia, glucocorticoid replacement treatment

Introduction

21-hydroxylase deficiency has been divided into classical and non-classical forms. The classical form is characterized by absence or severe deficiency in enzyme activity. The most serious form is the classical form of CAH with salt loss and is characterized by adrenal insufficiency with cortisol and aldosterone deficiency and excessive androgen production (1,2). If the disease is not recognized, salt wasting crises (hyponatremia, hyperkalemia, acidosis, hypovolemia and shock) develop in 75% of classic CAH cases in the first three weeks of life. In the simple virilizing form, enzyme activity is at the level of 1-5%, and cortisol deficiency and androgen excess are prominent. Milder forms of the disease are defined as 'late-onset' or 'non-classical' CAH (NCCAH), and partial enzyme deficiencies are compensated by elevations in adrenocorticotropic hormone (ACTH) (1). In non-classic

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CAH, mild subclinical impairment in cortisol synthesis does not usually lead to adrenal crises.

This evidence-based review with good practice points is developed by the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes'. We developed this evidence-based review for 'Treatment and follow-up of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency in Childhood and Adolescence'. The overall purpose of this evidence-based review is to provide good practice points, with focus on recommendations for daily management.

Treatment of Classical Congenital Adrenal Hyperplasia

Clinical goals are to ensure normal growth, development, and pubertal maturation from birth to adolescence and to prevent adrenal crisis, virilization, and other long-term complications (3).

Glucocorticoid (GC) therapy forms the basis of the treatment for CAH. The aim of treatment is to eliminate the symptoms of deficiency by replacing steroids that cannot be synthesized by the adrenal gland, and to prevent excessive production of adrenal androgens by normalizing ACTH secretion (3). The GC dose required to suppress ACTH secretion in CAH is generally above the physiological dose. However, in primary adrenal insufficiency other than CAH, physiological dose is sufficient. While inadequate treatment causes adrenal crisis, increased virilization, advanced bone age and short adult height; excessive treatment results in inadequate growth, Cushing syndrome, osteoporosis, increased cardiovascular diseases and impaired metabolic control (2,4).

The aim of treatment with GC is to prevent adrenal crisis, prevent hyperandrogenemia, and ensure normal age-appropriate growth and puberty (3,4,5). GC replacement therapy has many challenges. The first is the difficulty of current treatment strategies to mimic the physiological cortisol rhythm, which is high in the morning and low at midnight (6). The second is the difficulty of imitating adaptation to stress (7). A continuous infusion pump that best mimics the physiological rhythm can be used, but the cost of the pump, the difficulty of constantly carrying the pump, the need for training, technical problems and local irritation make its use difficult (2,8,9). The third challenge is the difficulty of suppressing ACTH and controlling high androgen levels with negative feedback. Both overtreatment and undertreatment adversely affect fertility in both sexes (2,3,10).

A good knowledge of the pharmacokinetic and pharmacodynamic properties of GCs is important in evaluating the treatment of individual CAH patients. The first choice GC in growing children is hydrocortisone (HC), a synthetic form of cortisol. Among GCs, HC has a shorter half-life and fewer side effects, such as growth suppression (2,3). Cortisone must be converted to cortisol for its bioactivity, and its use is not recommended because differences in these conversion rates may change drug effectiveness (2,3,11,12,13). Interestingly, HC clearance is 26% lower in the evening than in the morning. Since the absorption and clearance of GCs show individual differences, individuals' GC treatment should be evaluated and titrated at regular intervals. In children, it is recommended to divide the tablets and give them with water or food (14,15). Oral GCs are recommended to be given after a meal to prevent damage to the gastric mucosa.

Suspensions for young children were withdrawn from the market 20 years ago because the active components were not distributed homogeneously throughout the preparation (16). In recent years, 0.5, 1, 2 and 5 mg rapid-release granule formulation preparations of HC (Infacort®/Alkindi®, Diurnal Ltd.) have been approved for use in the European Union and the United States (17,18).

More potent, synthetic, long-acting GCs, such as prednisolone and dexamethasone are not preferred in children due to the severity of side effects (2,3). Long-acting and more powerful GCs are preferred to increase treatment compliance in adolescents who have reached adult height and adults. However, due to their pharmacokinetic properties, the risk of iatrogenic Cushing syndrome is higher in these forms. It has been reported that adult height decreased in adolescents using prednisone (19). HC has mineralocorticoid properties (20 mg HC ~0.1 mg fludrocortisone) and fludrocortisone has GC properties (0.1 mg fludrocortisone ~1-1.5 mg HC) (20).

1) Treatment in Newborn and Early Infancy

There is no single objective parameter for determining the optimal dose of GCs. HC should be given in 3 or 4 divided doses at a supraphysiological dose of 10-15 mg/m^2/day for adequate control of adrenal androgen production in most patients (2,3). There is insufficient data regarding the administration of HC doses predominantly in the morning or evening hours (21,22). Total dosage should be individualized based on adequate monitoring and may need to be increased for short periods in certain situations. Therefore, all children with CAH should be under the follow-up of a pediatric endocrinologist (23). Some clinicians exceed the recommended dose of GCs during the neonatal period to reduce high androgen levels as quickly as possible. If this treatment strategy is implemented, the dose should be rapidly reduced once the target metabolic regulation is

achieved to avoid the adverse effects of high doses of GCs (24). After a few months, maintenance daily totals of about 3 to 4 mg HC divided into three doses (ie, 1-2 mg 3 times daily) are usually sufficient. Infants have low sensitivity to androgens, and completely suppressed adrenal androgens should not be the main target in the first year of life (2,3,14,24)

Mineralocorticoid replacement is provided by fludrocortisone. Subclinical or overt aldosterone deficiency is present in all forms of classical CAH (25). Fludrocortisone is started in all newborns with classical CAH detected in neonatal screening programs before hyponatremia develops (2). There is relative mineralocorticoid resistance in newborns and young infants and antimineralocorticoid effects of 17-hydroxyprogesterone (17-OHP), which increases in this period. Due to these effects, fludrocortisone may be required at doses of 100-200 µg/day, and sometimes higher. However, to avoid iatrogenic hypertension, serum electrolytes, plasma renin, and blood pressure need to be closely monitored and the fludrocortisone dose titrated. Due to lower glomerular filtration rate, immature renal tubules, breast milk intake, and low sodium concentration in infant formula, infants often require supplemental sodium chloride (NaCl) to maintain sodium balance. The recommended daily amount of sodium is 2-4 mmol/kg/day. Salt solution or NaCl tablets containing approximately 1-2 g/day of NaCl (17-34 mmol/day, up to 10 mmol/day of Na) should be given in divided doses (26). NaCl supplementation may not be necessary in patients receiving high doses of fludrocortisone (27). In addition, 0.1 mg of fludrocortisone has the GC potency of approximately 1-1.5 mg of HC, so high fludrocortisone doses may allow for a reduction of the HC dose in young children. Unlike GC therapy, fludrocortisone does not need to be increased in stress situations (2).

2) Treatment During Childhood

Children younger than 18 months should be monitored at least every three months, and older children should be monitored every 4 to 6 months or more frequently after a dose change. The recommended target 17-OHP range should be 100-1200 ng/dL (3-36 nmol/L) when measured in the early morning hours before the drug dose is given, and age-appropriate androstenedione levels should be targeted (13,28). Attempts to normalize 17-OHP levels should be avoided due to the risk of HC overdose causing iatrogenic Cushing syndrome. As prepubertal children normally have low circulating sex steroid levels, adequate androgen suppression is important to achieve normal growth and puberty. To ensure hormonal control in growing children, long-acting GCs should be avoided, except for short periods when HC is not available (2,3). If long-acting GCs are used, care should be taken not to overdose and the dose should be reduced as quickly as possible after hormonal control is achieved (19,29).

After infancy, the need for fludrocortisone in classical CAH is generally 50-200 µg/day. Fludrocortisone half-life is approximately 3.5 hours, biological half-life is 18-36 hours and it is sufficient to give it once a day. However, doses above 0.1 mg can be divided to be given twice daily. In hot and humid weather conditions, some endocrinologists recommend a seasonal increase in fludrocortisone, although increased salt intake may be sufficient. Suspension forms are not recommended. Since daily salt intake through breast milk is insufficient until the first 6-8 months, salt should also be added to the treatment (2). Salt supplementation is generally not required beyond infancy.

3) Treatment During Puberty and Adolescence

During adolescence, hormonal control is often difficult even if the maintenance dose is adequate and treatment compliance is good. During this period, the clearance of HC increases due to the decrease in 11β-hydroxysteroid dehydrogenase type 1 activity (2). Therefore, higher GC doses are required during adolescence (30). Due to the negative effects of high doses on growth during puberty, HC doses above 17 mg/m^2/day are not recommended (28). To achieve treatment goals, treatment should be continued with the lowest effective dose and height should be allowed to increase. In case of completion of growth, long-acting GCs may be considered but are not preferred (31). However, long-acting GCs may be preferable, especially in patients with poor compliance with HC treatment.

Management of CAH during adolescence and the transition from pediatric care to adult healthcare are challenging. Continuous GC and mineralocorticoid administration during the transition from adolescence to adulthood is necessary to prevent morbidity and mortality, especially from adrenal crises (2). Multidisciplinary transition clinics that include pediatric and adult endocrinologists, gynecologists, urologists, and psychologists can promote good medical adherence among adults with CAH (2,3). Changing mineralocorticoid requirements from birth to adolescence should be re-evaluated during adolescence/young adulthood to prevent mineralocorticoid over- and under-intake. Gynecological evaluation should be recommended to all adolescents with CAH during the transition period, especially in cases of menstrual irregularity, planned sexual intercourse or desired pregnancy (2,3,32). After the completion of puberty, boys should undergo scrotal ultrasonography and regular testicular adrenal rest tumor (TART) examination

(33). All patients should be aware of the risk of reduced fertility with poor medical compliance (2,3). Psychosexual and genetic counseling is recommended for the adolescent patient during the transition to adulthood (34).

Good practice points:

1. In classical CAH treatment, it is necessary to replace both GC and mineralocorticoid hormones to prevent salt wasting crisis and reduce excessive corticotropin, which triggers adrenal androgen release (1⊕⊕⊕O).

2. In affected but stable cases in the neonatal period, HC is started at an average dose of 20-30 mg/m^2/day (15-20 mg/m^2/day in those without clinical symptoms). In early infancy, it should be continued at 10-15 mg/m^2/day (in 3 or 4 doses). Fludrocortisone should be given at 100-200 µg/day in 1 or 2 doses. Approximately 1-2 g/day NaCl can be given in divided doses as saline solution or NaCl tablets (1⊕⊕⊕O).

3. In childhood, instead of long-acting GCs, treatment should be continued at a maintenance dose with HC, which has the least negative effects and side effects on growth, and fludrocortisone should be added to the treatment regimen in those with mineralocorticoid deficiency. HC should be given in 3 or 4 divided doses at 10-15 mg/m^2/day for adequate control of adrenal androgen production in most patients. Fludrocortisone 50-200 µg/day should be given in 1 or 2 doses (1⊕⊕⊕O).

4. During puberty, instead of long-acting GCs, maintenance treatment should be performed with HC, which has the least negative effects and side effects on growth. To achieve treatment goals, treatment should be continued with the lowest effective dose and height should be allowed to increase. Fludrocortisone should be added to the treatment regimen in those with mineralocorticoid deficiency. At puberty, HC should be given at 10-15 mg/m^2/day in 3 or 4 divided doses for adequate control of adrenal androgen production in most patients. Long-acting GCs can be given to patients who have completed their growth. Fludrocortisone 50-200 µg/day should be given in 1 or 2 doses (1⊕⊕⊕O).

4) Monitoring

Patients should be monitored regularly with physical examinations that include measurements of height, body weight, and blood pressure. In addition to the symptoms of decrease or increase in growth rate, rapid weight gain, skin and mucosal hyperpigmentation, and virilization in children, particular attention should be paid to signs of central precocious puberty, such as pubic hair growth, apocrine odor development, and breast/testicular enlargement. The presence of salt cravings, unusual fatigue during the day, irregular menstrual cycles in girls, and hyperpigmentation on the skin indicate the necessity of drug titration (2).

Plasma renin activity and renin levels are highly variable, and therefore serum electrolytes should be measured along with ambulatory blood pressure to titrate the mineralocorticoid dose (2,3,35). Although not routine, adrenal-specific metabolites, such as 21-deoxycortisol and 11-oxyandrogens, can also be used in follow-up to evaluate adrenal androgen production in CAH (36,37). Steroids can be measured in blood, urine, saliva, and dried filter paper blood samples and may vary depending on both the circadian rhythm and the time of GC intake (2,3,38,39,40).

Bone age is evaluated by left-hand and wrist roentgenogram in children over two years of age to determine whether rapid progression is occurring as a result of exposure to excessive adrenal androgens. Since increased adrenal androgens may activate the hypothalamic-pituitary-gonadal axis, signs of early puberty should be monitored (testicular enlargement in boys, breast enlargement in girls). Clinical features are also important in adjusting HC and fludrocortisone doses and should not be based solely on laboratory data. Patients should be monitored for reproductive complications, especially decreased fertility in women and TART in men (2).

Good practice points:

1. In patients with CAH, close monitoring should be performed in the first 3 months of life, evaluation should be made every 3 months between 3-18 months, and every 4 months after 18 months. In addition to biochemical measurements to evaluate the adequacy of GC and mineralocorticoid treatment, growth rate, body weight, blood pressure and physical examination should be evaluated regularly, and cases should be monitored for central precocious puberty that may develop (1⊕⊕OO).

2. In patients with CAH over two years of age, bone age should be assessed annually until adult height is reached (ungraded good practice statement).

3. Evaluation of bone age is especially important in patients with inadequate growth rate or suspected puberty precocity (ungraded good practice statement).

5) Modified Glucocorticoid Preparations

Sustained slow-release HC preparations have been developed as an alternative to longer-acting synthetic GCs, such as prednisone/prednisolone or dexamethasone.

Plenadren (Shire Services BVBA, Belgium), a modified HC formulation, is approved in Europe for the treatment of adrenal insufficiency in adults. Plenadren is a modified HC formulation characterized by a dual-release mechanism, wherein the core of the formulation provides a delayed release of HC, while the peripheral components allow for rapid release. It has been shown that when given once a day to patients with primary adrenal insufficiency, it significantly improves metabolic variables such as body weight, body mass index and HbA1c compared to conventional HC replacement (41,42). However, data on its use in patients with CAH are lacking. Clinical experience shows that once-daily HC treatment cannot achieve a sufficient increase in morning cortisol value and adequate suppression of ACTH and androgens, thus requiring an additional dose of GC in the evening (43,44). Plenadren is a treatment that has not yet been approved for use in the treatment of CAH in children. Another modified-release preparation (Chronocort, brand name Efmody, Diurnal, UK) continues to be studied for the treatment of CAH. This preparation has a delayed effect, beginning four hours after intake, and a continuous effect (45). When administered at 23:00 at night, the cortisol level, which rises throughout the night due to delayed release, peaks in the morning, and when a second dose is administered in the morning (07:00), the cortisol need during the day is met (45,46). Chronocort received marketing authorisation in the UK and Europe in 2021 for CAH patients aged 12 years and older. The long-term safety extension phase of Chronocort is ongoing and additional studies are planned in the USA (2,47).

Continuous subcutaneous administration of HC mimics physiological cortisol release. It is especially useful in patients with rapid cortisol metabolism or impaired intestinal absorption, but this approach is not as practical as oral medications. A better cortisol release is achieved with continuous subcutaneous HC infusion via pump and has been reported to be superior in reducing serum androgen levels in CAH (48). Pump HC treatment is seen as a limited treatment option in patients with complete GC deficiency due to the complexity of device use, cost, need for family-patient education, local sensitivity problem, necessity of constantly carrying the device and risk of malfunction. However, in the long term, it is hoped that extended-release formulae or pumps will improve the quality of life compared to standard treatment (2,3,8,9,49).

6) Alternative Treatment Approaches

Treatment goals for classical CAH include both hormonal replacement and reducing adrenal androgen production. Drugs that reduce androgen production and/or effects can be added to physiological GC therapy. Adjuvant treatments for the control of hyperandrogenism in CAH are under investiagtion. The combination of testolactone (aromatase inhibitor) and flutamide (androgen receptor antagonist) with 8 mg/m^2/day HC normalized growth and bone maturation in a 2-year randomized study of 28 children (50). In various studies, it has been reported that letrozole and anastrozole treatment, which are selective aromatase inhibitors, are effective in correcting adult height calculated according to bone age in CAH (51,52).

Abiraterone acetate is a potent CYP17A1 inhibitor used in the treatment of prostate cancer and is considered a promising alternative treatment by reducing the need for exogenous GCs at supraphysiological doses (53). Abiraterone acetate therapy may cause 11-deoxycorticosterone (DOC) accumulation via CYP21A2-mediated 21-hydroxylation of intra-adrenal progesterone, resulting in hypertension and/or hypokalemia in patients with prostate cancer. However, this transformation does not occur in patients with classic CAH. Abiraterone acetate is likely to be useful in prepubertal children with classical CAH to suppress androgens and estrogens until normal pubertal age, and a phase 1 trial testing this approach is ongoing (NCT02574910). Abiraterone acetate monotherapy, unless combined with GC therapy or a mineralocorticoid receptor antagonist, may cause DOC accumulation in patients with NCCAH. Furthermore, its use in teenage girls will require estrogen therapy with oral contraceptives (OCs) (2,54). Since it does not reduce ACTH levels and inhibits gonadal sex steroid production, its use is restricted in men with TARTs and in cases with fertility desire (55,56). Third-generation antiandrogens, such as enzalutamide, apalutamide, and darolutamide have not been tested in CAH patients (2,54).

One of the possible treatment approaches is the suppression of ACTH-mediated androgen production. Binding of corticotropin releasing hormone (CRH) to the type 1 receptor (CRHR1) stimulates ACTH secretion by increasing intracellular cAMP in corticotrophs. This is one of the new treatment options. In a study involving eight women with CAH who were given a single dose of 300 or 600 mg of CRHR1 antagonist, significant decreases in ACTH and 17-OHP were demonstrated compared to a control period with GC therapy (57). Theoretically, an anti-ACTH antibody or melanocortin type 2 receptor antagonist could also reduce adrenal androgen synthesis in patients with classical CAH, but these approaches have only been tested in preclinical models and their long-term effects are unknown. It should be kept in mind that most of these approaches do not eliminate the need for treatment and monitoring with GC replacement, even at lower doses (2,58,59,60).

Unilateral or bilateral adrenalectomy has been suggested as an approach in the long-term treatment of classical CAH to limit adrenal androgens (2,61). In a recent meta-analysis of 48 cases of CAH, 34 (71%) described symptomatic improvement after bilateral adrenalectomy. However, short-term adverse outcomes were reported in five cases (10%) and long-term adverse outcomes in thirteen cases (27%), including an increased risk of adrenal crisis (62). The development of adrenal rest tumors due to high ACTH levels has been reported, even in women (63). This adrenalectomy approach has currently fallen out of favor (3). Adrenolytic therapy with mitotane has been reported as an approach to restoring fertility in men with TARTs, but long-term results have not been published (2,3,64). Therefore, current data do not recommend the "medical adrenalectomy" approach.

7) Gonadotropin-releasing Hormone Analogue and Growth Hormone Therapy in CAH

In a meta-analysis that included 35 observational studies with methodological limitations and very low-quality evidence, it was reported that the adult height of patients with CAH was -1.05 standard deviation score (SDS) behind the target height (65). Similarly, individuals with NCCAH may be at risk of short adult height, but short stature is less severe than in classical CAH. In a non-randomized study, it was reported that growth rate and height z score increased with the use of growth hormone alone (n = 12) or in combination with gonadotropin-releasing hormone analogue (GnRHa) in children with CAH (66). In another study, fourteen patients treated with growth hormone and GnRHa for 4 years showed improvement in adult height (+1.1 SDS) compared to historical controls with CAH treated with conventional therapy alone (67). Individuals with CAH can reach normal adult height with the use of standard GC and mineralocorticoid treatments at appropriate doses, and height-enhancing drugs can only be considered for individuals whose height is, or is expected to be, significantly shorter than that of their peers (2,68).

8) Cell and Gene-based Treatments in Classic Congenital Adrenal Hyperplasia

Potential cell-based therapies have been studied in recent years. Somatic cells can be induced to differentiate into an embryonic stem cell-like phenotype by forcing the expression of specific transcription factors. Adrenocortical-like cells have been generated from skin, blood, and urine cells in humans using steroidogenic factor-1 expression, protein kinase A, and activation of the GnRH pathway (65). These reprogrammed cells exhibited ultrastructural properties similar to steroid-secreting cells and secreted steroid hormones in response to physiological (such as ACTH) and pharmacological stimuli, as well as expressing *de novo* steroidogenic enzymes. In the future, gene editing may be applied to reprogrammed cells obtained from patients to achieve normal steroidogenesis (2,69). Gene therapy using adeno-associated viruses has been used in an animal model of 21-hydroxylase deficiency. Intra-adrenal injection of viruses carrying the human *CYP21A2* gene reversed the CAH-like phenotype for 40 days (70,71).

Good practice points:

1. There is not enough data regarding the use of continuous slow-release or modified-release HC preparations and continuous subcutaneous HC infusion in children with CAH (2⊕⊕OO).

2. Although it is recommended not to use experimental treatment approaches in CAH patients, additional/alternative treatment approaches may be considered in those whose adrenal androgen production is not sufficiently suppressed (ungraded good practice statement).

3. In CAH, GnRHa should be considered in selected cases (those with advanced bone maturation or early puberty problems). It is not recommended to give additional growth hormone therapy (2⊕OOO).

4. Cell-based therapies and gene editing technology in CAH may offer new options for disease cure or treatment, but future data on their use are expected to become clearer (ungraded good practice statement).

Treatment of Non-classical Congenital Adrenal Hyperplasia

It has been shown that patients who are diagnosed with NCCAH and left untreated, may enter puberty earlier than the population average age, and this may negatively affect final height, resulting in short stature. Therefore, it has been stated that early diagnosis and treatment initiation may improve final height (72,73,74). In a previous study, it was reported that puberty and growth spurt occurred an average of 2.3 years earlier in the group of patients with untreated NCCAH (75). In another study, it was reported that patients with advanced bone age at diagnosis were significantly shorter than others. In the same study, individuals who were compound heterozygous for both the mild and severe alleles were shown to have significantly shorter final heights (76).

In individuals with asymptomatic NCCAH, treatment is not recommended (77,78). In cases of inappropriately early onset of body hair growth and body odor in children, treatment is recommended only if bone maturation has accelerated enough (two or more years advanced) to negatively affect final height. In the presence of premature

pubarche without advanced bone age, clinicians may opt for careful monitoring without treatment. In adolescents with menstrual irregularities and acne, symptoms usually improve within three months after GC therapy, whereas resolution of hirsutism is more difficult to achieve with GC monotherapy. As in other androgenic disorders, the use of OCs alone or in combination with anti-androgens appears to be the best approach to treating hirsutism in women with NCCAH (79,80,81,82). In patients with NCCAH, in whom treatment has already been initiated, discontinuation of GC therapy should be planned once they have reached final adult height or other symptoms have resolved (3).

In adolescent girls and adult women presenting with signs of hyperandrogenism, such as acne or hirsutism, therapy with estrogen and progesterone-containing OCs is the treatment of choice. Women who will receive OC therapy should be informed that hirsutism will begin to improve only after 6-12 months and that hair removal methods such as epilation or electrolysis may be used during this period (80). If OCs alone are not successful, anti-androgenic agents may be added. However, this treatment should never be used in women of reproductive age who are not receiving safe contraceptive treatment as it has negative effects on the development of the external genitalia of the male fetus during the intra-uterine period. Spironolactone is a mineralocorticoid antagonist that also has anti-androgenic effects (83). Other treatments for hirsutism include finasteride, a progesterone derivative that competes with DHT to bind to the androgen receptor, the 5α-reductase inhibitors, or cyproterone acetate. Flutamide, a nonsteroidal androgen receptor antagonist, is not recommended due to hepatotoxicity. Both spironolactone and finasteride have similar efficacy in improving hirsutism (72). GCs form the basis of androgen deprivation therapy only in classical CAH. Although GCs have been shown to be more effective than OCs or anti-androgens in suppressing serum adrenal androgen concentrations in women with NCCAH, they have been found to be less effective in improving hirsutism and have a greater risk of toxicity (81,84). Therefore, GCs are only used to manage hirsutism in female patients with NCCAH, when intolerance to OCs and/or anti-androgens develops (72).

Monitoring the Treatment of NCCAH

Due to the lack of reliable tests, monitoring the treatment of patients with NCCAH relies mostly on clinical assessment. Elevated testosterone and androstenedione levels need to be normalized, while 17-OHP levels may be allowed to increase as normalization of 17-OHP typically indicates GC overtreatment (72).

The first treatment option in women with NCCAH who have irregular or anovulatory cycles and want to get pregnant is the use of GCs. When pregnancy cannot be achieved with GC therapy, ovulation induction with clomiphene citrate and other reproductive endocrinological methods are recommended (85,86). If a woman with NCCAH conceives while not receiving GC therapy, she does not need to be treated during pregnancy. There are limited data on whether GC therapy reduces the risk of miscarriages in women with NCCAH (86). Therefore, women with subfertility may benefit from GC therapy to conceive and maintain pregnancy. HC, prednisone and prednisolone are safe to use in women who are planning pregnancy. However, the use of dexamethasone, which is not inactivated by the placenta, is not recommended during pregnancy, as it suppresses the fetal hypothalamic-pituitary-adrenal axis and growth. Maternal 17-OHP and androstenedione levels are elevated during pregnancy and should not be used as biomarkers of CAH control. Therefore, pregnant women should be monitored clinically. Guidelines are insufficient in terms of the optimal management of patients with NCCAH during pregnancy. In some practices, low-dose GC therapy is continued during pregnancy if the patient has been receiving GC therapy before conception, while in other practices, GC therapy is discontinued once pregnancy is confirmed or after the first trimester (3).

Available data show that TARTs are extremely rare in men with NCCAH (87). Therefore, GC prophylaxis therapy is not recommended in men.

There is no evidence of clinically significant cortisol deficiency or adrenal crisis in NCCAH. Some individuals with NCCAH (60 % in a small study) have shown inadequate response to the ACTH stimulation test (stimulated cortisol level less than 500 nmol/L), but overt episodes of adrenal insufficiency have not been observed (82,88,89). GC therapy may be recommended for severe illness in individuals with previously untreated NCCAH, who have a subnormal cortisol response to the diagnostic ACTH test. However, it should be taken into consideration that when daily GC therapy is initiated, the hypothalamic-pituitary-adrenal axis will be suppressed and the risk of adrenal crisis will increase in cases of severe stress. Therefore, it is extremely important to inform the patients and their families about treatment and stress dosing (74).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (90).

Good practice points:

1. GC therapy is recommended in children with inappropriately early onset and rapidly progressive pubarche or accelerated bone age progression, and in adolescents with NCCAH who have overt virilization (2⊕⊕OO). However, the family of the patient should be adequately informed considering the risks and benefits of GC therapy.

2. In patients with NCCAH, in whom treatment has already been initiated, discontinuation of GC therapy should be planned once they have reached final adult height or other symptoms have resolved (2⊕⊕⊕O).

3. GC therapy is not recommended in most adult men with NCCAH (2⊕OOO).

4. In non-pregnant women with NCCAH, who are asymptomatic, therapyi is not necessary (1⊕⊕⊕O).

5. Treatment of women with NCCAH, who show signs of hyperandrogenism and are not planning pregnancy, is similar to treatment of those with polycystic ovary syndrome and includes OCs and/or anti-androgen therapy. However, infertility treatment in women with NCCAH is initiated with GCs. In infertile women with NCCAH low-dose GCs can induce ovulation and lead to pregnancy (1⊕⊕⊕O).

6. In patients with NCCAH, stress doses of HC are given for major surgery, trauma, or childbirth only if the patient has a suboptimal (14-18 mg/dL, 400-500 nmol/L) cortisol response to the ACTH test (2⊕OOO).

Footnotes

Authorship Contributions

Surgical and Medical Practices: Havva Nur Peltek Kendirci, Zeynep Şıklar, Concept: Havva Nur Peltek Kendirci, Zeynep Şıklar, Design: Havva Nur Peltek Kendirci, Zeynep Şıklar, Data Collection or Processing: Havva Nur Peltek Kendirci, Edip Ünal, İsmail Dündar, Ayşe Derya Buluş, Sevinç Odabaşı Güneş, Zeynep Şıklar, Analysis or Interpretation: Havva Nur Peltek Kendirci, Edip Ünal, İsmail Dündar, Ayşe Derya Buluş, Sevinç Odabaşı Güneş, Zeynep Şıklar, Literature Search: Havva Nur Peltek Kendirci, Edip Ünal, İsmail Dündar, Ayşe Derya Buluş, Sevinç Odabaşı Güneş, Zeynep Şıklar, Writing: Havva Nur Peltek Kendirci, Edip Ünal, İsmail Dündar, Ayşe Derya Buluş, Sevinç Odabaşı Güneş, Zeynep Şıklar.

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REVIEW

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Rare Types of Congenital Adrenal Hyperplasias Other Than 21-hydroxylase Deficiency

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Abstract

Although the most common cause of congenital adrenal hyperplasia (CAH) worldwide is 21-hydroxylase deficiency (21-OHD), which accounts for more than 95% of cases, other rare causes of CAH such as 11-beta-hydroxylase deficiency (11β-OHD), 3-beta-hydroxy steroid dehydrogenase (3β-HSD) deficiency, 17-hydroxylase deficiency and lipoid CAH (LCAH) may also be encountered in clinical practice. 11β-OHD is the most common type of CAH after 21-OHD, and CYP11B1 deficiency in adrenal steroidogenesis causes the inability to produce cortisol and aldosterone and the excessive production of adrenal androgens. Although the clinical and laboratory features are similar to 21-OHD, findings of mineralocorticoid deficiency are not observed. 3β-HSD deficiency, with an incidence of less than 1/1,000,000 live births, is characterized by impairment of both adrenal and gonadal steroid biosynthesis very early in life, with inadequate virilization in boys and varying degrees of virilization in girls. It may present with salt wasting crisis or delayed puberty in both genders. While 46,XY disorders of sex development is frequently observed in boys with 17-hydroxylase deficiency, immature pubertal development and primary amenorrhea are observed in girls due to estrogen deficiency throughout adolescence. Patients with LCAH, which develops due to steroidogenic acute regulatory protein deficiency, typically present with salt wasting in the first year of life. It is characterized by complete or near-complete deficiency of adrenal and gonadal steroid hormones and progressive accumulation of cholesterol esters in the adrenal gland.

Keywords: Congenital adrenal hyperplasia, 3-beta-hydroxysteroid dehydrogenase deficiency, 17-alpha hydroxylase deficiency, 11-hydroxylase deficiency, lipoid congenital adrenal hyperplasia

Introduction

Although the most common cause of congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency (21-OHD), other rare causes of CAH may also be seen. In some cases, the diagnosis of other types of CAH may be delayed and a clear differential diagnosis cannot be made. Although increase of 17-hydroxyprogesterone (17-OHP) level is typical for 21-OHD, it can also be seen in cases of CAH due to 3 beta-hydroxysteroid dehydrogenase (3β-HSD) deficiency, 17-alpha-hydroxylase deficiency (17-OHD) and 11 beta-hydroxylase deficiency (11β-OHD). Since this group of CAH types is rare, it has generally been reported as case reports. There are very few studies including large series.

This evidence-based review with good practice points is developed by the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes'. We developed this evidence-based review for "Rare types of congenital adrenal hyperplasias other than 21-hydroxylase deficiency" 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.

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11-beta-hydroxylase Deficiency

11β-OHD; is the most common type of CAH after 21-OHD. It was described by White et al. (1) in 1991. The disease is inherited in an autosomal recessive manner. Its frequency is estimated to be < 10% (0.2-8%) among all types of CAH. Its frequency is estimated to be 1/250,000 (2). In communities where consanguineous marriage is common, its frequency has been reported as 1/5,000-7,000 live births (3).

11-beta-hydroxylase Gene

11β-hydroxylase is a steroid enzyme and it is found in the zona glomerulosa and zona fasciculata of the adrenal cortex. Cytogenetic location of the gene is in 8q24.3. There are two cytochrome P450 isoenzyme, CYP11B1 and CYP11B2. CYP11B1 converts 11 deoxycortisol to cortisol in steroidogenesis in the adrenal cortex. CYP11B2 is expressed at low levels in zona glomerulosa, but it increases in aldosterone-secreting tumors [aldosteronism, glucocorticoid (GC) remediable hypertension] (4,5,6,7).

Mutations

In CYP11B1 deficiency, depending on the type of mutation, the degree of enzyme deficiency may vary. Mutations in *CYP11B1* are homozygous or compound heterozygous mutations. In the classical form, c.954G > A;p.Thr318Thr, p.Arg141, p.Leu299Pro, p.His125Thrfs*8, p.Leu463_Leu464dup, p.G379V, p.Q356X, IVS7 + 1G > A, R448H mutations have been reported. In the non-classical form, Arg143Trp, p.Arg332Gln, p.Ser150Leu, p.Gly446Ser, p.F79I;p.R138C, p.R143W, p.P159L, p.M88I; p.R383Q, p.R366C, p.T401A, p.P42S, p.N133H, p.T319M mutations have been reported (7). It has also been reported that in male cases without clinical findings of increased virilization in the R451W mutation, salt loss is not observed at diagnosis, but mild salt loss and androgen deficiency are observed at older ages (8).

Pathophysiology

In adrenal steroidogenesis, CYP11B1 deficiency results in the inability to produce cortisol and aldosterone and the overproduction of adrenal androgens (especially testosterone). Although aldosterone cannot be synthesized, the clinical findings of mineralocorticoid deficiency are not observed, because the deoxycorticosterone (and e.g. 19-nordeoxycorticosterone) levels, which have a potent mineralocorticoid activity, are increased. Renin is suppressed, while adrenocorticotropic hormone (ACTH), total testosterone, and 11 deoxycortisol are elevated. The laboratory marker for CYP11B1 deficiency is 11 deoxycortisol (9).

Clinical and Laboratory Features

There are two clinical forms of 11β-OHD: the classical and non-classical forms. In the classical form the clinical findings are present at birth, and in the non-classical form, the clinical findings present in childhood, adolescence and adulthood (9).

In the classical form, low renin, aldosterone, cortisol, and potassium levels and high corticotropin-releasing hormone, ACTH, testosterone, 11 deoxycortisol levels and metabolic alkalosis are laboratory findings and surrenal hyperplasia is reported on imaging. Hyperpigmentation and virilization of the external genitalia in female babies and hypertension (it has been reported that hypertension is seen in two-thirds of cases in the neonatal period) are clinical findings. In untreated or inadequately treated cases, advanced bone age, short stature, and hyperpigmentation (especially in the nipples and gums) are observed, as in CAH due to 21-OHD. Hyperandrogenism can also occur with peripheral precocious puberty and delayed menarche in girls or poor spermatogenesis in boys/men. Hypokalemia seen in 11β-OHD has been shown not to correlate with blood pressure (10). Cases of paralysis due to hypokalemia have also been reported (11).

Salt wasting is not expected during the neonatal period. However, salt wasting has been observed in a very small number of cases, the mechanism of which has not been fully elucidated. It has been suggested that this may be due to the natriuretic activity of 16-hydroxylated steroids, progesterone and pregnenolone from fetal adrenal tissue. No cases were reported to receive treatment due to salt loss during clinical follow-up (2). Rarely, salt wasting due to suppression of deoxycorticosterone by GC therapy is also mentioned. In acute critical illness, relative GC dose is insufficient and it has been reported that hyperkalemia, hyponatremia and hypovolemia may develop, and a temporary salt wasting situation may develop (12,13).

In non-classical CYP11B1 deficiency, atypical genitalia is not observed in girls, clinical findings due to androgen increase (mild virilization) are observed, acceleration in somatic development, premature closure of the epiphyses, and short final height may occur. Hyperandrogenism, hirsutism and oligomenorrhea may develop at older ages in girls. In the non-classical form, hypertension is not seen (9,14).

In untreated or inadequately treated male cases, macropenis, pubertal gynecomastia, Leydig cell hyperplasia, and testicular adrenal rest tumor (TART) may develop (14).

Diagnosis

In 11β-OHD, low cortisol and increased precursor adrenal androgens are observed. The main elevated adrenal hormones are 11-deoxycortisol and deoxycorticosterone. Increased 11-deoxycortisol levels also cause an increase in 17-OHP levels as increased adrenal androgens increase production of androstenedione and testosterone. As with 21-OHD, there are no clear values for 17-OHP in 11β-OHD. 17-OHP levels used in newborn screening programs may be misleading for diagnosis of 11β-OHD. Therefore, clinical evaluation and repeated hormone measurements are important. In 11β-OHD, urinary tetrahydrometabolites of steroid precursors, such as tetrahydro-11-deoxycortisol and tetrahydrodeoxycorticosterone are definitely high and can be used in monitoring. These tests are used in treatment monitoring, along with 24-hour urine measurements. Increased mineralocorticoid precursor hormones, such as deoxycorticosterone, cause renin suppression and decreased CYP11B2 synthesis. Basal high level 11 deoxycortisol levels, renin suppression, normal or mildly elevated 17-OHP level, high ACTH level, low aldosterone and cortisol level, all together, have been shown to be diagnostic (9,10).

For the non-classical form, diagnosis is made by high basal or ACTH-stimulated serum 11-deoxycortisol levels (9,14). Although standard dose ACTH-stimulated deoxycortisol levels at three times the 95th percentile of normal are considered significant, they are not considered definitive diagnostic criteria. Mutation analysis and enzyme activity measurement are important in confirming the diagnosis and providing genetic counseling. In *CYP11β1* heterozygous mutation carriers, slightly higher stimulated serum 11-deoxycortisol and deoxycorticosterone levels and varying degrees of enzyme activity have been reported, but cases in which no hormonal changes were detected have also been reported (7).

Good practice points:

1. In virilized female cases with a history of consanguineous marriage, CAH due to 11β-OHD should be considered, especially if the history of consanguineous marriage is common in the society (1⊕⊕⊕O).

2. Non-classical form 11β-OHD should also be included in the differential diagnosis in cases of hyperandrogenism, hirsutism and oligomenorrhea (1⊕⊕⊕O).

3. Low renin, aldosterone, cortisol, potassium levels, and high ACTH, testosterone, 11 deoxycortisol levels, with metabolic alkalosis and adrenal hyperplasia are diagnostic for 11β-OHD (1⊕⊕⊕O).

4. If measurable, high urinary tetrahydrometabolites of steroid precursors, such as tetrahydro-11-deoxycortisol and tetrahydrodeoxycorticosterone are diagnostic for 11 beta-hydroxyalse deficiency (1⊕⊕⊕O).

5. If standard dose ACTH-stimulated deoxycortisol levels are found at three times the 95th percentile of normal, the genetic analysis for 11β-OHD should be performed (1⊕⊕⊕O).

Management and Treatment

With GC replacement therapy, cortisol deficiency is corrected and ACTH and adrenal androgen levels are controlled. For GC replacement therapy, oral hydrocortisone (HC) is the first choice as it has the same potency as physiological GC. HC 15-25 mg/m^2/day is given as three doses per day, with the morning dose being approximately 50% of the total dose. In cases of illness or stress, the dose can be increased two, three or even five times until the stressful situation improves. If there is accompanying long-term hypertension, spironolactone, amiloride and calcium channel blockers can be used as antihypertensive treatment. In addition to anthropometric data and bone age monitoring, regular hormonal and laboratory results should be collected. Corrective operations of the external genitalia in virilized females are planned by the decision of a multidisciplinary team/council (5).

Complications/Comorbidities

Excessive doses of GCs cause hypercortisolism, underdoses cause hyperandrogenism and hypertension. Both metabolic states have been found to be associated with comorbidities that increase the risk of cardiovascular disease. Complications/comorbidities may be related with overdose or lowdose GC treatment, or insufficient GC dose due to treatment non-compliance. The complications/comorbidities may include: obesity, insulin resistance/type 2 diabetes, non-alcholic fatty liver, dyslipidemia, hypertension, complications due to hypokalemia (paralysis/tubulopathy/ileus), complications due to metabolic alkalosis (hypoxemia, lethargy, delirium, convulsion), hypertensive mortality, TARTs, short stature, bone health problems, cardiovascular problems, fertility problems, gynecomastia, and skeletal problems (cases associated with short fourth metatarsal bone and Schmid-type metaphyseal chondrodysplasia have been reported but with the current knowledge, these skeletal problems are considered coincidental) (5,7).

Good practice points:

1. The GC replacement dose is 15-25 mg/m^2/day for 11-beta hydroxylase deficiency. In cases of illness or stress, the dose can be increased two, three or even five times until the stressful situation improves. For follow-up, in addition to anthropometric data and bone age monitoring, hormonal and laboratory results are also collected (1⊕⊕⊕O).

2. If there is accompanying long-term hypertension, spironolactone, amiloride and/or calcium channel blockers can be used as antihypertensive treatment (1⊕⊕OO).

3. Corrective operations of the external genitalia in virilized females are planned by the decision of a multidisciplinary team/council (1⊕⊕⊕O).

3-beta-hydroxysteroid Dehydrogenase Deficiency

3β-HSD deficiency is one of the rare types of CAH with autosomal recessive inheritance, characterized by impairment of both adrenal and gonadal steroid biosynthesis. An estimated incidence of this rare CAH type is less than 1/1,000,000 live births (15). There are two isozymes for 3β-HSD: HSD3B1 and HSD3B2. HSD3B1 is expressed in placenta and peripheral tissues while HSD3B2 is expressed in the adrenal gland, ovary, and testis.

Mutations in *HSD3B2* cause a rare form of CAH. Mutations in *HSD3B1* have never been reported in humans. Placental deficiency is thought to be embryonically lethal by affecting progesterone production (16).

In 3β-HSD depending on the enzyme activity, as in other forms of CAH, a wide spectrum of clinical findings (from mild to severe) develop. In the severe form (complete absence of enzymatic activity), a salt wasting crisis occurs very early in life, with insufficient virilization in boys and varying degrees of virilization in girls. Enzymatic defect in the gonads can cause delayed/arrested puberty and infertility in boys and girls. In very mild enzyme activity deficiency, although no mutation is detected, hirsutism and slightly elevated dehydroepiandrostenedione-sulfate (DHEA-S) levels may be observed (17).

In newborns with adrenal insufficiency and atypical genital structure, slightly elevated 17-OHP level should raise suspicion for this diagnosis. In this enzyme deficiency, the production of cortisol, aldosterone, progesterone, androgens and estrogens is affected (18).

In one study, basal and standard dose ACTH-stimulated 17-hydroxy (17-OH) pregnenolone concentrations were between 26-160 nmol/L and 72-378 nmol/L (+5.3-54 standard deviation (SD)] by radioimmunoassay in eight patients with 3β-HSD deficiency. In this study, it was shown that basal and ACTH-stimulated 17-OH pregnenolone/cortisol ratios ranged between 94-1943 and 216-4010, respectively. Other Δ5 steroids, including pregnenolone, DHEA, and DHEA-S, have also been reported to be significantly higher, although overlapping values may be found in healthy individuals without genetic mutations (19).

Definitive diagnosis can be made with the elevation of all 3β-hydroxy-Δ5-steroids, especially the 17-OH pregnenolone/cortisol ratio, which has a high diagnostic value. A ratio >0.4 (normal is <0.01) is diagnostic. High gonadotropins and low testosterone are detected in most male newborns in minipuberty due to gonadal insufficiency. In fact, the male 3β-HSD deficient newborn with severe gonadal failure may be raised as female (20).

Management and Treatment

It should be kept in mind that cases with the severe form are more prone to adrenal crisis. In the treatment, GC and mineralocorticoid replacement therapies are given, similar to cases of CAH due to salt wasting 21-OHD. During follow-up, anthropometric data and bone age are monitored, as well as hormonal and laboratory values. Cases with severe enzyme deficiency are very prone to adrenal crisis. In addition to mineralocorticoid replacement, salt replacement is also administered in the first postnatal year. Blood pressure, serum electrolytes and renin levels, and intermittent echocardiography are important in follow-up. Testosterone administration is required for boys with micropenis, and gender-specific sex steroid replacement therapy is required during adolescence in both boys and girls. If this treatment is not performed in men, gynecomastia develops (18).

Good practice points:

1. If there are: 1) salt wasting crisis very early in life, with insufficient virilization in boys and varying degrees of virilization in girls, 2) delayed/arrested puberty and infertility in boys and girls 3) hirsutism and slightly elevated DHEA-S, 3β-HSD deficiency should be considered (1⊕⊕⊕O).

2. If there are low cortisol, aldosterone, progesterone, androgens and estrogens levels, high DHEA-S levels, elevation of all 3β-hydroxy-Δ5-steroids, a diagnosis of 3β-HSD deficiency should be considered (1⊕⊕⊕O).

3. In the severe form of 3β-HSD deficiency, GC and mineralocorticoid replacement therapies are necessary (1⊕⊕⊕O).

17α-hydroxylase/17,20-lyase Deficiency

P450c17 is a microsomal P450 enzyme that catalyzes both 17α-hydroxylase and 17,20-lyase activities in the adrenals and gonads. There is no genetic or structural difference between these two enzymes, only functional differences. The gene for the enzyme P450c17, called *CYP17A1*, is located on chromosome 10q24.3. 17α-hydroxylase/17,20 lyase deficiency (17-OHD) is a rare autosomal recessive form of CAH caused by biallelic mutations in the *CYP17A1* gene, and accounts for 1% of all CAH forms (21,22,23).

In 17-OHD, both adrenal and gonadal steroid hormone synthesis is impaired. Therefore decreased cortisol and sex steroid production, resulting in sexual infantilism and pubertal failure, with increased mineralocorticoid precursors causing hypertension and hypokalemia is present (24,25).

In complete deficiency of the enzyme, the synthesis of adrenal and gonadal sex steroids is impaired and since there is no androgen accumulation, 46,XX individuals are phenotypically normal, but adrenarche does not occur and puberty does not begin. They present as young girls who have not developed secondary sexual characteristics and have primary amenorrhea and hypertension. Undiagnosed cases may present with hypertension in adulthood. In 46,XY individuals, the internal genital organs are normal. Since sufficient androgens are not synthesized, the development of the external genital structure in the male direction is not complete. Depending on the level of enzyme deficiency, the external genital structure may appear completely female or have a suspicious genital structure appearance (26).

In partial deficiency of the enzyme, 46,XY individuals generally appear as patients with ambiguous genitalia and intra-abdominal or inguinal testicles in infancy. In genetically 46,XX individuals, small uterus and ovaries are noted and during adolescence, large cysts may occur in the ovaries due to high levels of gonadotropin and progesterone (27).

Early clinical presentation and diagnosis in 17-OHD are associated with symptomatic hypertension in both 46,XX and 46,XY patients or inadequate virilization of external genitalia in 46,XY partial 17-OHD. In the absence of these, the clinical presentation is at late pubertal ages at which time amenorrhea and elevated gonadotropins are the hints for diagnosis (28).

In an article published in 2022, the characteristics of 144 cases were reported, 140 of which were reported in the literature and four of which were the authors' patients. Most of these cases (n = 135, 93.7%) were raised as female and all patients ≥14 years of age (n = 106) presented with primary amenorrhea. Absent breast (95.2%) and pubic hair (97.1%), hypertension (89.6%), hypokalemia (69.8%) (hypokalemic paresis in six patients) were the most common findings. Patients aged < 14 years (n = 25) presented frequently with hypertension, and/or hypokalemia (n = 19). Genital abnormality was detected in six cases (29).

In 17-OHD, cortisol production decreases and ACTH production increases, proximal reactions of P450c17 enzyme are stimulated. In these patients, symptoms of GC deficiency are mild due to excessive production of corticosterone, which has GC activity. In 17-OHD, 11-deoxycorticosterone (11-DOC) is produced excessively in patients, sodium retention, hypertension, and hypokalemia occur, and aldosterone production in the zona glomerulosa is suppressed (18,28).

It was shown that hypertension, hypokalemia and suppressed renin levels were much more frequent, ACTH level was much higher, and cortisol, androstenedione and testosterone levels were much lower in combined severe deficiency than in combined partial deficiency, but serum progesterone, 11-DOC and corticosterone levels were similar in both groups. It has been reported that the most predictive test in distinguishing combined severe deficiency from combined partial deficiency is serum cortisol level measured by LC-mass spectrometry (MS)/MS. Truncating mutations that lead to severe loss of function (< 1% / < 1%) in both enzyme activities are common in combined severe deficiency. Among patients with the clinical phenotype of combined severe deficiency, 11.5% had partial 17-OHD and severe 17,20-lyase deficiency based on enzyme activity (> 1% / < 1%). Baseline serum cortisol was significantly higher whereas serum progesterone tended to be lower in this subgroup (29).

In isolated deficiency of 17,20-lyase enzyme, ambiguous genitalia, micropenis, hypospadias, and gynecomastia may be observed in boys, and puberty delay and absence of adrenarche may be observed in girls (30). In a report by Maheshwari et al. (29) a total of seven patients (median age at evaluation of 15 years) with apparent isolated 17,20-lyase deficiency were identified. All these patients presented with atypical genitalia and had normal morning serum cortisol levels. Insufficient virilization in isolated 17,20-lyase deficiency is less severe than in partial 17-α-hydroxylase/severe 17,20-lyase combined

deficiency. This may be related to the inability to produce sufficient 17-OHP compared to the increased production of androgen precursors via the back-door pathway in isolated 17,20-lyase deficiency (29,31).

The largest series of pediatric endocrine cases of 17-OHD was published very recently. In this study, data from a total of 97 cases (mean age at admission was 13.54 years) from 78 families were analyzed. Fifty-nine of the 97 cases (60.8%) had a 46,XY karyotype and 38 (39.1%) had a 46,XX karyotype. The majority of cases were 46,XY and they had primary amenorrhea with pubertal delay, and hypertension was found in 65% of all patients. Among the cases with a 46,XY karyotype, only six presented with ambiguous genitalia. When laboratory findings were evaluated in this largest series, serum sodium levels were normal, hypokalemia was seen as one of the prominent features of the disease and some patients were followed up with the diagnosis of isolated hypokalemia (32).

17-OHD typically leads to low-renin, low-aldosterone hypertension due to the accumulation of excess mineralocorticoid precursors, with consequent transcriptional downregulation of aldosterone synthase (33). Biochemical hyperaldosteronism with low renin levels has been reported in several studies (34,35). Aldosterone level is affected by age, severity of mutation, and methodological (kit-related) factors (36). A high aldosterone level was reported by radioimmunoassay and a low aldosterone level by high-performance liquid chromatography (LC) in a 17-OHD patient with hypertension with low renin level (37). To avoid falsely high values in low-renin hypertension, measuring with LC-MS/MS will be much more guiding for diagnosis.

More than 150 mutations have been identified in the *CYP17A1* gene to date. Although certain mutations may be more common in some countries, the phenotype-genotype relationship has not yet been clearly determined. In approximately half of the cases in which genetic analysis was performed in Turkey, there were exon 1-6 deletions. In other cases, different mutations, mostly point mutations (missense, frameshift, etc.), were identified. This finding suggests that requesting MLPA analysis would be appropriate as a first step in Turkey (32).

Treatment

The aim of treatment is to prevent GC deficiency, reduce the effects of mineralocorticoid elevation, and ensure age-appropriate development of secondary sex characteristics. GC therapy is for mineralocorticoid suppression rather than correcting GC deficiency. Generally, symptoms of GC deficiency due to increased corticosterone are not expected. GCs must be given in supraphysiological doses to suppress mineralocorticoids and control hypertension. If hypertension cannot be controlled with GC treatment, spironolactone treatment may be necessary. Spiranolactone dose is started at 1 mg/kg/day (in 1-2 doses), and can be increased to 3.3 mg/kg/day or 100 mg/day, if necessary. Clinical monitoring is done with arterial blood pressure, sodium, potassium and deoxycorticosterone. Since renin suppression can last for years despite adequate treatment, renin can be used in long-term monitoring (21). In patients diagnosed before puberty, estrogen replacement therapy should be started at the time of puberty. Estrogen replacement therapy can be used orally or transdermally. It should first be started at a low dose and gradually increased to the adult dose (21). *In vitro* fertilization, pregnancy and live birth have been reported in partial 17-OHD (38).

In patients with 46,XY 17-OHD that has caused severe undervirilization, female sexual identity is selected. This situation can be explained by the lack of androgen exposure of the fetal brain, as in complete androgen insensitivity syndrome. In 17-OHD patients with atypical genital structure, the gender to be raised is determined on the basis of sexual identity (29). Since 46,XY individuals with partial 17-OHD and who are raised as males do not produce sufficient testosterone, androgen replacement therapy is required (21).

In 17-OHD cases, data on final height were given in reports of a small number of cases and until recently, there was no detailed data on this subject. Karyotype characteristics are often not taken into account in final height SD score (SDS) calculations. In the study by Siklar et al. (32) 37 (38.5%) cases (16 cases had 46,XX and 21 cases had 46,XY karyotype) reached their final height. Final height SDS was calculated according to their karyotype, and were normal in both 46,XX and 46,XY patients. In 46,XX cases, the final height SD values were 0.015 ± 0.94 SD and an improvement of height SDS was approximately 1.5 SD. In 46,XY cases, the final height SDS was -1.43 ± 1.06 SD. Also, there were no patients whose final height was taller than +2 SDS.

Good practice points:

1. In patient with 46,XY karyotype and insufficient virilisation or in 46,XX patients presenting with immature pubertal development and primary amenorrhea due to estrogen deficiency throughout adolescence, especially having low potassium, low cortisol levels and high ACTH and gonadotropin levels, 17-OHD should be considered (1⊕⊕⊕O).

2. In cases with hypokalemia, the presence of accompanying hypertension should be a warning for the diagnosis of 17-OHD (2⊕⊕OO).

3. When requesting genetic analysis in cases diagnosed with 17-OHD, it would be appropriate to request MLPA analysis as a first step in our country (ungraded good practice statement).

4. Treatment for 17-OHD is GC replacement and adrenal steroid hormone replacement. In addition to these treatments, calcium antagonists, spironolactone, angiotensin 2 receptor blockers and cortisone may need to be used to control blood pressure (1⊕⊕OO).

5. Final height SDS (according to the karyotype) are expected to be normal in both 46,XX and 46,XY patients (ungraded good practice statement).

Lipoid Congenital Adrenal Hyperplasia (StAR Deficiency)

Acute stimulation of steroidogenesis results in the entry of cholesterol into the mitochondria, and this occurs via *StAR*, encoded on chromosome 8. After cholesterol is taken into the mitochondria, the conversion of cholesterol to pregnenolone by the side chain cleavage system consisting of CYP11A1, and ferredoxin/ferredoxin reductase for electron transfer occurs (39). StAR-mediated transport of cholesterol to the inner mitochondrial membrane is essential for steroidogenesis. Therefore, in *StAR* mutations, all steroidogenesis products are reduced (39,40,41).

Lipoid CAH (LCAH) is one of the rarest causes of CAH. In the literature, there are a limited number of patients. There are two case reports from Turkey, one of which was a non-classical form. In addition, in a study analyzing 95 cases with primary adrenal insufficiency, it was reported that the frequency of *StAR* mutation was 12% (42,43,44).

LCAH is characterized by adrenal hyperplasia marked by complete or almost complete deficiency of adrenal and gonadal steroid hormones, increased ACTH secretion, and progressive cholesterol ester accumulation. The adrenal gland enlarges with cholesterol ester deposits at birth. LCAH was formerly misnamed '20,22-desmolase deficiency and cytochrome p450scc deficiency was thought to be responsible for LCAH. Hovever in most patients with LCAH, the defect is found in *StAR* not the *CYP11A1* gene for P450scc (25). In cytochrome p450scc deficiency, placental progesterone synthesis is often inadequate. This usually results in spontaneous abortion. Only a few cases of p450scc deficiency have been reported and occur between infancy and early childhood with signs of adrenal insufficiency. Unlike *StAR* gene mutation, adrenal gland hyperplasia was not observed in these cases (41,45).

Phenotypically, StAR deficiency can be seen in classical and non-classical forms. The classical form usually occurs with loss-of-function in the *StAR* gene (39).

As fetal androgen production is inadequate, placental estradiol production (produced by the metabolism of DHEA) is also inadequate, and maternal estradiol levels are low. Placental progesterone production is not affected by StAR deficiency (45).

Affected 46,XY genetic males are born with female external genitalia, due to severely affected testosterone biosynthesis between 6-12 weeks (46).

In cases born with female phenotype, signs of adrenal insufficiency are seen within a few weeks to a few months after birth. Laboratory evaluation shows typical findings of GC and mineralocorticoid deficiency. Absence of pregnanolone production in the steroid profile is one of the diagnostic findings (39). Affected infants have low but measurable levels of GC and mineralocorticoids and require physiological dose replacement. If replacement therapy is not started immediately, patients will die in a short time due to adrenal insufficiency (46).

Although StAR is required for acute and maximal steroidogenic response, low levels of StAR independent steroidogenesis are present (40,47). It has been concluded that the LCAH phenotype is the result of two separate events. First, an initial defect in steroidogenesis due to *StAR* mutation, and second, a subsequent further defect in steroidogenesis due to cellular damage from accumulated cholesterol esters. This mechanism, called the 'two-hit hypothesis', occurs in the first stage with a decrease in steroid production and an increase in ACTH secretion, and then with secondary toxic damage due to intracellular lipid accumulation (39,47).

In cases with 46,XY karyotype and growing girls, spontaneous puberty will not occur, so sex hormone replacement is required. 46,XX girls often enter spontaneous puberty. Unlike the testicles and adrenal glands, the ovaries begin to synthesize steroid hormones only at the beginning of puberty. Thus, in 46,XX females affected by LCAH, the ovaries do not receive the second hit until the onset of puberty. As ovarian failure gradually develops, hypergonadotropic hypogonadism occurs (39,45,46).

Patients with mutations in the *StAR* or *CYP11A1* genes cannot be distinguished by clinical and laboratory findings, and their treatments are similar, treated with physiological

doses of GCs and mineralocorticoids (48). Most patients with LCAH have massive adrenal enlargement, but small adrenal glands have been reported in classical LCAH although rarely (49). On the other hand, adrenal enlargement has not been reported in any of the patients with *CYP11A1* mutation (49). However, ultrasonography may not be as sensitive as computed tomography, and the adrenal glands may not have yet grown in ultrasonography performed in the first week of life. Thus, P450scc and StAR deficiency may not be distinguished by clinical imaging and hormonal findings alone, and gene sequence is the only definitive diagnostic method. Differentiation of these two very similar conditions allows prenatal diagnosis and genetic counseling (49).

Classic StAR deficiency cases can be fatal because it is a very severe form. Physiological doses of GC and mineralocorticoid replacement, with supplementary salt are required for the neonatal period. In these patients, the GC dose is lower than those in 21-OHD, as it is not necessary to suppress androgen levels (25).

Some patients have late and mild clinical findings, and these cases are called 'non-classical lipoid congenital adrenal hyperplasia'. StAR enzyme activity is around 20-25%. The degree of mineralocorticoid insufficiency is variable and the onset of cortisol deficiency can be as early as two years of age or in late adulthood. In the non-classical form, 46,XY cases can be born with normal male genitalia. However, there may be minor findings, such as hypospadias and cryptorchidism. Gonadal functions are often normal in childhood and gradually deteriorate in adulthood. As a result, hypergonadotrophic hypogonadism develops (39).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (50).

Good practice points:

1. The possibility of lipoid adrenal hyperplasia should be considered in cases of female phenotype with adrenal insufficiency seen after birth. The absence of pregnenolone production in the steroid profile is one of the diagnostic clues (2⊕⊕OO).

2. In cases of classical StAR deficiency, physiological dose of GC and mineralocorticoid replacement are given and additional salt may be required for the neonatal period (1⊕⊕⊕O).

Footnotes

Authorship Contributions

Concept: Şenay Erdeve, Semra Çetinkaya, Design: Şenay Erdeve, Semra Çetinkaya, Analysis or Interpretation: Şenay Erdeve, Semra Çetinkaya, Literature Search: Mehmet İsakoca, Writing: Mehmet İsakoca.

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REVIEW

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Antenatal Diagnosis and Treatment in Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency and Congenital Adrenal Hyperplasia Screening in Newborns

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Abstract

Signs of virilization, such as clitoromegaly, labio-scrotal fusion, and urogenital sinus may be observed in females with 21-hydroxylase deficiency (21-OHD) and other rare virilizing forms of congenital adrenal hyperplasia (CAH). This makes sex determination difficult, and multiple reconstructive surgeries in the postnatal period may be required. As 21-OHD is an autosomal recessive disease, the chance of any child being affected is one in four and so only one in eight will be an affected female. The primary objective of antenatal diagnosis is to identify only the affected fetus in the early gestational weeks before the onset of genital organogenesis and to treat that case. Therefore, studies aimed at antenatal diagnosis and preventing adrenal androgen exposure in the female fetus with CAH have long been of interest. Antenatal steroid treatment is considered experimental and controversial for safety reasons in recent clinical guidelines. If antenatal treatment is to be used, it is recommended that it should be performed in experienced centers that can collect data on a large number of cases which will help to define the benefits and harms of treatment better. In the postnatal period, a severe deficiency of the 21-hydroxylase enzyme leads to life-threatening adrenocortical insufficiency in both sexes and varying degrees of pathology of the external genitalia in females. This condition is also associated with high mortality in the first days of life and an increased risk of incorrect sex assignment. Neonatal screening for 21-OHD CAH effectively detects the severe forms and reduces mortality, and it is instrumental in the correct sex assignment of female cases.

Keywords: Congenital adrenal hyperplasia, 21-hydroxylase deficiency, antenatal diagnosis, antenatal dexamethasone, newborn screening

Introduction

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is an autosomal recessive disorder caused by pathogenic variants in the *CYP21A2* gene (MIM*613815). Many of the variants in the *CYP21A2* gene are caused by recombinations between the *CYP21A2* and its pseudogene *CYP21A1P* (aliases *CYP21A, CYP21P, P450C21A*). The complexity of this locus due to the chromosomal arrangement of the active gene and the pseudogene makes the genotyping of 21-OHD sophisticated. However, accurate molecular genetic diagnosis is crucial to provide families with appropriate genetic counseling concerning future pregnancies. Genetic testing should be performed by certified molecular laboratories with expertise in the analysis of the *CYP21A2* gene with sequence analysis and multiplex ligation-dependent probe amplification (MLPA) (1,2,3,4).

The adrenal cortex begins to function in the seventh gestational week (gw). Female fetuses with CAH are exposed to elevated levels of androgens between 8^{th}-12^{th} gw which is a critical period for sex differentiation. Exposure to excess androgens in the first trimester causes the formation of a

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urogenital sinus with a conjoined urethra and vagina, and continued exposure throughout pregnancy causes varying degrees of labial fusion and clitoral enlargement (5). Signs of virilization, like clitoromegaly, labio-scrotal fusion, and urogenital sinus may be observed in females with CAH due to 21-OHD and 11β-hydroxylase deficiency (11β-OHD) (6,7). This makes sex determination difficult and may lead to multiple reconstructive surgeries in the postnatal period (8). The routine practice of genital surgery in infancy has been questioned, and shared decision-making among parents, patients, surgeons, endocrinologists, and mental health providers is currently being promoted. Therefore, studies aimed at preventing adrenal androgen exposure in the female fetus with CAH have long been of interest (9).

This evidence-based review, which includes good practice points, was developed by the Adrenal Working Group of the Turkish Society for Pediatric Endocrinology and Diabetes. We have also developed this evidence-based review for "Antenatal Diagnosis and Treatment in Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency and Congenital Adrenal Hyperplasia Screening in newborns". The overall purpose of this evidence-based review is to provide good practice points, focusing on daily management recommendations.

Molecular Genetic Analyses in Antenatal Diagnosis

Antenatal diagnosis requires accurate and reliable *CYP21A2* sequence analysis and MLPA testing in the index case and confirmation of the variant through segregation analysis in the family (7).

Several approaches for antenatal diagnosis of affected fetuses with CAH have been used. The hormonal diagnostic test for 21-OHD is amniotic fluid 17-hydroxyprogesterone (17-OHP) but hormonal diagnosis is rarely used and considered only when molecular diagnosis is unavailable (10).

For the antenatal diagnosis of CAH, invasive procedures may be used, such as chorionic villus sampling (CVS) at 10-12 gw and amniocentesis (AS) at 16-20 gw. CVS is preferred over AS for early diagnosis in the first trimester of pregnancy. However, even with CVS, diagnosis cannot be made before the ninth gw, leading to unnecessary treatment of male fetuses and unaffected female fetuses. CVS and AS are invasive procedures that may pose risks to both the mother and fetus. Therefore, it is important to identify cases of CAH, before the onset of genital organogenesis, so that only affected female fetuses receive treatment. As 21-OHD is an autosomal recessive disease, the risk of any one child being affected is one in four, and given the 50/50 chance of gender this trnaslates to a risk of one in eight being an affected female. This would equate to seven out of eight fetuses receiving antenatal steroid treatment unnecessarily if all at risk fetuses were treated before definitive diagnosis. The primary objective, therefore, is to identify only the affected fetus in the early weeks of gestation and to treat only those cases (6).

Advances in *CYP21A2* genotyping are expected to make molecular analysis of fetal DNA the ideal diagnostic tool for fetuses at risk for 21-OHD (11). Conditions such as undetectable mutations, allele drop-out (ADO), or maternal DNA contamination can complicate antenatal diagnosis (11,12,13). Analysis of CVS material may cause false positive or false negative results if there is a genetic mismatch between the fetus and the placenta however, this is not an issue in AS, because the fetal cells that are released into the amniotic fluid are analyzed (14).

Cell-free Fetal DNA

Non-invasive prenatal testing (NIPT), including cell-free fetal DNA (cffDNA), appears to be a promising technique for early diagnosis of 21-OHD (3). Lo et al. (14) first described the high concentration of cffDNA in maternal blood. Early in pregnancy, fetal DNA represents approximately 3.4% of maternal plasma DNA. In maternal blood, fetal DNA molecules are detected with maternal DNA sequences. The paternal allele is the fetal-specific sequence because the maternally inherited allele of the fetus is genetically identical to the maternal allele. The fetal genotype can be assessed by the detection of the specific molecular characteristics of the paternally inherited fetal allele using cffDNA. These specific characteristics include the Y chromosome or sex-determining region Y (*SRY*) and paternally inherited variants or polymorphisms. If the parents carry different variants (compound heterozygosity), CAH can be excluded if no variant is detected in the paternal allele (11).

Rijnders et al. (15) first reported successful sex determination from maternal blood in a fetus at risk for 21-OHD. The male fetus could be detected as early as 13th gw by demonstrating the presence of the *SRY* in maternal blood samples. Bartha et al. (16) were able to accurately identify the male fetus as early as the sixth gw. A proposed algorithm for antenatal diagnosis recommends testing for the *SRY* at the fifth gw. Further testing is recommended until there is evidence of a male fetus in two separate samples or until the 11th week of pregnancy. Procedures such as CVS are not required if these tests indicate that the fetus is 46,XY (17). This protocol eliminates the need for invasive diagnostic procedures and prevents unnecessary exposure of male fetuses to prenatal

steroid therapy (11). Some publications suggest that as early as four weeks and five days of gestation, *SRY* analysis can be used for antenatal sex determination (18). Although antenatal sex determination can be performed by cffDNA using NIPT, the results obtained by this protocol should be confirmed by CVS and AS (2).

Fetal sex determination is a relatively straightforward procedure based on the presence or absence of Y chromosome sequences (3,18). However, antenatal sex determination in CAH only prevents male fetuses from receiving treatment and does not preclude unaffected females from receiving steroid treatment. Since most variants in the *CYP21A2* gene are caused by gene conversions and are also present in the fetal (and maternal) DNA, the detection of variants in the antenatal period is technically challenging. Advances in next-generation sequencing techniques have been used to detect single nucleotide polymorphism (SNP) haplotypes in the *CYP21A2* region. This technique generates millions of small fragments (100 base pairs, bp) and assembles them into longer sequences. Determining the maternal allele is difficult because the maternal allele of the fetus is only 2.0% higher than the other allele. High sequencing depth is required for accurate quantification however, this is costly and technically challenging when using whole genome sequencing. Current approaches involve amplifying several hundred kilobases around the *CYP21A2* locus or capturing DNA from the target region prior to sequencing and all have the potential to reduce the amount of sequencing required (19,20). These techniques are still under development and are subject to improvement.

The use of targeted massively parallel sequencing (MPS) for the non-invasive diagnosis of CAH using cffDNA was first reported in 2014 (20). In this study, 14 families, each with an index diagnosis of classical 21-OHD and parents with at least one mutant allele in the *CYP21A2*, were analyzed by NIPT. The authors reported successful fetal sex and CAH genotype identification by NIPT. In one family, CAH was detected by the analysis of maternal plasma as early as five weeks and six days of gestation. In addition, it has been reported that this new NIPT avoids the risks associated with invasive procedures such as CVS and AS. The advantage of this method is that it ensures that only affected fetuses receive treatment. However, it is should be highlighted that cffDNA testing has not completely replaced invasive diagnostic procedures and that confirmation with invasive tests is still necessary (20,21).

CYP21A2 genotyping by MPS is more complex than simply detecting specific *CYP21A2* variants. This technique requires targeted MPS on the genomic DNA of the affected proband and parents. SNPs on both sides of the *CYP21A2* locus generate haplotype blocks, which are needed to detect paternal and maternal alleles. Dosage analysis quantifies the amount of DNA inherited from the parents, taking into account the mother's alleles as well as the alleles she passes on to the fetus. If the fetus carries a CAH-associated haplotype, more DNA will be present with a linked SNP than with no linked SNP (22,23). Distinguishing between maternal and fetal alleles in maternal blood poses a significant challenge. These technical limitations restrict the broad application of cffDNA in diagnosing fetal monogenic disorders (24). However, studies have reported successful results with the use of cffDNA to sequence the fetal genome as early as the first trimester of pregnancy (24,25). Advances in genome sequencing techniques will eliminate the controversial issues associated with the accurate detection of fetal alleles. Despite ethical and technical challenges in the interpretation of fetal genomic data, the use of cffDNA from maternal blood for the diagnosis of single-gene disorders such as CAH is an exciting development in fetal genetic diagnosis (24).

Preimplantation Genetic Test for Monogenic Gene Defects

Preimplantation genetic test for monogenic (PGT-M) is a valuable reproductive option for families who are at risk of having a child affected by CAH due to the ability to identify and prevent the transmission of monogenic diseases. PGT allows the identification of genetic abnormalities in preimplantation embryos before transfer, ensuring that only unaffected embryos are transferred (11). Preimplantation genotyping allows the identification of affected and unaffected embryos as well as the determination of the gender of the embryos. PGT-M can be used for any monogenic disease where the causative variant can be accurately identified. The objective of PGT-M is to select against embryos carrying a monogenic disease for which an individual or couple is at risk, to reduce the likelihood of a pregnancy resulting in the birth of an affected individual. As genetic technologies continue to improve and costs continue to fall, genetic testing is becoming more common in various settings, particularly in fertility clinics. This allows more patients to be eligible for PGT-M (26).

There are three PGT approaches: (1) polar body biopsy, which uses female gametes (oocytes); (2) blastomere biopsy, performed on day three of a 6- to 8-cell cleavage stage embryo; and (3) trophectoderm biopsy, performed on a 5- to 6-day blastocyst containing approximately 120 cells (27).

When performing PGT for single gene disorders, such as 21-OHD, it is recommended to use SNPs or short tandem repeats for linkage analysis. This is necessary to rule out ADO, which can lead to the loss of the mutant allele. ADO can be caused by dsDNA breaks or failure of the host DNA to bind with the targeted primer. If ADO occurs, it may lead to the erroneous conclusion that the allele detected is the only allele present in the embryo. If ADO carries the mutant recessive allele and is not detected, it may be falsely concluded that the embryo is homozygous wild-type. ADO is caused by preferential amplification of one allele over the other and can lead to misdiagnosis of the genetic status of the oocyte or embryo (28). PGT should include multiple linked polymorphic microsatellite markers around the disease-associated gene to mitigate these problems (29,30). Invasive diagnostic testing is recommended to confirm PGT results due to the technical limitations of non-invasive methods that may result in false negative results (14).

Although most of the literature is related to 21-OHD in the antenatal diagnosis of CAH, the same molecular approaches, and PGT procedures can be applied to 11β-OHD, 3β-hydroxysteroid dehydrogenase (HSD3B2) deficiency, and other rare CAH types.

Couples who have a child with CAH and who are at risk for this condition are candidates for genetic counseling at the time of pregnancy planning. The accuracy of the molecular genetic diagnosis of the proband is important for genetic counseling. During counseling, parents should be informed about the possibility of the potential fetus being affected and the consequences of this condition. Another goal of antenatal diagnosis of CAH is to ensure that treatment is initiated in the early weeks of pregnancy to prevent virilization of the affected female fetus and so the need for genital surgery and gender confusion may be minimized, or even avoided (9). Several approaches have been used for the identification of fetuses with CAH during the antenatal period. Due to the rapid advances in molecular genetic methods, targeted approaches will become progressively more achievable.

Good practice points:

1. The protocol should include testing of maternal blood for Y chromosome material to distinguish male fetuses from the potential antenatal treatment group in research protocols (ungraded good practice statement).

2. Genetic counseling should be provided to families of a proband with CAH, adolescents and young adults transitioning to adult clinics, those diagnosed with non-classical CAH in adulthood, and their spouses when individuals diagnosed with CAH plan to have children.

3. Counseling must be given by clinicians experienced with CAH and its genetic characteristics (1⊕⊕⊕O).

Antenatal Treatment

Antenatal treatment of CAH, particularly 21-OHD, has been the focus of interest for many years. Nevertheless, this treatment is still considered controversial and experimental. In 1984, Forest et al. (30) first reported maternal treatment during pregnancy to reduce the virilization of female fetuses with CAH. Dexamethasone (Dex) is the glucocorticoid of choice for antenatal treatment due to its long half-life, its ability to cross the placenta as Dex is not metabolized by placental 11β-HSD2, and its ability to reduce androgen levels by suppressing fetal ACTH secretion (2).

The experimental approach for antenatal treatment of 21-OHD is the use of Dex in early pregnancy (before 6th gw) with the consent of parents who are heterozygous for a *CYP21A2* variant. Treatment may be discontinued in 46,XY fetuses following AS or CVS. The primary objective is to identify the affected fetus early in the gestation period and provide antenatal treatment only if necessary (2).

The antenatal treatment protocol includes the use of Dex at a dose of 20 μg/kg (maximum 1.5 mg/day), calculated based on the mother's pre-pregnancy weight. For a mother weighing 60 kg pre-pregnancy, this dose is 1.2 mg/day, which is approximately six times the physiological dose (31,32). Lower doses of Dex for antenatal treatment have not been reported, and the reason for the recommendation of such a high dose is not clear (18). Fetal cortisol concentration is low in early pregnancy but rises during external genital differentiation between 8-12 gw. It is only 10% of maternal levels in mid-pregnancy and then increases in the last trimester of pregnancy (31,32,33). This high therapeutic dose can result in fetal levels that are 30-60 times higher than normal, which can cause elevations in glucocorticoid concentrations that exceed physiologic levels in the second trimester (34,35).

In pregnancies in which the fetus is treated to term, treatment efficacy is monitored by maternal serum dehydroepiandrosterone sulfate DHEA-S (beginning at the 7th gw) and estriol measurements. Low DHEA-S levels indicate sufficient fetal adrenal suppression, while low estriol levels indicate maternal adrenal suppression and poor compliance (36). Many studies have reported that infants with CAH treated antenatally, are less virilized than their affected sisters who did not receive treatment, provided that treatment is initiated on time and the mother is compliant with the

treatment (37). To prevent genital virilization in females with 21-OHD or 11β-OHD, treatment should be initiated before an increase in genital sensitivity to androgens occurs, at the latest in the 7th-9th week of amenorrhea (37,38). This protocol may result in unnecessary steroid treatment for the majority of potential fetuses, as fetal genotyping is typically not feasible before 10-12 weeks of gestational age (9,38). The timing of Dex initiation is crucial for the genital morphology of females with CAH. To ensure the effectiveness of Dex treatment, it is recommended to continue until delivery in female fetuses with CAH (39).

Antenatal Dex treatment has the potential to prevent or reduce virilization of the external genitalia and brain, as well as reduce the need for multiple corrective genital surgeries in the postnatal period. This treatment option should only be offered to parents with an affected child with CAH whose heterozygous carrier status is established by molecular analysis. Antenatal diagnosis typically begins at 6 to 8 gw, even when fetal sex can be determined from maternal plasma by cffDNA analysis. This diagnosis may lead to the avoidance or early discontinuation of Dex in male fetuses. In female fetuses, the diagnosis of CAH can be made by CVS at 12-13 gw (2).

While animal studies have shown that early *in utero* exposure to Dex can cause adverse neurodevelopmental effects, human evidence is inconclusive. Several studies have reported a potential link between antenatal Dex use and neuropsychological development, but a consensus has not yet been reached (40).

Exposure to Dex between 7-12 gw coincides with neurogenesis and neuronal migration (38,41). Epigenetic processes may also have long-term programming effects on brain development and so questions remain about the behavioral and developmental effects of Dex. Although a Swedish study reported good school performance and psychological well-being, it did not identify concerns about memory and gender behavior (42). Impaired verbal memory and social anxiety were reported in cases that were not affected by CAH but received antenatal treatment (40). However, a larger follow-up study examining cognitive outcomes in Dex-exposed fetuses detected no impairment in memory. Instead, the study reported slower mental processing in antenatally treated females with CAH compared to controls (43).

The effects of steroids on neurodevelopment during the second and third trimesters have been the primary focus of research to date. Synthetic glucocorticoids are commonly administered to induce fetal lung maturation in fetuses at risk of preterm birth during the third trimester, but their use has been associated with a decrease in rostral anterior cingulate cortex thickness (44). In addition, high antenatal maternal cortisol concentrations have been linked to reduced fetal brain growth and altered functional and structural connectivity during childhood (44,45). The amygdala develops early in fetal life and is particularly sensitive to early abnormalities in cortisol concentrations. Increased amygdala volume has been associated with depression risk in girls (38,45). The effect of Dex treatment in the first trimester on changes in brain structure in adulthood was also investigated in a recent study (38). Magnetic resonance imaging scans of male and unaffected females at risk of CAH, as well as antenatally treated subjects, were compared with controls. It was reported that Dex exposure during the first trimester was associated with structural changes in the brain during adulthood. Moreover, methylation changes have been reported. In a previous study, changes in gene methylation associated with brain development were detected in individuals treated with Dex but not diagnosed with CAH. The candidate genes were brain-derived neurotrophic factor (*BDNF*), glucocorticoid receptor (GR) (*NR3C1*), GR co-chaperone *FKBP5*, and mineralocorticoid receptor gene (*NR3C2*) (46). It has been suggested that altered methylation of some of these genes may be associated with depression (46,47). Changes in brain structure may occur as a result of the effects of synthetic steroids on antenatal programming. Antenatal Dex treatment may have detrimental effects on cognitive function, as cognitive function and mood regulation depend on networks with high GR density. These findings raise concerns about the safety of antenatal steroid treatment in CAH (2).

Recent clinical guidelines consider antenatal steroid treatment to be an experimental treatment that is controversial for safety reasons. Therefore, Endocrine Society Guidelines also do not recommend specific antenatal treatment protocols (2).

Good practice points:

1. Clinicians should continue to regard antenatal therapy as experimental. Thus, we do not recommend specific antenatal treatment protocols (ungraded good practice statement).

2. In pregnant women at risk for having a fetus with CAH and who are considering treatment, we recommend therapy only through protocols approved by Institutional Review Boards at centers capable of reporting the outcomes in a large number of patients, so that risks and benefits can be defined more precisely (2⊕⊕OO).

Neonatal Congenital Adrenal Hyperplasia Screening

Newborn CAH screening is implemented in over 50 countries (48). According to these screening data, the incidence of classical CAH has been found to be approximately 1:14,000 to 1:18,000 in most populations (2). In the screening program conducted in our Turkey, this ratio has been similarly determined to be 1:15,067 (49).

The CAH screening program significantly reduces the time to diagnosis for infants with CAH, thereby decreasing morbidity and mortality (50,51,52,53). In a study involving 242 cases diagnosed with sudden infant death syndrome, dry blood samples obtained during the neonatal period were retrospectively analyzed, and classical CAH diagnosis was genetically confirmed in 3 (1.2%) cases (54). In contrast, another study found no cases of CAH in dry blood samples collected from 1,198 infants who died between 5 days and 6 months of age (55). In males with salt-wasting CAH, where there is no genital ambiguity, diagnostic delay, and misdiagnosis are more likely compared to female CAH infants. Therefore, the relative rarity of males with salt-wasting CAH in the patient population may serve as indirect evidence of unreported deaths (2).

Regarding morbidity, infants diagnosed through neonatal screening tend to experience milder hyponatremia and shorter hospital stays (51,53,55,56). Although males with salt-wasting CAH may seem to benefit more from screening, it also enables early determination of the correct gender in severely virilized girls identified through screening (53,57). Furthermore, the CAH screening program prevents diagnostic delays in male virilized CAH cases. In such cases, delayed diagnosis will result in rapid growth and accelerated bone maturation, leading to loss of final height in adulthood.

Screening is performed using methods that allow rapid results to be obtained from samples absorbed onto Guthrie cards and dried. A commonly used measurement method is time-resolved fluorescence immunoassay (DELFIA), which is an immunoassay technique (2). Several factors limit the accuracy of this test. Firstly, the level of 17-OHP is elevated at birth in healthy infants and decreases gradually in the following days. In contrast, in infants with CAH, 17-OHP increases progressively (58). Therefore, samples taken within the first two days have poor diagnostic accuracy, and follow-up samples are required for an accurate diagnosis. According to some reports, female infants have lower 17-OHP levels than males (58). Since nearly all of these infants exhibit virilization and salt loss, medical intervention is promptly sought, mitigating a significant issue. Thirdly, in premature, sick or stressed infants, the level of 17-OHP tends to be higher, which increases the likelihood of false positives.

For example, in a 26-year screening program in Sweden (evaluated using immunoassay for 17-OHP levels), the positive predictive value for term infants was found to be 25%. In contrast, for preterm infants, it was only 1.4%, and the predictive value of the test was reported to be strongly correlated with gestational age (59). Lastly, immunoassays may lack specificity. No universally standardized criteria are categorized according to infants, but most laboratories use cutoff limits based on birth weight.

Repeating the screening a few days after birth improves sensitivity and positive predictive value (60,61). It is indicated that repeated sampling should be done in the 2nd and 4th weeks for preterm infants and hospitalized babies (61). In a study, a positive predictive value of 5.6% was obtained between 48-72 hours, while samples taken after 72 hours yielded a positive predictive value of 14.1%, using the same cutoff value for CAH newborn screening (62). In a study conducted in the United States, the incidence of CAH was found to be 1:9,500 in the states where only a single sample was taken, whereas, in states where a second sample was taken, the incidence of CAH was 1:17,500 (63).

It has been found that classifying 17-OHP levels used in screening according to gestational age increases the specificity of newborn screening compared to birth weight (64). In a study where classification was made according to gestational age, screening increased the positive predictive value from 4.5% to 16% (56). In early gw, in addition to cross-reactions in immunologic tests, elevated levels of 17-OHP are observed due to functional deficiencies in several adrenal steroidogenic enzymes (adrenal steroidogenic enzymes are at their lowest point at the 29th week of gestation) (65). For example, due to cross-reaction with 17OH-pregnenolone sulfate, immunoassay may yield elevated levels of 17-OHP (66). Using organic extractions to remove steroid sulfates will increase the specificity of immunoassays (67). The corticosteroids used by the mother during the antenatal period may reduce 17-OHP levels in the baby and increase the likelihood of false negatives. Taking a second sample will minimize this issue.

Limitations of immunoassays for 17-OHP include proper elevation of levels in premature infants or those who are sick or stressed and lack of antibody specificity. In the second tier, direct measurement of steroids using the liquid chromatography-tandem mass spectrometry (LC-MS/MS) method is more effective than immunoassays in addressing these issues (68). However, since each sample takes 6-12 minutes to analyze, it is not practical for evaluating a large

number of samples. This type of analysis is only suitable for smaller numbers of samples (69). Approximately 40% of the positive tests in the first sample have normal levels of 17-OHP. This supports the suboptimal antibody specificity in the first tests.

Measuring steroid ratios further enhances the specificity of LC-MS/MS used in screening. Measuring additional analytes or analyte ratios can also improve screening results. For example, 21-deoxycortisol (produced by 11β-hydroxylation of 17-OHP) is not normally secreted in large amounts (even in premature infants), so elevated levels are highly specific for 21-OHD. In a study using a modified LC-MS/MS protocol, where the ratio obtained by dividing the sum of 17-OHP and 21-deoxycortisol values by cortisol was used, a 100% positive predictive value was observed, and no false positives were reported (62).

Good practice points:

1. The most common cause of CAH is 21-OHD. Due to the significant reduction in mortality and morbidity with early detection and treatment of the disease, it is recommended to be included in the neonatal screening program (1⊕⊕⊕O).

2. The first-line test for screening should include measurement of 17-OHP levels. Screening using standardized technological methods and evaluating the results according to gestational age is recommended (1⊕⊕OO).

3. Individuals with high results in the first-tier test should be recommended for a second-tier test (1⊕⊕⊕O). To improve the positive predictive value of CAH screening, the use of the liquid chromatography-tandem mass spectrometry (LC-MS/MS) method is recommended over all other methods (e.g., genotyping) to improve the positive predictive value of CAH screening (1⊕⊕OO).

Molecular Genetic Screening

CYP21A2 mutations can be detected from the DNA extracted from the same dried blood spots used for hormonal screening. Genotyping is a valuable diagnostic tool and a good complement to neonatal screening, especially in confirming or discarding the diagnosis in cases with slightly elevated 17-OHP. Because over 90% of mutant alleles carry one or more of a discrete number of mutations, patients carrying none of these mutations are unlikely to be affected. If at least one mutation is detected, the patient undergoes further evaluation (2). Genotyping of samples from screening programs has been suggested as a potentially helpful adjunct to hormonal measurements, but no large-scale study of efficacy has been reported as a second-tier screen in actual use (2). Also, genotyping, which has a lower positive predictive value, is time-consuming and more costly than LC-MS/MS on a per-sample basis, so it is not recommended as a second-tier screening test (2).

Newborn Congenital Adrenal Hyperplasia Screening in Turkey

The first CAH screening in Turkey was conducted in 2017 in four pilot provinces (Konya, Kayseri, Samsun, Adana) by the Ministry of Health. In this study, 38,935 infants were evaluated to determine the incidence of CAH and investigate the effectiveness of screening. Heel blood spot samples taken from infants at 3 to 5 days or after 48 hours were measured for 17-OHP values using fluoroimmunoassay, and those with high values underwent second-tier evaluation with LC-MS/MS. In this study, cutoff values were determined based on the infants' gestational age and birth weight. For infants with gestational age ≥37 weeks and/or birth weight ≥3500 grams, 10 ng/mL was accepted, while for infants with gestational age between 32-37 weeks and/or birth weight between 2500-3500 grams, 15 ng/mL was considered. In the second tier, 17-OHP, 21-deoxycortisol, cortisol, 11-deoxycortisol, and androstenedione were measured using the LC-MS/MS method, and infants with a (21-deoxycortisol + 17-OHP)/cortisol ratio ≥0.5 were referred to pediatric endocrinology clinics for further evaluation. It was found that second-tier steroid profiling increased the effectiveness of screening and reduced the number of false positives. In this pilot study, the frequency of 21-OHD was found to be 1:7,787 in the screened population (70).

Subsequently, in 2018, this pilot study was expanded and conducted in 241,083 infants in 14 provinces. According to the data from the initial study, the cutoff value used in the second-tier test was changed to (21-deoxycortisol + 17-OHP)/cortisol ratio ≥1 in this screening. No salt-wasting CAH cases were missed by newborn screening (sensitivity 100%). According to the results of this larger study, the frequency of classical 21-OHD in the screened population was 1:15,067, in line with other published frequencies, and 11β-OHD was 1:60,270 (49). The current screening does not detect non-classical CAH cases. If a CAH diagnosis is present as a result of the screening program, cortisol therapy initiation is appropriate. According to the screening results conducted in our country (49,70), if the first-tier screening using the fluorescent immunoassay (FIA) shows 17-OHP >90 ng/mL, treatment should be initiated immediately. In retrospectively analyzed cases diagnosed with CAH (49,70), the first-tier screening 17-OHP levels using the FIA method

were determined as >15 ng/mL in term and normal birth weight infants and >50 ng/mL in preterm and low birth weight infants. For these values, further investigations should be performed directly without waiting for second-tier test results, if possible. In addition, if the 11-deoxycortisol level is >10 ng/mL, further investigation for 11β-OHD should be conducted (Figure 1).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (71).

Good practice point:

1. In the first tier, if 17-OHP >90 ng/mL using the immunoassay method (FIA), treatment should be initiated immediately. In the first tier, if FIA 17-OHP >15 ng/mL (term, normal birth weight), >50 ng/mL (preterm, low birth weight), further investigations should be conducted. In the second tier, if (21-S + 17-OHP)/Cortisol ≥1 and 21-deoxycortisol >0.4 ng/mL and/or 17-OHP >2 ng/mL, further investigations should be conducted (1⊕⊕OO).

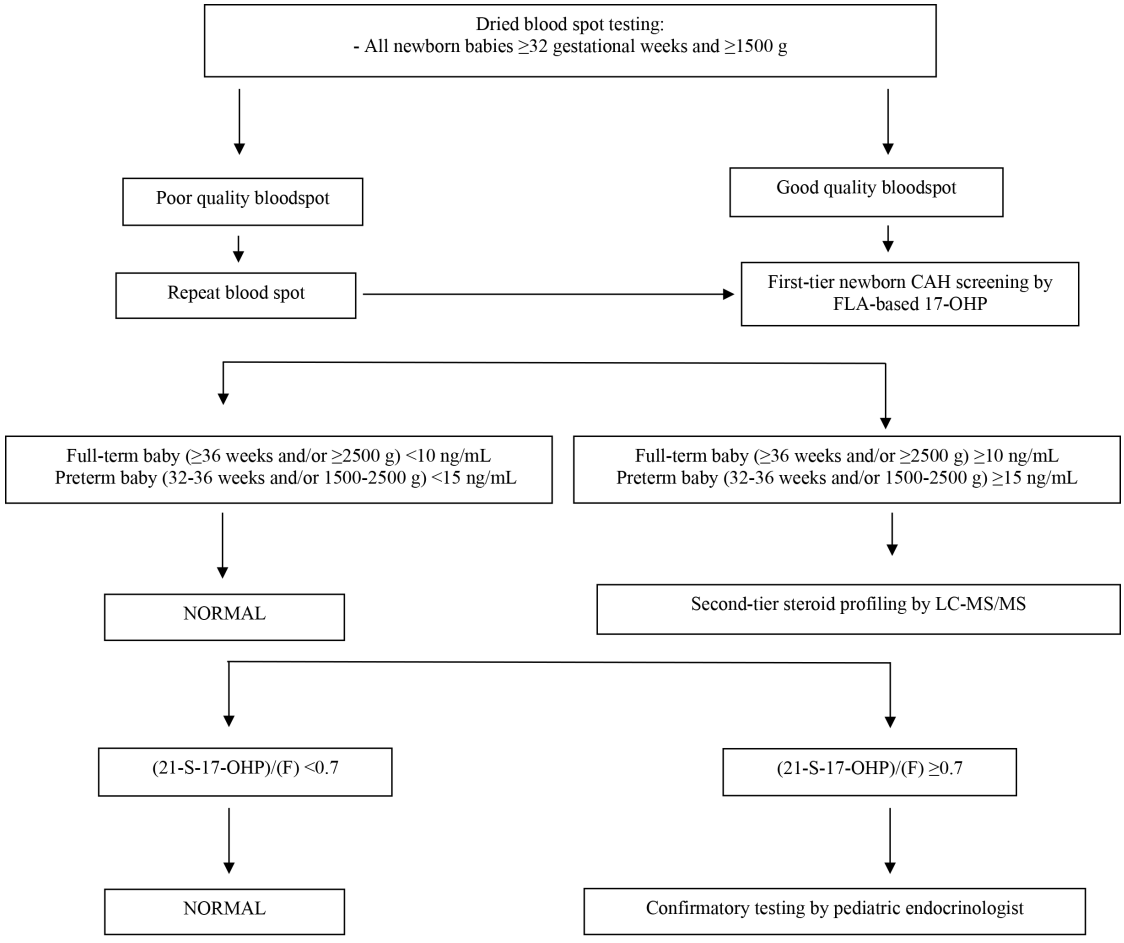

Figure 1. Flowchart for extended neonatal congenital adrenal hyperplasia screening initiated by the Turkish Directorate of Public Health (17-OHP conversion factor from ng/mL to nmol/L: multiply by 3.02)

CAH: congenital adrenal hyperplasia, FIA: fluoroimmunoassay, LC-MS/MS: liquid chromatography-tandem mass spectrometry, 17-OHP: 17-hydroxyprogesterone, 21-S: 21-deoxycortisol, F: cortisol

Footnotes

Authorship Contributions

Concept - Design - Data Collection and Processing - Analysis or Interpretation - Literature Search - Writing: Zehra Yavaş Abalı, Erdal Kurnaz, Tülay Güran.

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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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REVIEW

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Psychosocial Development, Sexuality and Quality of Life in Congenital Adrenal Hyperplasia

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Abstract

Exposure of the developing brain to androgens during fetal life is known to affect sexual development, including postnatal sex and sexual orientation. However, these relationships are both multifactorial and unpredictable. It is generally assumed that congenital adrenal hyperplasia (CAH) has greater effects in women than in men due to non-physiological adrenal androgen excess. Outcome information on patients with CAH often indicates poor quality of life, general maladjustment, problems with sexuality, and decreased fertility. With advances in medical treatment and surgery and changes in societal perspectives on gender and sexuality, there is a need for greater consideration of quality of life factors, including socialization and sexuality.

Keywords: Congenital adrenal hyperplasia, sexuality, quality of life, psychosocial development

Introduction

In disorders of sex development, compatibility between psychosexual identity and assigned gender is important. Sexuality in congenital adrenal hyperplasia (CAH) should be evaluated by taking into account the patient's karyotype and the gender being raised. The frequency of disorders in psychosocial and cognitive domains in patients with CAH is higher than in the normal population, and these disorders are related to the high prenatal androgen load, the patient's karyotype, and supraphysiological glucocorticoid treatment in the postnatal period.

Evaluating the quality of life in children with CAH and identifying and improving the factors affecting it are of critical importance for making the lives of these children and their families easier. A multidisciplinary approach that provides good clinical control and appropriate surgical management positively affects the quality of life.

This review was developed by the 'Adrenal Study Subgroup' of the 'Pediatric Endocrinology and Diabetes Association of Turkey'. We have prepared a review of Psychosocial Development, Sexuality and Quality of Life in Congenital Adrenal Hyperplasia in childhood and adolescence. The overall aim of this evidence-based review is to provide good practice points with a focus on recommendations for daily management.

Psychosexual Development in Congenital Adrenal Hyperplasia

Gender Identity and Sexual Health

46,XY male patients: It is reported that patients reared as males in parallel with karyotype do not have gender identity disorder and their frequencies of marriage or sexual intercourse are similar to those of healthy individuals. Gender dysphoria has not been reported (1,2). In a case-controlled study including males with CAH and healthy

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European counterparts, sexual health in males with CAH was shown to be comparable to those of healthy controls, and sexual problems in these patients were attributed to psychosocial problems, such as anxiety and depression (3).

46,XX female patients: Although virilized females tend to have more interest in games for males than age-matched healthy counterparts, gender dysphoria has not been reported (4,5,6,7). The preference for male toys in 46,XX females with CAH has been associated with parental guidance (8). Increased androgen excess in the perinatal period is not associated with sexual orientation in the postnatal period. However, homosexual or bisexual orientation has rarely been observed in 46,XX virilized females in the postpubertal period. A recent review suggested a greater tendency for gender identities in 46,XX females with CAH other than heterosexuality compared to the normal population (9).

A case series study investigating the impact of the diagnosis of CAH on sexuality has suggested lack of sufficient knowledge in young adult patients with CAH and differences among the patients in perception of the impact of the disease on sexuality (10).

46,XX females with classical CAH have been reported to spend more time with their female peers and have a higher frequency of male-specific activities than their non-classical CAH counterparts (11,12).

46,XX patients raised as males: Although an increased frequency of gender identity disorder has been noted in 46,XX patients raised as males, gender dysphoria is not encountered in the presence of adequate social support. It has been suggested that caution should be practiced in assessment of the studies that drew data mostly from non-validated interviews (9).

Cognitive and Neurological Functions in Patients with Congenital Adrenal Hyperplasia

Prenatal androgen overload, prenatal use of dexamethasone and the dose of the glucocorticoid treatment are significant factors associated with adverse impact on the neuropsychiatric development of patients with CAH (1). The hypothalamohypophyseal axis and sex hormones interact with the hypothalamus, amygdala and hippocampus. Intellectual impairment has been shown to be associated with endogeneous hormonal imbalance, nonphysiological glucocorticoid replacement and subclinical cerebral ischemia owing to differentiation of oligodendroglia (13).

Prenatal dexamethasone has been reported to lead to improvement in cognitive functions in girls with CAH. However, prenatal dexamethasone may have detrimental effects on the cognitive functions of healthy girls (14).

Females with CAH have been reported to have better spatial targeting performance than healthy controls but similar capacities of mental rotation when compared to healthy counterparts. Mental rotation capacity is disturbed in 46,XY male patients with CAH while the targeting capacity is intact. A recent meta-analysis reported spatial cognition to be comparable to healthy controls in 46,XX girls with CAH (15) whereas in 46,XY male patients it was shown to be compromised (15). Gender related differences in spatial capacities have been associated with mini-puberty or different social factors (15).

Studies on learning difficulties in patients with CAH are scanty (16,17,18). Salt-wasting patients with CAH are reported to have learning difficulties more frequently than simple virilizing counterparts (17,18), although a study with contradictory results does exist (16).

46,XX females with CAH have lower verbal and performance IQ values than healthy controls. In addition, salt-wasting patients have lower total and verbal IQ values than simple virilizing females (19). Attention deficit and hyperactivity disorder is reported to be more frequent in patients with CAH than in healthy controls (20). The frequencies of psychiatric problems and substance abuse are higher than the general population in 46,XX females with CAH (21).

Fertility

In 46,XX female patients with CAH, fertility is reduced and this reduction is more pronounced in salt-wasting forms of CAH. The reasons for reduced fertility in these patients may be: delayed psychosexual development; decreased sexual activity; reluctance for marriage; negative impact of alterations in stature on sexual functions; menstrual irregularity and anovulation; polycystic ovary syndrome; disturbance in the clitoral neural network; morphological changes owing to genital surgery; and vaginal stenosis (1). When patients with classical CAH and those with non-classical CAH were compared with healthy controls in terms of sexual dysfunction and associated anxiety, patients in the latter group were found to be more disadvantaged than the others, which is most likely due to delayed diagnosis in non-classical CAH patients (22). In 46,XX female patients with CAH, the fear of stigmatization was reported to have an adverse impact on romantic relationships (23).

In 46,XX female patients with CAH, a relative reduction in offspring number was reported. However, successful spontaneous pregnancies occur following corrective surgery in severely virilized patients with CAH (24).

In patients with late onset CAH, hyperandrogenism and related menstrual problems are more frequent than healthy

controls, and the total number of pregnancies and birth rates are lower (25).

46,XY male patients with classical CAH are reported to have reduced fertility, and this is associated with the presence of testicular adrenal rest tumors (TARTs) (26). These benign tumors compress the seminiferous tubules leading to testicular atrophy and reduction in sperm counts. Increased adrenal androgens may also lead to infertility via suppression of the hypothalamo-hypophyseal-gonadal axis (27).

In conclusion, patients with CAH should be regularly followed in a multi-disciplinary center with state-of-the art care in endocrinology, psychological assessments and surgery. Sexuality in CAH should be assessed considering the karyotype of the patient and gender of rearing. The frequencies of disturbances in psychosocial and cognitive areas in patients with CAH are higher than those in the normal population, and these disturbances are related to excess prenatal androgen overload, the karyotype of the patient and supraphysiological glucocorticoid treatment in the postnatal period. There is a call for consensus in psychosocial evaluation of patients with CAH.

Good practice points:

1. In patients with CAH due to 21-hydroxylase deficiency, sexuality should be evaluated in accordance with the peripheral blood karyotype and gender of rearing (2⊕⊕OO).

2. The frequencies of psychosocial and cognitive disturbances in patients with CAH are higher than those in healthy controls owing to prenatal androgen excess, postnatal supraphysiological glucocorticoid treatment and the karyotype of the patient (2⊕⊕OO).

3. Fertility is reduced in patients with CAH, and it is associated with the disease phenotype (2⊕⊕OO).

Quality of Life in Patients with Classical Congenital Adrenal Hyperplasia

Quality of life is defined as an individual's perception of his/her position in life in relation to his/her goals, expectations, standards, and concerns in the context of the culture and value systems in which he/she lives. It is a broad concept that is affected in a complex fashion by a person's physical health, psychological state, level of independence, social relationships, and relationships with salient features of his/her environment (28). Health-related quality of life refers to "the patient's sense of health and well-being in broad areas of physical, psychological, and social functioning" (28). In recent years, advances in medical treatment of chronic diseases leading to increased survival rates have shifted the focus to quality of life of affected patients (29).

In patients with classical CAH, problems that become prominent in different age groups can affect the quality of life of patients (30,31,32). These start from the moment of diagnosis, and include factors such as the need for lifelong treatment, treatment compliance, operations performed due to ambiguous genitalia and their outcomes, complications related to the disease or treatment (short stature, obesity, osteoporosis, TARTs), problems related to sexual life, and fertility concerns. While many studies investigating quality of life in adults with CAH, particularly women, have focused on exploring the impact of high androgen exposure during brain development, only a few studies have been conducted to examine quality of life in children with CAH (20,33,34,35). Since there is no health-related quality of life scale specifically designed and validated for children with CAH, validated health-related quality of life scales that assess pediatric chronic diseases have been used (36,37,38).

Numerous studies have shown that health-related quality of life may be adversely affected in children with CAH compared to the general population (30,33,39). It has been reported that there is a general decrease in quality of life in children and adolescents with CAH, with psychological and social domains showing lower scores than physical and environmental domains (39,40). Similar studies have reported increased rates of psychiatric symptoms in children and adolescents with CAH (21,33,41,44).

Children with CAH have impaired physical, emotional, social, and school functioning compared to the general pediatric population (33). Parents of children with CAH perceive their children as more vulnerable than their peers. Considering the specific areas of parent reports, lower scores were found in the emotional domain (consisting of questions covering feelings of fear, sadness, anger, and fear about the future) and the school domain (absenteeism problems and keeping up with school work) (33). However, in a study from the Netherlands, although the disease had a slightly negative impact on the physical, social, and community functioning of children with CAH, their quality of life did not decrease. These children experienced several daily health-related problems that did not interfere with their daily activities and participation in society (34).

Older children and adolescents have lower quality of life scores in psychological and social domains, in addition to lower total scores (39). Adolescent patients are more concerned about their health, more fearful of lifelong complications of their chronic diseases, and more uncomfortable with long-term medications. Meanwhile,

since it may be related to high ACTH exposure, cases with higher Prader scores and higher virilization reported lower scores in the physical domain and total scores (39).

Recent studies have demonstrated a decrease in quality of life in CAH patients, who tend to be single and less sexually active, exhibit less self-confidence, are less sociable and feel less social acceptance, and have a negative body image (45,46).

Considering the difference between sexes, the quality of life in females with CAH is lower than in males. Operations due to ambiguous genitalia and their outcomes, body structure, difficulties in sexual life, fertility problems, and psychosocial problems are more common in females and adversely affect the quality of life (21,39,40,43). However, there are also studies reporting no difference between sexes in terms of health-related quality of life (32,33).

Women who underwent clitoroplasty scored higher in the psychological domain than those who did not have surgery. After feminizing genitoplasty, women were shown to have a better quality of life and mental health since they have fewer distressing symptoms (39). Furthermore, there may be poor quality of life and psychiatric symptoms due to too late genital intervention, poor surgical outcomes, or distressing memories (19,47). There is a correlation between the timing of surgery and quality of life. Whereas patients who undergo clitoroplasty at an older age have lower quality of life scores in the psychological domain, it has been shown that early surgery and early creation of an external genital appearance appropriate to the genetic sex contribute to reducing the anxiety of parents and children and lead to better psychosocial adjustment (48,49). However, in contrast to these studies, some studies do not show a correlation between behavioral outcomes or psychological adjustment and age at genitoplasty in women with CAH. It has been reported that genital surgery in childhood frequently leads to feelings of loss of body ownership and resentment (50,51). In general, the current evidence supports early feminizing genitoplasty (39).

Studies have shown that childhood adrenal crisis has a significant impact on health-related quality of life (30,52). Patients who are compliant with treatment receive higher scores in social and environmental domains and total scores than those who are non-compliant. Easy access to medical services and regular follow-ups are known to lead to better health-related quality of life. Furthermore, regular follow-ups and good compliance with treatment lead to fewer complications, better CAH control, and, therefore, higher quality of life (39). On the contrary, it has been reported that CAH patients who develop chronic diseases, such as hypertension, score lower in physical and social relationships and environmental domains (42). Of note, health-related quality of life scores of patients with salt-wasting CAH were found to be lower than those with simple virilizing types (20,32,39).

No correlation was found between quality of life and hydrocortisone dose (33,39). Moreover, patients receiving high doses of mineralocorticoids have lower quality of life scores in the psychological domain. It was shown that patients with high serum Δ4 androstenedione levels score lower in psychological and social domains. No significant relationship was detected between serum 17-hydroxyprogesterone and testosterone levels and quality of life, except for the physical domain (39,44,50).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (53).

Good practice points:

1. CAH patients and their families should be supported in terms of the physical and psychosocial problems they experience in childhood and adolescence before patients reach adulthood (1⊕⊕⊕O).

2. The currently available evidence suggests early feminizing genitoplasty to improve quality of life (2⊕⊕OO).

3. Good compliance with treatment is a factor that increases the quality of life, and cases should be followed up closely and regularly (ungraded good practice point).

Footnotes

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Authorship Contributions

Concept: Ahmet Uçar, Eda Mengen, Zehra Aycan, Design: Ahmet Uçar, Eda Mengen, Zehra Aycan, Data Collection or Processing: Ahmet Uçar, Eda Mengen, Zehra Aycan, Analysis or Interpretation: Ahmet Uçar, Eda Mengen, Zehra Aycan, Literature Search: Ahmet Uçar, Eda Mengen, Zehra Aycan, Writing: Ahmet Uçar, Eda Mengen, Zehra Aycan.

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Long-term Complications and Testicular Adrenal Rest Tumors in Congenital Adrenal Hyperplasia

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Abstract

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency accounts for approximately 95% of all CAH cases and is one of the most common inborn errors of metabolism. While glucocorticoid therapy has significantly improved patient outcomes, the focus has shifted towards managing the long-term effects. Numerous adverse outcomes have been associated with CAH, including those resulting from supraphysiological doses of glucocorticoid and mineralocorticoid replacement, excessive adrenal androgen secretion, and elevated levels of steroid precursors and adrenocorticotropic hormone. Despite advances in treatment, long-term complications persist due to the inability to replicate physiological hormone secretion fully. In this review, we explore critical aspects of managing CAH, focusing on cardiometabolic health, bone integrity, fertility, and other significant long-term consequences, informed by the latest literature.
Keywords: Congenital adrenal hyperplasia, complications, long term, outcome

Introduction

The management of congenital adrenal hyperplasia (CAH) during the transition from childhood to adulthood requires careful consideration. Key objectives include achieving normal growth and puberty, minimizing virilization, preparing for fertility, and preventing metabolic complications, all important for improving quality of life in adulthood (1). Early diagnosis and treatment are essential for preventing morbidity and mortality. The primary goal of treatment is to ensure adequate glucocorticoid and mineralocorticoid replacement while effectively controlling androgen excess. In clinical practice, glucocorticoid doses are often administered supra-physiologically or sub-physiologically to suppress androgen excess. However, excessive glucocorticoid and mineralocorticoid therapy may lead to adverse outcomes, such as short stature, osteoporosis, obesity, and increased cardiovascular risk. Conversely, inadequate glucocorticoid treatment or poor compliance can result in androgen excess, leading to infertility and the development of adrenal rest tumors (2,3). One significant complication in male patients with CAH is the development of testicular adrenal rest tumors (TART), which are the leading cause of infertility in these individuals. The prevalence of TART varies, but averages around 40%. However, rates as high as 94% have been reported in adults depending on detection methods, patient age, and disease severity (4,5).

Since TART can lead to infertility in adulthood, early diagnosis and adequate treatment during childhood are important. The preservation of gonadal function is directly related to tumor size, as an increase in tumor diameter over time may compromise gonadal function and fertility. TARTs smaller than 2 cm are challenging to detect by physical examination, making early imaging and differential diagnosis from Leydig cell tumors important considerations.

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Histopathologically, TART can be classified into five stages, with stage 5 representing irreversible damage characterized by hyalinization, loss of testicular parenchyma, and obstructive azoospermia, ultimately resulting in infertility (6).

The etiopathogenesis of TART has not been fully elucidated. Recent studies have explored the genotype-phenotype correlation, indicating a higher prevalence of TART, particularly in salt-wasting forms of CAH (7).

This evidence-based review, which includes good practice points, was developed by the Adrenal Working Group of the Turkish Society for Pediatric Endocrinology and Diabetes. We developed this evidence-based review for the management of long-term complications, including TARTs in children and adolescents with CAH.

Final Height

Patients with CAH often fail to reach their target height. Factors determining the final height at the time of diagnosis include chronological age, bone age, the adequacy of treatment, and the degree of hormonal control. Inadequate treatment can result in androgen excess and early epiphyseal closure. In addition, high-dose steroid use, especially in infants and during puberty, can suppress growth and impact final height (8,9,10). In a cohort study of 104 subjects divided into three age groups: early childhood (0-5 years), middle childhood (5-10 years), and adolescence (10-15 years), every 1 mg/m^2/day increase in hydrocortisone dose was associated with a 0.37 cm decrease in predicted height. In this study, hydrocortisone doses ranged from 9.4 mg/m^2/day to 39.2 mg/m^2/day and this effect was observed in cases receiving hydrocortisone doses above the lowest dose of 9.4 mg/m^2/day (11). A meta-analysis evaluating 35 studies on final height found that patients receiving mineralocorticoid treatment had better final height than those who did not. However, it was highlighted that this difference could be due to patients with a diagnosis of simple virilizing CAH receiving a delayed diagnosis compared to those with a salt-wasting CAH diagnosis. Furthermore, recent improvements in patient care, better nutrition or general health care, and changes in treatment dosage and preparation have been suggested as effective factors in improving patients' height (12). Bone age is commonly used as a clinical marker for metabolic control in CAH, and accelerated bone age indicates inadequate glucocorticoid treatment (13). It is recommended that annual bone age in cases under the age of two years be assessed until they reach adult height (14,15).

Obesity, Metabolic Issues, and Cardiovascular Risks

Cardiovascular outcomes related to steroid treatment in CAH patients are uncertain. CAH patients have been observed to exhibit increased systolic blood pressure, diastolic blood pressure, insulin resistance, and carotid intima thickness compared to the normal population. However, no differences have been found in fasting blood glucose and lipids. Cardiometabolic risk factors are associated with an increased risk of future cardiac problems. Factors contributing to this include high-dose glucocorticoid and mineralocorticoid treatment and uncontrolled androgen excess. Children and adolescents with CAH tend to have increased fat accumulation, which is also a contributing factor to obesity. The primary factor leading to obesity is the use of supra-physiological doses of glucocorticoids (16). The key factors in reducing these risks include the administration of glucocorticoids close to physiological doses and using the lowest necessary mineralocorticoid doses (15,16,17). Maintaining a healthy body weight and body mass index associated with normal blood pressure is key. However, CAH patients with accompanying hypertension from the time of diagnosis and those who develop obesity during follow-up may need to be evaluated for these comorbidities earlier than recommended by standard guidelines.

Bone Health

Gonadal and adrenal androgens stimulate the proliferation and differentiation of osteoblasts in both genders. Dehydroepiandrosterone sulfate (DHEAS) affects bone by binding to the androgen receptor and stimulating osteoblast growth and differentiation. DHEAS and other adrenal androgens particularly impact bone metabolism during adrenarche and throughout life. In children with classical CAH, there is no physiological increase in DHEAS (18). Glucocorticoids, which are the most important drugs causing secondary osteoporosis, lead to decreased bone mineral density (BMD) in CAH patients receiving lifelong glucocorticoid replacement therapy (19). Glucocorticoid treatment affects BMD through multiple mechanisms that result in increased bone resorption and reduced bone formation, leading to decreased BMD. It also causes secondary hyperparathyroidism by reducing intestinal calcium absorption and increasing renal calcium excretion (20). A lack of physiological increase in DHEAS at puberty, coupled with high-dose glucocorticoid treatment, represents a significant contributing factor to the observed decline in BMD. There are publications reporting that long-term glucocorticoid replacement therapy in CAH patients results in normal BMD (21). In adulthood, it is noted that low-dose glucocorticoid treatment is associated with normal BMD, and prednisolone treatment leads to greater BMD reduction compared to hydrocortisone treatment (22). During the

transition to adulthood, baseline BMD measurement can be conducted. To maintain good bone health, weight-bearing exercises should be combined with age-appropriate vitamin D and calcium intake (14).

Good practice points:

1. In the follow-up of patients, it is appropriate to carefully evaluate the growth rate and adjust the treatment dose. In terms of final height, it is appropriate to evaluate the growth rate, metabolic control and bone age (1⊕⊕OO).

2. Patients with CAH should be provided with standard lifestyle advice (ungraded good practice steatment).

3. Routine screening for cardiac and metabolic diseases is not recommended (ungraded good practice steatment).

4. CAH patients should be monitored for the development of metabolic and cardiac diseases according to standard guidelines applied to the general population (1⊕⊕OO).

5. There is no data to provide recommendations regarding bone health in childhood for individuals with CAH, and routine screening of BMD is not recommended in adults. However, assessment of BMD is appropriate for adults who have been exposed to above-average glucocorticoid doses for an extended period or have experienced non-traumatic fractures (2⊕OOO).

Testicular Adrenal Rest Tumors

Diagnosis

Ultrasonography (USG) is the preferred method for diagnosing and monitoring TARTs, as it can detect nodules as small as <2 mm. Annual testicular ultrasound is recommended from early childhood due to its accessibility, non-invasive nature, and the potential for TART to affect young children, particularly in those with poorly controlled CAH. This approach is supported by evidence of disease progression without obvious clinical symptoms.

One study reported a TART prevalence of 18.3% in patients with 21-hydroxylase deficiency aged 2-18 years, making it one of the few studies to provide long-term follow-up data. Notably, the youngest case reported in the literature was a 2-year-old patient. The frequency of TART increases with age, becoming more common during and after puberty (4,23,24). In addition, magnetic resonance imaging has not demonstrated any significant advantages over ultrasound for detecting or monitoring TART.

The Relationship Between TART and Specific CAH Phenotypes/Genotypes

The association between TART and specific CAH phenotypes/genotypes has not been definitively established. There may be a bias towards diagnosing TART in patients with salt-wasting CAH, as these individuals face greater health risks and are more challenging to manage in terms of hormonal balance. On the other hand, patients with simple virilizing CAH are often diagnosed later, and treatment may be less stable, particularly in low- and middle-income countries.

In our published series, approximately 83% of the 40 TART cases in patients with 21-hydroxylase deficiency were of the salt-wasting type. The *CYP21A2* variants detected in this cohort primarily belonged to groups 0 and A (variants in CYP21A2 are classified into four groups: Group 0, A, B, and C, based on residual 21-hydroxylase activity. Group 0 and Group A are associated with the salt-wasting form. Group 0 (null variants) exhibit 0% enzyme activity, while Group A variants have minimal residual activity (<1%). Group B variants retain approximately 2% residual enzyme activity, and Group C variants have 20-50% residual activity (37) with the mutations c.293-13C>G and c.955C>T (p.Gln319Ter) being the most common (7,17). In addition, in cases of TART associated with 11β-hydroxylase deficiency, the most frequently detected variant was c.896T>C (p.Leu299Pro). The fact that TART is reported more frequently in the classical forms of CAH compared to non-classical forms supports this observation. However, it is important to note that TART does not develop in all poorly controlled patients (7,25,26).

Treatment

The presence of high concentrations of adrenocorticotropic hormone (ACTH) receptors in TART tissues stimulates tumor growth, making ACTH suppression crucial in preventing the development of TART. Currently, no definitive and effective treatment exists for TART, and future research should focus on identifying potential drug targets. There are no clear guidelines for the treatment or prevention of TART, and current treatment strategies primarily focus on restoring fertility in adult patients. However, there are no prospective studies investigating the effect of intensified glucocorticoid therapy on TART, and high doses are associated with adverse effects, including hypertension, striae, weight gain, and impaired final height (27).

Testicular adrenal hyperplasia or small tumors have been shown to respond better to high-dose glucocorticoid therapy, leading to a reduction or disappearance of the tumor when monitored regularly by USG or Doppler scans

(25). Treatment modulation in well-managed patients may not be straightforward, as TART resolution typically requires higher steroid doses, which have implications for growth and other side effects. In cases where patients are non-compliant, on sub-therapeutic doses, or inconsistently taking prescribed hormones, resuming proper therapy has often been sufficient.

Mitotane has been used to restore fertility in adult patients with TART. However, it leads to irreversible chemical adrenalectomy and is recommended only as a last-resort treatment for fertility (28). Follicle stimulating hormone (FSH) and human chorionic gonadotropin have been administered to CAH patients with TART and hypogonadotropic hypogonadism, resulting in the restoration of testicular testosterone production and fertility. Successful testicle-sparing surgeries have been reported in small cohorts of CAH patients with TART, but gonadal function did not significantly improve after surgery. TART can cause pain due to compression of the testicular parenchyma, though malignancy has not been reported in any cases. Since TART lacks malignancy markers, such as high mitotic rates or atypical mitoses, surgery is only indicated for severe pain, as it does not improve fertility (29).

Treatment Follow-up

Poor hormonal control has been reported in approximately 58 % of TART patients (30,31,32,33). However, not all studies indicate a direct relationship between poor control and the development of TART. TART has also been reported in well-controlled CAH cases. ACTH, 17-hydroxyprogesterone, and androstenedione can be used as indicators of poor hormonal control and are thought to contribute to the development of TART (27,28,29). The presence of TART in rare cases of non-classical CAH suggests that poor control is not the only factor involved in its etiopathogenesis. Patients with the severe salt-wasting form of CAH are likely at higher risk of TART formation due to prolonged exposure to elevated ACTH concentrations (33).

This also highlights the relationship between specific variants and TART development. In Turkey, *CYP21A2* mutations c.293-13C > G and c.955C > T (p.Gln319Ter), and the *CYP11B1* mutation c.896T > C (p.Leu299Pro), have been associated with a predisposition to TART (7). Patients with these mutations require more careful monitoring.

Gonadal Function-fertility

There is no definitive predictive parameter for identifying which patients will develop TART, but it remains a significant cause of infertility in male CAH patients. Gonadal dysfunction and infertility, often becoming apparent during puberty, are adverse outcomes associated with TART. In men, gonadal dysfunction can stem from primary gonadal failure caused by TART or secondary gonadal failure due to hypothalamic suppression as a result of poor hormonal control.

Studies have shown a positive correlation between total functional testicular volume and sperm parameters, as well as inhibin B levels. Recent findings indicate that semen quality in men with CAH is highly compromised, with 100 % of cases considered pathological according to World Health Organization criteria (34). Given the risk of irreversible testicular damage with the development of TART, sperm cryopreservation is recommended. Guidelines suggest that sperm storage should be considered before TARTs enlarge significantly (33). There is evidence linking elevated FSH and low luteinizing hormone (LH) levels to oligospermia (25). In some cases, successful conception has been reported following sperm preservation during TART surgery in azospermic azoospermic patients (31,35,36).

Further research is needed to determine whether specific variants in *CYP21A2*, *CYP11B1*, or other regulatory genes contribute to TART development and infertility risk, independent of poor hormonal control. Understanding the genetic basis of TART and its association with infertility may help identify new treatment strategies.

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (37).

Good practice points:

1. In the pediatric population, TART screening with testicular USG every two years starting from the age of 8 years and annually during the peripubertal period would be appropriate (2⊕⊕OO).

2. The incidence of TART is higher in CAH patients with salt-wasting phenotypes; therefore, close monitoring of these cases is appropriate (ungraded good practice steatment).

3. Since ACTH plays a role in TART development, lowering ACTH may prevent TART formation in CAH patients, and treatment should focus on this goal (2⊕⊕OO).

4. It is appropriate to closely monitor CAH patients with poor hormonal control with a specific hormone profile, such as ACTH, 17-hydroxyprogesterone and androstenedione (2⊕OOO).

5. Spermiogram and sperm cryopreservation should be considered in TART patients due to the high risk of infertility (2⊕OOO).

6. Annual evaluation of gonadal function is advised by measuring LH, FSH, testosterone, and inhibin B levels as appropriate (ungraded good practice steatment).

Footnotes

Authorship Contributions

Surgical and Medical Practices: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan, Concept: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan, Design: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan, Data Collection or Processing: Aylin Kılınç Uğurlu, Elif Özsu, Analysis or Interpretation: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan, Literature Search: Aylin Kılınç Uğurlu, Elif Özsu, Writing: Aylin Kılınç Uğurlu, Elif Özsu, Zehra Aycan.

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The Causes and Diagnosis of Non-congenital Adrenal Hyperplasia Primary Adrenal Insufficiency in Children

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Abstract

Primary adrenal insufficiency (PAI) is a critical condition that requires prompt diagnosis and initiation of treatment. Diagnosis can be challenging due to various underlying causes, including defects in adrenal gland development, resistance to adrenocorticotropic hormone, autoimmune causes, and metabolic problems. A specific diagnosis is essential for developing a treatment plan and identifying other possible accompanying pathologies. Biochemical studies, genetic analyses, and imaging techniques are helpful in establishing a specific diagnosis. This evidence-based guideline includes the specific diagnoses that cause PAI and their clinical and genetic features. It also provides evidence-based steps to follow when making a diagnosis.

Keywords: Primary adrenal insufficiency, diagnosis, children, adolescent

Introduction

Primary adrenal insufficiency (PAI) is a rare but life-threatening condition that requires urgent diagnosis and treatment. It is characterized by inappropriate synthesis of glucocorticoids and/or mineralocorticoids and/or adrenal androgens (1). Unlike adults, congenital causes due to genetic disorders are predominant in the etiology of childhood PAI (2,3). Although most of these diseases start in the neonatal period and infancy, the diagnosis of mild or non-classical forms can occur at later ages or in adulthood (4). The most common cause of PAI is congenital adrenal hyperplasia (CAH) (5,6). Non-CAH, as a sub-group of PAIs, can be categorized into four groups: i) defects in adrenal gland development; ii) resistance to adrenocorticotropic hormone (ACTH) and similar conditions; iii) autoimmune causes; and iv) metabolic causes.

In childhood, PAI may rarely develop due to physical conditions, such as adrenal hemorrhage, infiltration (e.g., neuroblastoma), and some viral (e.g., Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus) and bacterial infections (e.g., tuberculosis) (5,7,8). In addition, medications that disrupt cortisol synthesis, such as ketoconazole, aminoglutethimide, and etomidate, and medications that accelerate glucocorticoid metabolism, such as phenytoin, phenobarbital, and rifampicin, are involved in the etiology of PAI (9).

This evidence-based review with good practice points was developed by the Adrenal Working Subgroup of the Turkish Society for Pediatric Endocrinology and Diabetes. We developed this evidence-based review for "The Causes and Diagnosis of Non-CAH Primary Adrenal Insufficiency in Children".

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Clinical Findings and Etiological Clues

Clinical signs of cortisol deficiency include fatigue, weakness, weight loss, arthralgia, orthostatic hypotension, hyponatremia, hypoglycemia, hypercalcemia, direct hyperbilirubinemia, lymphocytosis, and eosinophilia (6). Clinical signs of mineralocorticoid deficiency include growth retardation, nausea, vomiting, abdominal pain, dizziness, hypotension, dehydration, and hypovolemic shock (8). Neonates have the highest predisposition to present with mineralocorticoid deficiency (10). Typically, aldosterone production in newborns is higher than in childhood (11). This may be due to the relative mineralocorticoid resistance in the kidneys during the neonatal period, unpredictable fluid intake, and/or low sodium content of the breast milk (12). Related to aldosterone deficiency, hyponatremia, and hyperkalemia can be biochemically detected within the first two weeks of life (4). Mineralocorticoid deficiency is always associated with adrenocortical dysfunction (6).

Patients with PAI may present with adrenal crisis, causing signs of acute cardiovascular decompensation, such as hypotension, tachycardia, and shock (1). In contrast, chronic PAI may present with non-specific symptoms, such as malaise, fatigue, weakness, anorexia, and weight loss. Absence or delayed adrenarche suggests a deficiency of adrenal sex steroids (13). Hyperpigmentation (on the skin, areola, genitalia, axillae, nail beds, joints, and scars) does not occur in secondary adrenal insufficiency but is present in 90 % of patients with PAI. However, it may not be detected in infancy until the sixth week or in the first episode of the disease (9).

The age at onset of adrenal insufficiency is an important clue in the diagnosis (4). A family history of similar cases is instructive, and a history of sudden death or death secondary to gastroenteritis or infection suggests potential missed cases. The presence of comorbid findings, such as intrauterine growth retardation, steroid-resistant nephrotic syndrome, hypogonadotropic hypogonadism, and enteropathy, and detailed examination of history and physical examination are essential in providing guidance to the specific diagnosis (Table 1) (6,9).

Making a specific diagnosis of PAI is essential in determining the need for mineralocorticoid use and diagnosing and monitoring other related non-adrenal pathologies (4,6). Sanger sequencing or targeted next-generation sequencing techniques can help with a genetic diagnosis if a specific cause is suspected. In cases where the alleged mutation cannot be detected, next-generation sequencing and panel, whole exome analysis, or whole genome analysis are used as further investigations (14). Reaching a specific genetic diagnosis is also important for providing genetic counseling for families (5,15,16).

Adrenal imaging modalities that can be used as an aid in the diagnosis of PAI include ultrasound, radiography, magnetic resonance imaging, and computed tomography. They have limited indications for diagnostic use in childhood. In CAH and congenital lipoid adrenal hyperplasia, the adrenal glands are usually large but may be normal on adrenal imaging. In Cytochrome P450scc deficiency, adrenal glands may be small. In diagnosing PAI, they help to investigate etiological causes, such as hemorrhage, tuberculosis, and tumor infiltration. Calcifications are present in adrenal glands in Wolman's disease, tuberculosis, and sphingosine-1-phosphate lyase (SGPL1) deficiency. (17,18).

The clinical conditions associated with PAI and adrenal crisis have been adequately defined following previous studies and clinical experience (Table 1). Since the clinical presentation of chronic adrenal insufficiency in childhood may be insidious, there may be a delay in diagnosis. However, delayed diagnosis leads to high mortality, especially in case of adrenal crisis. Therefore, the indication for testing for adrenal insufficiency should be at an optimum level, avoiding delays in testing (1,19).

Good practice point:

1. Patients with clinical findings compatible with glucocorticoid or mineralocorticoid deficiency should be investigated for adrenal insufficiency. Blood samples should be reserved for biochemical tests, and waiting for test results should not delay treatment (1⊕⊕⊕O).

Diagnostic Tests for Primary Adrenal Insufficiency

Serum and salivary cortisol: The most accessible assessment to confirm the diagnosis of PAI is low basal cortisol levels compared to high ACTH levels. ACTH levels above 300 pg/mL are sufficient for maximal cortisol response (1,20). However, the kit and reference ranges should be taken into consideration. Failure to reach adequate levels of cortisol synthesis despite elevated ACTH indicates that the adrenal cortex cannot adequately respond to ACTH stimulation and provides strong evidence for PAI.

In early PAI cases, adequate cortisol response to elevated ACTH may be found, and elevated ACTH may be the first

Table 1. Hereditary causes of primary adrenal insufficiency (non-CAH)

Disease	Gene	Associated clinical features
Developmental adrenal gland disorders		
X-linked congenital adrenal hypoplasia (DAX-1)	*NR0B1*	Hypogonadotropic hypogonadism, gonadotropin independent precocious puberty
Adrenal hypoplasia associated with steroidogenic factor-1 defect	*NR5A1*	46, XY DSD and 46, XX DSD, primary ovarian failure, disorders of spermatogenesis
IMAGe syndrome	*CDKNC1*	IUGR, metaphyseal dysplasia, genital anomalies
IMAGEI syndrome	*POLE1*	IUGR, skeletal deformities, immune deficiency, developmental hip dysplasia, atypical facial appearance
Pallister-Hall syndrome	*GLI3*	Hypothalamic hamartoma, hypopituitarism, polydactyly, imperforate anus, bifid epiglottis
MIRAGE syndrome	*SAM9D*	Myelodysplasia, growth retardation, infections, enteropathy, genital anomalies
SeRKAL syndrome	*WNT4*	46, XY DSD, renal dysgenesis, pulmonary hypoplasia
Pena-Shokeir syndrome	*DOK7* *RAPSN*	Fetal akinesia, IUGR, arthrogryposis, facial anomalies, pulmonary hypoplasia, intestinal malrotations, cystic hygroma, cleft palate, cryptorchidism
Meckel-Gruber syndrome	*MKS1*	Cystic renal disease, CNS malformation, polydactyly, hepatic abnormalities
Galloway-Mowat syndrome	*WDR73*	Early onset severe encephalopathy, epilepsy, microcephaly, optic atrophy, hiatal hernia, nephrotic syndrome
Hydrolethalus syndrome	*HYLS1*	Hydrocephalus, absent midline structure of the CNS, micrognathia, polydactyly, pulmonary defects
Resistance to the effect of ACTH and similar disorders		
Familial glucocorticoid deficiency type 1	*MC2R*	Mostly normal MC activity, tall stature, subclinical hypothyroidism, characteristic facial appearance (hypertelorism, medial epicanthus, frontal bossing)
Familial glucocorticoid deficiency type 2	*MRAP*	Normal MC activity
AAA-Triple A syndrome	*AAAS*	Alacrima, achalasia, mental retardation, deafness, hyperkeratosis, autonomic nervous system disorders
DNA repairing defects	*MCM4*	Natural killer cell defects, short stature, microcephaly, recurrent viral infections, chromosomal breaks
Bioinactive ACTH	*POMC*	Symptoms of POMC deficiency accompanied by high ACTH levels
Mitochondrial ROS detoxification defects		
Nicotinamide nucleotide transhydrogenase deficiency	*NNT*	Isolated GC deficiency, subclinical hypothyroidism, insulin-dependent type 1 DM, precocious puberty
Thioredoxin reductase deficiency	*TXNRD2*	Isolated GC deficiency, cardiac defects
Glutathione peroxidase deficiency	*GPX1*	Isolated GC deficiency
Peroxiredoxin deficiency	*PRDX3*	Isolated GC deficiency
Autoimmunity		
Isolated autoimmune adrenalitis	*CLTA-4* *HLA-DR3* *HLA-DR4*	
APS (autoimmune polyglandular syndrome) type 1 (APECED)	*AIRE*	Chronic mucocutaneous candidiasis, hypoparathyroidism, and other autoimmune diseases (autoimmune thyroid diseases, type 1 DM, pernicious anemia, alopecia, vitiligo, hypergonadotropic hypogonadism, hypophysitis)
APS type 2	*CLTA-4* *HLA-DR3* *HLA-DR4*	Autoimmune thyroid disease, type 1 DM, premature ovarian failure, vitiligo, and pernicious anemia
APS type 4	*CLTA-4* *HLA-DR3* *HLA-DR4*	One or more autoimmune diseases (atrophic gastritis, pernicious anemia, celiac disease, myasthenia gravis, hypophysitis, alopecia, vitiligo, hypogonadism)

Table 1. Continued

Disease	Gene	Associated clinical features
Metabolic causes		
Disorders of cholesterol synthesis/metabolism		
Smith-Lemni Opitz syndrome	*DHCR7*	IUBG, mental retardation, microcephaly, atypical facial appearance, polydactyly, urogenital anomalies, syndactyly between 2nd and 3rd toes
Abetalipoproteinemia	*MTP*	Ataxia, retinopathy, acanthocytes in peripheral smear, fat malabsorption
Familial hypercholesterolemia	*LDLR*	Xanthomas, coronary artery disease, corneal arcus
Wolman disease	*LIPA*	Subcapsular punctate calcifications in the adrenal glands, growth retardation, malnutrition secondary to malabsorption, xanthomatous changes in the hematopoietic system and intestines, lungs, brain
Peroxisomal diseases		
X-linked adrenoleukodystrophy	*ABCD1*	Progressive neurodegeneration, cognitive and behavioral changes, progressive hearing and vision loss, dementia, spasticity, seizures
Zellweger spectrum disorders	*PEX*	Hypotonia, seizures, encephalopathy, hepatic failure
Endoplasmic reticulum defects		
Sphingosine-1-phosphate lyase 1 deficiency	*SGPL1*	Steroid-resistant nephrotic syndrome, ichthyosis, neurological disorders, hypothyroidism, undescended testis
Mitochondrial diseases		
Kearns Sayre syndrome	MtDNA deletions, *MTTL1*	Progressive external ophthalmoplegia, ptosis, cardiac conduction defects
GFER-associated mitochondrial encephalopathy	*GFER*	Encephalomyelopathy, congenital cataract, hypotonia, hearing loss, lactic acidosis, respiratory failure
Mitochondrial DNA polymerase deficiency	*POLG*	Infantile epilepsy, metabolic strokes, chronic ataxia, neuropathy, ophthalmoplegia, type 1 DM, hypothyroidism
MELAS syndrome	Various mitochondrial genes	Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like attacks
Pearson syndrome	Various mitochondrial genes	Low birth weight, growth retardation, sideroblastic anemia, exocrine pancreatic dysfunction
Mitochondrial complex 1 deficiency	*NDUFAF5*	IUGR, agenesis of the corpus callosum, abnormal hair, congenital left diaphragmatic hernia, lactic acidosis
Impaired synthesis and action of aldosterone		
Aldosterone synthase deficiency	*CYP11B2*	Isolated mineralocorticoid deficiency
Mineralocorticoid resistance	*NR3C2*	Isolated mineralocorticoid deficiency

ROS: reactive oxygen species, ACTH: adrenocorticotropic hormone, POMC: proopiomelanocortin, DM: diabetes mellitus, IUGR: intrauterine growth retardation, CAH: congenital adrenal hyperplasia, GC: glucocorticoid, CNS: central nervous system, DSD: disorders of sex development

finding (1). In infancy, basal serum cortisol level may not be reliable due to variations in circadian rhythm, sleep patterns, intrauterine growth retardation, maternal stress level, and corticosteroid-binding globulin levels (4,21). Threshold cortisol values indicating adequate cortisol levels may vary depending on the laboratory device and method used (22). The diagnosis of adrenal insufficiency should be confirmed with dynamic tests in the presence of low morning serum cortisol levels and normal or low serum cortisol levels in times of stress.

Circadian rhythm may not develop until the age of three years. There is no definite consensus regarding the serum cortisol level sufficient to exclude the diagnosis of PAI. Still, a cortisol level above 17.3-20 mcg/dL is considered sufficient in children without stress (23,24). Recently, the ability to evaluate serum cortisol with methods including liquid chromatography/tandem mass spectrometry (LC-MS/MS) has become valuable in preventing drug, diet, and other steroid hormone interactions in immune methods. Another essential advantage of LC-MS/MS over immunoassays is the ability to evaluate multiple steroids in a single analysis, up to 15 or more in some methods, thus significantly expanding the identification of different forms and underlying causes of adrenal insufficiency (25).

A different method for assessing cortisol synthesis capacity is salivary cortisol. Since salivary cortisol is 10-50 times less abundant than serum cortisol levels, it should be evaluated with sensitive measurement methods. This method is less invasive because it does not require blood sampling. In contrast to serum cortisol, salivary cortisol assessed by LC-

MS/MS is not affected by changes in corticosteroid-binding globulin levels (26). Salivary cortisol levels during Synachen test measured by LC-MS/MS method have been shown to correlate with serum cortisol levels when the cut-off values are set at 18 mcg/dL for serum cortisol and 500 ng/dL for salivary cortisol, respectively, for adrenal sufficiency with 100% sensitivity and specificity (27) Although serum and salivary cortisol levels can be used for PAI assessment, exact cut-off values still need to be determined. However, the diagnosis based on serum and salivary cortisol levels is only valid in acute situations where it is not possible to wait for the Synacthen (cosyntropin or tetracosactide) test (1).

Synacthen (synthetic ACTH) tests: Tetracosactide or cosyntropin (Synacthen) is a synthetic peptide containing 39 amino acids with the same amino acid sequence as the N-terminal 24 amino acids of ACTH (28). In the high-dose Synacthen test, adrenal insufficiency is diagnosed by evaluating cortisol levels taken at 30 and 60 minutes following intravenous administration of the Synacthen. A peak cortisol level above 18-20 mcg/dL is considered as sufficient response (1,29). At the same time, a 2-3-fold increase in the cortisol level from basal cortisol or a rise of 7 mcg/dL at 30 or 60 minutes of the test is also considered a sufficient response (1,6,30). The one mcg Synacthen test is recommended for diagnosing PAI only in case of difficulty in accessing the 250 mcg Synacthen test (1).

Mineralocorticoid levels: Increased plasma renin concentration or plasma renin activity (PRA) and concomitant low aldosterone levels before deteriorating electrolyte levels are essential for mineralocorticoid deficiency (31). However, interpretation of the data obtained from these tests requires consideration of many variables, including sample storage and processing conditions, dietary salt intake, physical activity, sex steroids, and the patient's position (supine or prone position) at the time of sample collection (6). PRA measurement is based on the level of angiotensin 1 produced during the renin-catalyzed conversion of angiotensinogen to angiotensin 1. Therefore, PRA is affected by conditions that alter both renin and angiotensinogen levels.

Plasma angiotensinogen levels increase in pregnancy, glucocorticoid and estrogen exposure, and decrease in liver diseases (32). Renin is synthesized as prorenin, an inactive zymogen. To prevent the conversion of prorenin to renin during measurement, it is recommended to centrifuge and freeze the sample, especially in laboratories where the sample cannot be studied rapidly (33). In addition, if the sample is kept at a high temperature, renin will continue to form angiotensin 1 from angiotensinogen and cause angiotensin 1 level to be higher than normal in PRA measurement (32). Whether the patient is supine or standing at the time of sampling and the change in the amount of daily sodium consumption cause fluctuations in renin levels (34). Since PRA levels vary for these reasons, it is recommended to be measured twice a day while the patient takes 100-200 mEq of sodium daily for precise evaluation (34). The most objective way of the assessment is to have the first measurement in the morning after spending the night in the supine position and the second measurement after spending four hours standing (8).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (35).

Good practice points:

1. A diagnosis of PAI can be made if the cortisol level taken between 06:00-10:00 a.m. is below five mcg/dL and the ACTH value is above two times the normal value for the kit used (1⊕⊕⊕O).

2. The "gold standard" method for diagnosing PAI is the high-dose Synacthen test. It should be administered at 250 mcg in patients over two years of age, 125 mcg in patients under two years of age, and 15 mcg/kg in infants. The test can be performed at any time of the day (2⊕⊕OO).

3. One mcg low-dose Synacthen test is recommended for diagnosing PAI only in case of difficulty in accessing the 250 mcg Synacthen test (2⊕⊕OO).

4. In patients with suspected PAI, plasma renin or PRA should be evaluated simultaneously for concomitant mineralocorticoid deficiency (1⊕⊕⊕O).

Footnotes

Authorship Contributions

Concept: Müge Atar, Leyla Akın, Design: Müge Atar, Leyla Akın, Literature Search: Müge Atar, Leyla Akın, Writing: Müge Atar, Leyla Akın.

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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

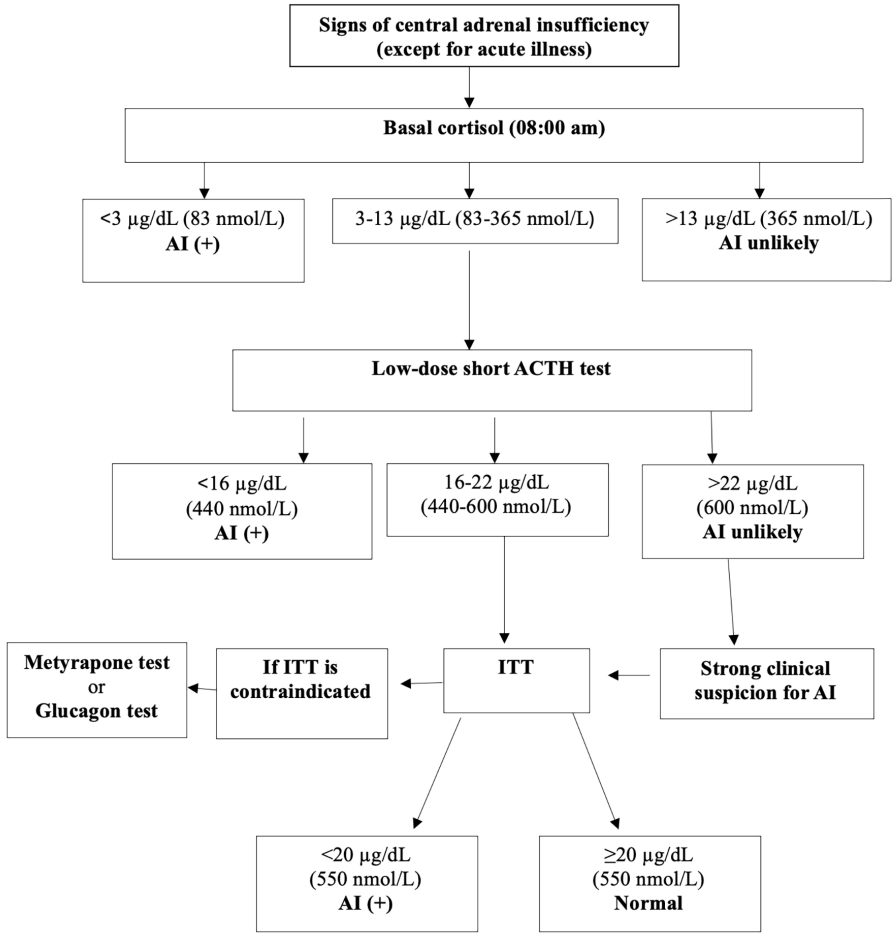

Figure 1. Diagnostic approach in patients with suspected central adrenal insufficiency (modified from references 15 and 19)

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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Treatment and Prevention of Adrenal Crisis and Family Education

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Abstract

Adrenal crisis is a life threatening complication of adrenal insufficiency (AI). Its treatment is urgent and parenteral hydrocortisone (HC) should be given at 10-15 times physiological doses in this situation. If HC is not available, alternatively prednisolone or methyl prednisolone may be used. In cases where peripheral venous access cannot be achieved quickly, intramuscular (IM) administration should be performed without delay. Fluid deficit, hypoglycemia, hyponatremia and hyperkalemia should be evaluated and corrected. Stressful conditions, such as physical stress, accidents, injuries, surgical interventions and anesthesia increase the need for cortisol and may lead the development of adrenal crisis. In order to prevent adrenal crisis, glucocorticoid dose should be increased according to the magnitude and severity of the stress situation as described in this review. Patients' and/or their families' education may improve the management of AI and reduce the frequency of adrenal crisis and/or mortality. They should be trained about conditions leading to adrenal crisis, how to increase the glucocorticoid dose in stress situations, recognizing signs of adrenal crisis and using IM HC if it is needed. All patients should be encouraged to carry a card/information sheet/medical alert bracelet or necklace indicating the diagnosis of AI and need for HC administration. It is useful for patients and parents to have an emergency glucocorticoid injection kit and to receive self-injection training.

Keywords: Adrenal crisis, treatment, prevention, stress, family education

Introduction

Adrenal crisis is the most frightening complication of adrenal insufficiency (AI). The annual incidence has been reported as 4.4-17/100 patient years, and 1/200 cases of adrenal crisis result in death every year (1). Acute adrenal crisis usually occurs when a child with undiagnosed chronic AI is exposed to additional stress. Various infections, especially respiratory infections in early childhood and gastrointestinal infections in older ages, play an accelerating role in the emergence of adrenal crisis (2,3). Furthermore, any condition that increases the need for cortisol, like physical stress, accidents, injuries, surgical interventions and anesthesia may lead the development of adrenal crisis (4).

There is no agreement upon the definition of adrenal crisis. It is considered to be acute clinical deterioration of a patient with AI (5). A definition of adrenal crisis in adults has been reported as the presence of at least two of the following symptoms or findings: hypotension, nausea/vomiting, severe weakness, hyponatremia, hypoglycaemia and hyperkalemia, as well as deterioration in general health and well-being. Adrenal crisis may be the first clinical presentation of undiagnosed AI. Signs and symptoms of AI and adrenal crisis are summarized in Table 1.

In individuals without AI, glucocorticoid release is increased in situations that stress the body (anesthesia, surgery, major trauma, febrile infections, sepsis, and so on) (3,6,7,8,9,10,11). Since endogenous glucocorticoid release cannot increase during stressful situations in individuals

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with AI, the glucocorticoid dose should be increased to the stress dose to prevent the onset of AI symptoms and adrenal crisis (3,12,13). Two case reports published in 1952 and 1953 reported that a patient on chronic steroid treatment died of cardiovascular collapse related to secondary AI after surgery, which was considered to be the first evidence of this (14). There are no randomised controlled trials investigating the dose of glucocorticoids that should be given in stressful situations that increase cortisol requirements in children with AI. As it is thought that unnecessarily high doses of glucocorticoids may cause side effects, such as hyperglycaemia, impaired wound healing, increased risk of infection, gastrointestinal ulcers, osteopenia, growth suppression and adipogenesis, it is important to determine the actual dose required in stressful situations (15,16). However, it is suggested that preventing the negative effects associated with insufficient steroid use is more important than the problems that may arise from short-term high dose steroid use (3).

The most important way to protect patients from life-threatening adrenal crisis is to ensure patient awareness through appropriate education (2,17). Education of children with AI and/or their families about the diagnosis and treatment, stressful situations, and how to increase the dose of steroids in stressful situations, may improve management of the disease and reduce the frequency of adrenal crisis. Training them to recognize symptoms of adrenal crisis and using intramuscular (IM) hydrocortisone (HC) if it is needed may reduce morbidity and mortality. It is important to repeat training periodically. When the patients with known AI are evaluated 6 months after a three-hour training session, it was found that they gave significantly more accurate answers to scenarios in which a possible adrenal crisis could develop (18). It is appropriate for patients/caregivers to have a written document or identification material (card, medical alert bracelet etc.) to be shown to the first consulted healthcare professional regarding what can be done in emergency situations.

Since AI and its complications are rare life-threatening conditions, it is important to ensure standardised approaches by physicians in its management. This evidence-based review with good practice points is developed by the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes'. We developed this evidence-based review for "Treatment and Prevention of Adrenal Crisis and Family Education" in children and adolescents with AI. The overall purpose of this evidence-based review is to provide good practice points, with focus on recommendations for daily management.

Treatment of Adrenal Crisis

Adrenal crisis may be the first sign of AI. Symptoms such as fatigue, weakness, tachycardia, hypotension, nausea, vomiting, abdominal pain and seizures generally respond very quickly to parenteral HC administration. If it is not recognized and treated quickly, coma and death may occur (19). For these reasons, adrenal crisis treatment should never be delayed for reasons such as waiting for test results. However, it is extremely important to take a blood sample for diagnostic tests, especially basal serum cortisol and ACTH levels, before treatment (3). Achieving clinical improvement after HC administration is considered as an essential diagnostic criterion (20).

Since adrenal crisis is a life-threatening situation, treatment should not be delayed (3,21). An example for algorithm of AI treatment for emergency department can be seen in Figure 1. Although the intravenous (IV) route is preferred in hospital conditions, IM administration is also effective in cases where vascular access cannot be established (4).

Table 1. Clinical findings of adrenal insufficiency and adrenal crisis* (3)

	Symptom	Finding	Laboratory
Adrenal insufficiency	Weakness	Hyperpigmentation (PAI only)	Hyponatremia
	Weight loss	Growth failure	Hyperkalemia
	Postural dizziness	Low blood pressure	Hypoglycemia
	Anorexia, abdominal discomfort		Occasionally hypercalcemia
Adrenal crisis	Severe weakness, syncope	Hypotension	Hyponatremia
	Abdominal pain, nausea, vomiting, sometimes back pain	Abdominal sensitivity, defence	Hyperkalemia
	Confusion	Confusion, delirium	Hypoglycemia
			Rare hypercalcemia

*Since many symptoms are non-specific and have been present for a long time, there are often delays in diagnosis. Hyponatremia and hyperkalemia often mediate the diagnosis. Hyperpigmentation is a specific finding but varies among individuals and requires comparison with the individual's past pigmentation status. Adrenal crisis requires emergency treatment. Preventing adrenal crisis is an important part of patient management. Findings of autoimmune diseases that may accompany adrenal insufficiency, neurological findings in patients with adrenoleukodystrophy, and findings of diseases that cause adrenal infiltration may also be observed.
PAI: primary adrenal insufficiency

Regardless of the route of administration, HC absorption occurs at similar levels (22).

It is known that the level of endogenous cortisol increase in acute stress situations, such as critical illness, anesthesia, and surgery, varies greatly from patient to patient (8,9,23). It is thought that increased glucocorticoid secretion during critical illnesses is necessary for the proper functioning of defense mechanisms (such as cytokine release) as well as to prevent the negative physiological changes that may occur due to excessive stress response (24). There are no randomized clinical studies examining the glucocorticoid doses that should be used in cases where cortisol requirement increases. However, it is thought that this need is directly proportional to the duration and severity of the stressful situation. Traditionally, it is estimated that adults will release 75-100 mg/day of cortisol in major surgery and 50 mg/day in minor surgery. It has been observed that cortisol release rarely exceeds 200 mg per day after some procedures (11). The purpose of using these high doses is not only to mimic the cortisol response in normal individuals, but also to meet unexpected needs that may arise as a result of complications. There is no direct evidence to suggest that these doses are harmful or that lower doses are safe. It is known that approximately 50 mg of HC is equivalent to 100 mcg fludrocortisone (25). Since sufficient mineralocorticoid effect is achieved when approximately 50 mg/day HC is used, additional mineralocorticoid use is not recommended at these doses (3,23). If a cause, such as infection, that triggers adrenal crisis is present, that should be treated separately (26).

Glucocorticoids are secreted into the systemic circulation in a pulsatile and circadian manner. Cortisol release rate has not been found to be related to gender or pubertal status in children (27). A person with normal adrenal function secretes cortisol approximately 5-10 mg/m^2/day (28). Under conditions of stress, cortisol release rate can increase up to 10-15 times. Insufficient use of glucocorticoids during adrenal crisis are potentially dangerous. However, there are no systematic dose-response studies done on this subject, and the recommended glucocorticoid doses in treatment are largely empirical.

In the treatment of adrenal crisis, a continuous infusion of HC 2 mg/kg/day can be performed after administration of HC IV bolus 4 mg/kg, until stabilization is achieved.

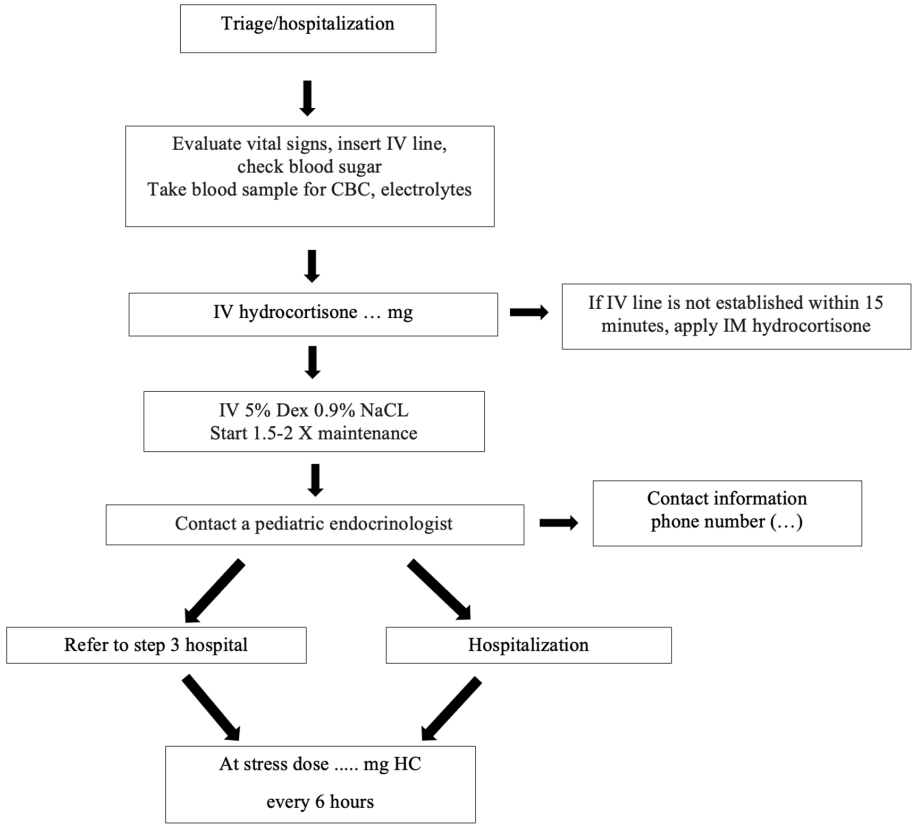

Figure 1. Algorithm sample of adrenal insufficiency treatment for emergency department (4)

HC: hydrocortisone, IV: intravenous, IM: intramuscular, SC: subcutaneous, CBC: complete blood count

Alternatively, the same dose can be divided and IV/IM bolus can be applied at 4-6 hour intervals. Initial administration of 50-100 mg/m^2 HC bolus followed by 50-75-100 mg/m^2/day continuous infusion or at 6-hour intervals has also been suggested (21). When the bolus dose is adjusted according to age and body surface practically, the dosing regimens are: children under two years of age/weighing < 15 kg, between 2-6 years of age/weighing 15-25 kg and over six years of age/weighing more than 25 kg, doses are 25, 50 and 100 mg HC, respectively (21). In cases where peripheral venous access cannot be achieved quickly, IM administration should be performed without delay.

It is recommended to avoid synthetic, long-acting steroids, such as dexamethasone in childhood (3,20). HC and prednisolone are active glucocorticoids. Cortisone acetate and prednisone are activated by hepatic 11 beta hydroxy steroid dehydrogenase. The use of inactive precursor glucocorticoids may show greater pharmacokinetic changes due to individual differences. However, this issue has not been studied systematically (3).

If HC is not available, prednisolone can be used as an alternative. Dexamethasone should not be used, except as a last resort, as it has a high growth suppressant effect but a very low mineralocorticoid effect (3). Prednisolone has four times the glucocorticoid activity of HC, and methylprednisolone has five times the glucocorticoid activity. Therefore, if prednisolone is to be used, the dose should be calculated as 1/4, and if methylprednisolone is to be used, the dose should be 1/5 of the HC dose (20,21). Although the use of steroids other than HC is not recommended, in cases where there is no other option, calculation of the equivalent doses of the other steroids is needed (29).

Dehydration, hypoperfusion and hypotension may occur in glucocorticoid and mineralocorticoid deficiency. If there is hypotension, 0.9% saline bolus can be given at a dose of 20 mL/kg; in case of shock, this dose can be increased up to 60 mL/kg in one hour (3,4,30,31).

The amount of IV fluid to be given during adrenal crisis treatment is calculated as maintenance + deficit and can be adjusted as 150-180 mL/kg/day in newborns and 2.5-3 liters/m^2/day in older children, depending on the age and needs of the patient (20,21). For this purpose, 5% Dextrose 0.9% NaCl (or 5% Dextrose 0.45% NaCl) is often the appropriate treatment option (3,21). Deficit treatment replaces the fluid lost by the patient according to the degree of dehydration. In order to calculate the deficit fluid, the patient's weight and degree of dehydration must be known (32). Assessment of clinical dehydration can sometimes be misleading, and patients need to be closely monitored and fluid needs should be re-evaluated during treatment. The patient's fluid and electrolyte therapy should be rearranged according to clinical and biochemical monitoring (such as blood pressure, heart rate, urine output, state of consciousness, glucose level) (33).

Glucocorticoids play an important role in maintaining blood glucose balance. Hypoglycemia, a symptom of acute AI, is more common in children than adults. Blood glucose should be monitored hourly (21). In case of hypoglycemia, IV bolus 10% Dextrose given at a dose of 2-10 mL/kg should be continued with a fluid containing 5% or 10% Dextrose to maintain normoglycemia, depending on the patient's blood glucose level. If it is needed, 25% Dextrose (0.5-1 g/kg, maximum 25 g at a time, at a rate of 2-3 mL/hour) can be given using a central vein (3,4,21,30,31).

Sodium and potassium levels should be monitored carefully (21). Hyponatremia is the most consistent biochemical finding seen in acute AI (34). Sodium is the dominant cation of extracellular fluid and is very important for maintaining intravascular volume as it is the determinant of osmolality. Hyponatremia in AI occurs due to renal losses as a result of glucocorticoid and mineralocorticoid deficiency (32). To correct hyponatremia, 10-15 mEq/kg/day NaCl can be given in rehydration fluids containing Dextrose, but the rate of increase in plasma sodium level should not exceed 0.5-1 mEq/hour (10-12 mEq/24 hours or 18 mEq/48 hours). It should be taken into account that sodium levels may rise rapidly when HC is applied. In cases of severe findings, such as seizures, IV hypertonic saline (3% NaCl) is recommended to increase serum sodium and protect against brain edema. Each 1 mL/kg of 3% NaCl increases serum sodium by approximately 1 mEq/L. Clinical improvement is often observed in a child with active symptoms after receiving 4-6 mL/kg of 3% NaCl. Problems such as central pontine myelinosis, which may occur with rapid correction of hyponatremia, are observed during the treatment of chronic hyponatremia rather than acute hyponatremia (3,32).

If patients have severe, symptomatic or persistent hyperkalemia despite HC and rehydration fluid, potassium-lowering agents can be used (35). Clinical symptoms often occur when the potassium level exceeds 7 mmol/L. The most important finding of hyperkalemia is related to the cardiac conduction disorders. When potassium levels are above 6-6.5 mEq/L, an electrocardiogram (ECG) should be taken to evaluate the urgency of the situation. ECG changes begin with a sharpening of the T waves. As potassium levels increase, the P-R interval becomes longer, the P wave

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becomes flatter and the QRS complex expands. Patients might experience palpitations, atrioventricular block, ventricular fibrillation or asystole. Paresthesia, weakness and tingling may be observed in some patients. Cardiac toxicity caused by hyperkalemia increases when accompanied by hyponatremia and metabolic acidosis. Drugs used in the treatment of hyperkalemia are summarized in Table 2 (36,37).

After correction of hypovolemia, hypoglycemia, electrolyte irregularities and clinical improvement, with parenteral treatments, oral HC treatment (30-50 mg/m^2/day) can be started (21). At least three times the usual HC dose should be given on the first day, then gradually reduced over a few days and switched to the normal dose (20). In this case, fludrocortisone (0.05-0.1 mg/day) can be added if necessary. Using dexamethasone alone in glucocorticoid replacement therapy may lead to adrenal crisis because it has no mineralocorticoid effect.

Good practice points:

1. Adrenal crisis treatment is urgent and should never be delayed for reasons such as waiting for test results. However, it is very useful to take a blood sample for diagnostic tests before treatment (1⊕⊕⊕O).

2. In the initial treatment of adrenal crisis, HC bolus 2-4 mg/kg (50-100 mg/m^2) should be started IV. The use of mineralocorticoids is not necessary in a patient receiving a stress dose of HC exceeding 40 mg (1⊕⊕⊕O).

3. If HC is not available, alternatively prednisolone or methylprednisolone may be used. The use of dexamethasone is not recommended (1⊕⊕⊕O).

4. In adrenal crisis, the presence of fluid deficit, hypoglycemia, hyponatremia and hyperkalemia should be evaluated and corrected with appropriate treatment (parenteral fluid support aimed at correcting hypoglycemia, hyponatremia and hyperkalemia) (1⊕⊕⊕O).

Management of Stressful Situations in Patients with Adrenal Insufficiency

Exercise

Exercise is defined as any activity involving the generation of force by activated muscle(s) that results in an alteration of the homeostatic state. In dynamic exercise, the muscle may perform shortening or be overcome by external resistance and perform lengthening. When muscle force results in no movement, the contraction is termed static or isometric. Most activities combine varying amounts of both isometric and dynamic exercise (38). A way to understand and measure the intensity of physical activity is by understanding intensity and how physical activity affects heart rate and breathing. The talk test is a simple way to measure relative intensity. If you can talk and sing during activity you are doing light intensity activity (LIA). Daily activities such as sleeping, watching television, writing, desk work, typing or walking slower than three miles per hour are LIAs. In general, if you're doing moderate-intensity activity (MIA), you can talk but not sing during the activity. Walking briskly (three miles per hour or faster, but not race-walking), water aerobics, bicycling slower than 10 miles per hour on primarily flat or level terrain without hills), tennis (doubles), ballroom dancing, general gardening are examples of MIAs. If you're doing vigorous-intensity activity, you will not be able to say more than a few words without pausing for a breath. For example: race walking, jogging, or running, swimming laps, tennis (singles), aerobic dancing, bicycling 10 miles per hour or faster that may include hills, skipping rope, heavy gardening (continuous digging or hoeing), and hiking uphill or with a heavy backpack (39).

Studies about the need for additional steroids during exercise in children with PAI are lacking. In patients with PAI, the use of an extra dose of HC before short-term intense exercise has not been shown to be superior to placebo in terms of exercise performance and blood glucose levels (40,41). Therefore, the use of extra doses of steroids for short-term exercise is not recommended. There are few published studies on the need for stress dosing in the case of intense, prolonged physical activity (running a marathon, cycling race, ski race, etc.). One study showed healthy athletes exhibited cortisol elevations similar to major surgery after running a marathon (42). Another study reported that healthy athletes participating in ultra marathons were more prone to decreased adrenal responsiveness, and in severe cases, AI (43). In a case report, a 50-year-old male endurance athlete with known PAI reported severe fatigue, nausea, and malaise after competing in prior marathons and intensive endurance exercise. After supplementing with 3-fold daily glucocorticoids and mineralocorticoids before competition, he experienced decreased symptoms and improved performance (44). To better care for these patients, further studies should be conducted to provide safe and effective glucocorticoid and mineralocorticoid dose adjustments before intensive endurance exercise. Close symptomatic surveillance while adjusting adrenal replacement therapy before the event will likely result in less adverse side effects and improved performance (44). The guideline of the French Endocrine Society recommends an additional dose of 5 mg of HC every three hours, starting

Table 2. Medications used in the treatment of hyperkalemia (36,37)

Medicine	Dose	Effect duration	Side effect/complication
Dextrose/insulin	0.5-1 g/kg dextrose and 0.2 units of insulin for every 1 g of glucose	Fast	Hypoglycemia, hyperosmolarity
Salbutamol	Nebulized: 2.5 mg < 25 kg 5 mg > 25 kg	Fast	Tachycardia
Sodium bicarbonate	1-2 mmol/kg in 30-60 min	moderate	Sodium overload (hypertension)
Furosemide	1-2 mg/kg	moderate	Ototoxicity, nephrotoxicity
Ion exchange resins	p.o. or p.r. Calcium resonium 1 g/kg Sodium resonium 1 g/kg	Slow	p.o.: Nausea, constipation, paralytic ileus. If mixed with sorbitol, diarrhea p.r.: Cecal perforation
Ca-gluconate 10 %	0.5-1 mL/kg in 5-10 minutes		Hypercalcemia, tissue necrosis NOTE: Calcium gluconate antagonizes cardiac effects although does not have a potassium-lowering effect.

one hour before the activity, for long-duration, high-intensity activities (expert opinion) (45).

Other Drugs That Change Cortisol Metabolism

Some drugs, such as carbamazepine, phenytoin, phenobarbital, and rifampin, increase cortisol clearance by stimulating cytochrome p450 3A or P-glycoprotein efflux membrane transporters. Therefore, the use of these drugs with glucocorticoids may require the use of higher replacement doses, and if the necessary dose increase is not made, adrenal crisis may be induced (3,46,47).

Febrile and Non-febrile Illnesses

The most common triggers of adrenal crisis in children with AI are upper respiratory tract infections in young children and gastrointestinal infections in older children (3). Cortisol release increases 2-5 fold in febrile illnesses in children; whereas this increase is milder (2-3 fold) in cases of pharyngitis, urinary tract infection and otitis. It is more pronounced (about 5 fold) in cases of pneumonia, bacterial meningitis and fever of unknown origin. However, no relationship has been found between the degree of high fever and cortisol release (10). Various guidelines on the management of AI also recommend increasing the dose of HC during febrile periods of infection (3,20).

Severe Trauma or Illnesses Requiring Intensive Care

One study showed mean admission cortisol levels were elevated (35 ± 3 µg/dL) and declined significantly over the following 10 days in severely injured patients (48). In this study, cortisol levels did not correlate with injury severity. In another study, plasma cortisol was found to be elevated in proportion to the degree of disease in patients followed up in intensive care (49). Patients with normal hypothalamic-pituitary-adrenal axis function consistently exhibit elevated total serum cortisol levels up to 10 times the upper limit of normal during critical illness (50,51). A cross-sectional study reported that serum free cortisol, 24-hour urinary cortisol and cortisol metabolite levels were significantly higher in acute major trauma and sepsis compared with healthy controls (7). The International Endocrine Society guideline recommends the use of an adrenal crisis dose of HC (initially 50 mg/m^2 IV HC, then 50-100 mg/m^2/day, IV or IM HC at 6-hour intervals) in children and adolescents with AI in cases of severe trauma, labor and in conditions requiring intensive care (3).

Minor Local Procedures without Sedation or General Anesthesia

Dental extractions and local anaesthetic procedures can induce stress in subjects. Many studies in adults and children have shown that dental procedures, like local anaesthetic injections, dental restoration and extractions elevated the levels of salivary cortisol (52,53,54,55). It was observed that salivary cortisol measured after tooth extraction was approximately twice (but not more) that of control subjects (52,53). When the difference in the effect of one or two tooth extractions was analysed, no significant difference was found between salivary cortisol levels (56).

Imaging Procedures Under General Anesthesia

It has been reported that cortisol levels did not increase during general anesthesia in children without AI when anesthesia was used for imaging procedures, and that cortisol levels at the level of the stress response (≥550 nmol/L) were found in 23 % of patients on awakening and 52 % on recovery from anesthesia (8). No effect of age, duration of anesthesia and recovery time on the cortisol response was found. It was concluded that anesthesia alone did not stimulate the stress response in children with AI, but cortisol levels increased significantly during the recovery process. The highest increase in cortisol levels seen in the study was 4-fold compared with baseline (8). Another study found that in children without AI, anesthesia increased cortisol levels 3-4-fold, the lowest increase was in imaging

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anesthesia (3-fold), and the depth of anesthesia did not affect the amount of cortisol increase (9).

Invasive Procedures Performed Under General Anesthesia

High-quality trials on perioperative steroid management in children with AI are lacking, and more research is needed to establish evidence-based clinical guidelines (15). The amount and timing of cortisol released from the adrenal cortex in response to surgery in individuals without AI is taken into account when determining the stress doses to be administered in the perioperative period in adult patients, and the dose is adjusted according to the level of surgical stress (57). However, the stress doses and application methods recommended to date are generally based on case series published before 2000 with a low level of evidence and small numbers of patients (6). According to the study published by Kehlet and Binder (58) in 1973, the estimated cortisol secretion in the first 24 hours due to surgical stress in healthy adults was 75-150 mg/day for major surgery and 50 mg/day for minor surgery. In older studies, cortisol secretion in the first 24 hours of major surgery generally does not exceed 200 mg/day (maximum 300 mg/day in one study) (11). To date, perioperative stress cortisol doses have been recommended based on this informations (59). As there is little data in children, adult doses are adapted to children.

A recent systematic review and meta-analysis evaluated 71 studies published between 1990-2016 that investigated the cortisol stress response induced by surgeries with different severity (excluding brain surgery) in adults without AI (6,60). In the trials conducted in patients undergoing minor surgery, no cortisol peak was observed during surgery, and cortisol levels within six hours after surgery did not increase significantly compared with baseline. However, the mean cortisol release in the first 24 hours after surgery was approximately doubled in this group compared to healthy, non-stressed individuals. Total serum cortisol was found to peak during the extubation period and between postoperative 6 and 18 hours for moderate and major surgery respectively. In addition, mean cortisol levels in these two groups remained higher than baseline for up to three days postoperatively (up to seven days in a smaller number of studies). Mean cortisol release in the first 24 hours after moderate and major surgery was 1.9 and 1.7 times higher compared to the minor surgery group, and 4 and 3.5 times higher compared to healthy and non-stressed people, respectively. In conclusion, the extent of surgery significantly influenced perioperative cortisol synthesis. Perioperative cortisol release was found to be higher in female patients compared with male patients, in open surgery compared with laparoscopic surgery, and in those who received general anesthesia compared with those who received regional (spinal/epidural) anesthesia (6).

In a recent case-control study (57), perioperative cortisol measurements were analysed in 93 adult patients (23 minor, 33 intermediate, 37 major/major + according to the severity of surgery) and it was found that serum cortisol peak and time to peak were positively correlated with the degree of surgical invasiveness. Cortisol peaks were observed at a median of 2 (0-21.5), 4 (0-19) and 8 (0-94) hours after induction of anesthesia in minor, intermediate and major/major + operations, respectively. Cortisol levels returned to baseline at a median of 8 hours and 2 (1-5) days after induction of anaesthesia in moderate and major/major + surgery, respectively. The authors suggested that the current recommendations for perioperative stress doses to achieve these levels are high and they can be reduced, and also they can be tapered to maintenance doses in a shorter time. However, this should be tested with prospective studies to show that it is safe and practically applicable (57).

Studies of the cortisol response to perioperative stress in children are very limited. In two studies investigated the effect of minor surgical procedures performed under general and epidural anesthesia, it was found that cortisol levels were 2.5-3 fold higher during perioperative process in the general anesthesia group but not epidural anesthesia group (61,62). Khilnani et al. (63) showed that postoperative cortisol levels in 98 children and young adults increased significantly. Age, duration of surgery and type of anesthesia were found to have no effect on cortisol levels. In another study, during follow up of 30 children (from preoperative period to one hour after the end of the surgery) who underwent minimally and moderately invasive urological surgery, it was found that cortisol levels peaked at one hour postoperatively. However, it was reported that mean serum cortisol levels did not increase significantly from baseline at any measurement (23). There was no difference in cortisol levels between age groups, general or caudal anesthesia and minimally or moderately invasive surgery. Based on this, it has been recommended that the perioperative glucocorticoid dose in minimally and moderately invasive urological surgery should not exceed three times the daily dose and that the dose increase should cover the postoperative period rather than the preoperative period.

Methods of perioperative administration of stress doses in adults were compared in a recent study (7). In first part of the study, postoperative serum cortisol levels were monitored in 22 patients (without AI) undergoing elective surgery (mostly moderately invasive). In the second part, ten patients with primary AI received 200 mg/day of HC by four different routes (oral, IM, IV or continuous IV infusion

of equal doses at 6-hour intervals) at 1-week intervals and serum cortisol levels were monitored 24 hours after the initiation of administration. Then data from these two part of studies were compared. The authors found that the mean cortisol concentrations observed in healthy volunteers during surgical stress could only be achieved by continuous infusion in patients with AI, and in the other application routes cortisol levels fell below these levels before the next dose. When pharmacokinetic modelling was performed, it was found that administration of 200 mg of HC via continuous IV infusion after a 50-100 mg HC bolus was the best way to achieve cortisol levels within the desired range. The authors recommended that continuous infusion of HC should be preferred for the prevention or treatment of adrenal crisis in high-stress situations (7). As most of the surgeries in the study were moderately invasive, it was noted that higher serum cortisol levels may be found in more invasive and longer surgeries. Chee et al. (64) criticised this study and suggested that adding information on blood pressure and intraoperative hemodynamic status to such a study could provide further physiological evidence when comparing treatment regimens.

In a systematic review of the need for perioperative glucocorticoids in adult patients on pharmacological doses of steroids for reasons other than AI, it was found that the use of steroids at the patients' daily dose did not lead to adrenal crisis in this patient group, without increasing the perioperative loading dose. In cases of postoperative hypotension, it was reported that there was often an explanation for this and that it resolved with volume repletion. The results of the preoperative ACTH stimulation test did not correlate with the postoperative clinical status of the patients. It has been suggested that perioperative glucocorticoid doses can be kept lower in this group of patients than in patients on glucocorticoids for PAI. However, further studies are needed in this area, as the sample size was small and the statistical power of the study was low (65).

Preferred Steroid Type

As HC also has a mineralocorticoid effect, the use of HC is preferred in situations of stress, especially in patients with mineralocorticoid deficiency. As 40-50 mg of HC can have a mineralocorticoid effect equivalent to 100 µg of fludrocortisone, the use of HC above this dose also meets the need for mineralocorticoid replacement. Prednisolone and methylprednisolone also have partial mineralocorticoid activity (66). As dexamethasone has no mineralocorticoid activity, it is not appropriate to use it alone in patients with mineralocorticoid deficiency (66). If necessary, it can be used in patients with secondary AI or isolated glucocorticoid deficiency. Otherwise, maintenance fludrocortisone should be given separately (3).

Good practice points:

1. Additional doses of steroids are not required for routine physical exercises (LIAs) (ungraded good practice statement).

2. Additional doses of steroids are not required for short-term (≤20 minutes) moderate and high-intensity exercises (ungraded good practice statement).

3. It would be appropriate to use additional doses of steroids during high-intensity excercise lasting longer than 30-60 minutes like marathon running, cycling race or etc (2⊕⊕OO).

4. It may be necessary to increase the HC replacement dose if a drug that increases cortisol metabolism or clearance is started (2⊕OOO).

5. Additional doses of steroids for mild, non-febrile illnesses are not required (2⊕OOO).

6. In febrile illnesses, the dose of oral HC used should be increased 2-3 times until the fever returns to normal. Infants and young children in particular should not be allowed to go hungry, and their fluid intake should be increased. For more serious infections, such as pneumonia or meningitis, the dose should be increased further (5 times) (1⊕⊕OO).

7. If there is diarrhea and/or vomiting, it is appropriate to give 3 times the current dose of oral HC (3-4 doses per day) until the condition improves (a few days). If diarrhea-vomiting persists, oral intake cannot be tolerated, there is severe weakness/impaired consciousness, and/or suspicion of adrenal crisis, 25, 50 and 100 mg HC or equivalent methylprednisolone should be administered IM to the patients < 3 years, 3-12 years and > 12 years, respectively (or 50-100 mg/m^2 for all ages) (or 2 mg/kg at all ages). Afterwards a healthcare provider should be consulted for IV fluid support (2⊕OOO).

8. In severe trauma or illnesses requiring intensive care, parenteral HC administration at adrenal crisis doses is appropriate until stability is achieved (1⊕⊕OO).

9. For minor dental procedures carried out under local anaesthetic, double the daily dose and return to the normal dose the following day (2⊕⊕OO).

10. For imaging procedures under general anesthesia, the HC dose should be increased (3-4 times), especially during waking and recovery from anesthesia. The normal dose should be resumed the following day (1⊕⊕⊕O).

11. Prior to colonoscopy under general anesthesia HC 50 mg/m^2/day IV/IM is used on the day of bowel evacuation. HC 50 mg/m^2/dose IV/IM is given before the procedure (2⊕OOO).

12. For invasive procedures performed under general anesthesia, increase the dose of HC (parenteral) for an appropriate period of time according to the degree of invasiveness of the surgery to be performed (1⊕⊕OO) (Table 3). Perioperative follow-up of these patients should preferably be carried out in a centre with a paediatric endocrinologist (2⊕OOO).

13. Stress doses should be given as HC, especially in patients with mineralocorticoid deficiency, and if HC cannot be given, equivalent doses of prednisolone (1/4 dose) or methylprednisolone (1/5 dose) is preferred (1⊕⊕OO).

Family Education

Several studies have shown that a significant proportion of patients with AI do not have sufficient information about personal management of the disease, do not carry a disease identification card or similar, or perform incorrect practices in stressful situations (3,18,45). So it has been suggested that continuous and effective education is needed. A Canadian study (1998-2007) found that only 47% of children with AI received a glucocorticoid dose increase prior to emergency admission (67). In a study analysing emergency admissions of children diagnosed with congenital adrenal hyperplasia (CAH) to three endocrine centres in Australia (2000-2015), it was found that 64% of patients received stress doses (22.1% IM), and this rate was lowest in the age group below 12 months (51.9%) (68).

The most important way to protect patients from life-threatening adrenal crisis is to constitute patient/family awareness through appropriate education (2,17). Informing patients and their families about the diagnosis and treatment of the child, stress states, symptoms of AI and increasing the dose of steroids in stress situations may improve management of the disease and reduce the frequency of adrenal crisis (45). They should also be trained in the use of IM HC in case of situations of severe stress, continuous vomiting or recognising symptoms of adrenal crisis, like an altered state of conscious. In a study conducted in the Netherlands, 246 patients receiving glucocorticoids for AI were trained in glucocorticoid treatment, dose increase in stress situations, and IM HC injection, and a questionnaire was administered before and six months after training. After the training, it was found that patients' correct answers to questions about managing stress situations increased significantly, and more patients started to carry informative materials about AI (18).

It is appropriate for patients to have a written document or identification bracelet/necklace to be shown to the first consulted healthcare professional regarding what should be done in emergency situations. IM or subcutaneous (SC) administration of HC in home settings may be life-saving when symptoms of adrenal crisis are felt or when oral HC cannot be taken due to vomiting. It may prevent the patient from deteriorating until he/she goes to a health institution. In a prospective study conducted in adults, Hahner et al. (69) showed that almost every patient carried an emergency card, but only 30% of the patients had a HC administration kit. In this study, it was highlighted that the rate of having an emergency injection kit was higher in people who had experienced adrenal crisis.

Many international and national guidelines recommend that all patients with AI (and/or their families) should be informed about the following topics: 1) diagnosis and routine medication doses; 2) stressful situations, symptoms of adrenal crisis and strategies to prevent adrenal crisis; and 3) to have an emergency glucocorticoid injection kit (HC hemisuccinate IM/IV ampoules, injector) and know how to use it (IM or SC injection) (3,13,20). Besides the IV/IM preparations containing HC, which are available in Turkey, auto-injectors containing ready-to-use HC are also available, in order to shorten the preparations for injection and prevent errors in application and are more widely used globally. The use of rectal HC suppositories is not recommended in cases of stress in patients with AI (70).

In order to provide a standardised approach in the prevention and treatment of adrenal crisis in children with AI in Turkey, the 'Emergency Treatment Plan for Patients Using HC Due to AI' (71) and the 'Perioperative Approach in Adrenal Diseases' protocol (72) were published by the Pediatric Endocrinology and Diabetes Association (CEDD). 'Patient identification cards' have been printed to be carried by patients diagnosed with CAH. The QR code on the card can be scanned to access the adrenal crisis management protocol available on the association's website. The cards also contain the patient's name and surname, the patient's family, the hospital where the patient is normally being treated and the doctor's contact details. In the guidelines of the French Society of Endocrinology, the framework of the educational programme that can be applied to patients diagnosed with AI has been presented (45).

In clinical practice, it is often observed that, even when patients receive education by written materials, some of the information is forgotten during follow-up. Therefore, it is

Table 3. Recommendations for the perioperative stress dose of glucocorticoids in children with adrenal insufficiency (3,20,72)

Surgical stress	Recommended HC dosage
Minor surgery (minimally invasive) - Examinations under anesthesia - Excision of skin lesions - Ear tube insertion - Cystoscopy - Circumcision - Bronchoscopy - Endoscopy, colonoscopy - Diagnostic laparoscopy - Inguinal hernia repair - Tonsillectomy	- HC 25 mg/m^2/dose is given intravenously before the procedure. When oral feeding is initiated after the procedure, HC is given at twice the normal dose, and the normal dose is continued the next day. OR - 50 mg/m^2/day or 2-3 times the HC replacement dose (first day) IM/IV.
Moderate surgery (moderately-significantly invasive) - Thyroidectomy - Ovarian cystectomy - Cholecystectomy - Hysterectomy - Nephrectomy - Major laparoscopic procedures - Gastrointestinal resections (segmental)	- 25-50 mg/m^2/dose of HC is given intravenously as a bolus before surgery. - Subsequently, 50-75 mg/m^2/day HC is administered as a continuous intravenous infusion or IV injection every 6 hours (the first one during surgery). - In uncomplicated cases, once the patient is stable, the dose is tapered by 25% per day within a few days to the previous maintenance dose. OR - HC 2 mg/kg is given as an IV infusion over 6 hours (or IM/SC every 6-8 hours) and the same dose is repeated until oral feeding is initiated. When oral feeding is initiated, HC is given orally at twice the daily dose and the dose is tapered back to the previous maintenance dose in 1-2 days.
Major surgery (severe invasive) - Cardiothoracic surgery - Intracranial surgery - Major oropharyngeal surgery - Major vascular, skeletal or neurological repairs - Major orthopedic spinal reconstruction - Major gastrointestinal reconstruction - Liver resection - Major genitourinary surgery - Multiple dental procedures under general anesthesia	- 50-100 mg/m^2/dose of HC is given intravenously as a bolus before surgery. - Subsequently, 100 mg/m^2/day of HC is given as a continuous intravenous infusion or intravenous injection every 6 hours (the first during surgery). - In uncomplicated cases, once the patient is stable, the dose is tapered by 25% per day and the previous maintenance dose is restored within a few days. OR - HC 2 mg/kg is given as an IV infusion over 6 hours (or IM/SC every 6-8 hours) and the same dose is repeated until oral feeding is initiated. When oral feedig is initiated, HC is given orally 3 times daily, and the dose is tapered back to the previous maintenance dose in 3-4 days.

*In patients with mineralocorticoid deficiency, fludrocortisone should be given preoperatively with a little amount of water if the calculated daily total HC is < 40 mg.
HC: hydrocortisone, IV: intravenous, IM: intramuscular, SC: subcutaneous

important to repeat training periodically (69,73,74,75). The precautions and rules to be taken during periods of illness should be repeated at each outpatient clinic follow-up and IM injections should be demonstrated.

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (76).

Good practice points:

1. In order to prevent adrenal crisis, all patients and/or their families should be educated about the conditions that trigger adrenal crisis, how to increase HC doses during illness, fever and other stressors. This education should also include, how to recognise signs of impending adrenal crisis, and what to do in this situation (ungraded good practice statement).

2. All patients should be encouraged to carry a card/information sheet/medical alert bracelet or necklace indicating the diagnosis of AI and need for HC administration (ungraded good practice statement).

3. All patients should have a glucocorticoid injection kit (100 mg HC hemisuccinate ampoule, syringe with needle) and be trained for self injection (SC or IM injection) in emergency situations (ungraded good practice statement).

Footnotes

Authorship Contributions

Concept: Emine Çamtosun, Özlem Sangün, Design: Emine Çamtosun, Özlem Sangün, Literature Search: Emine Çamtosun, Özlem Sangün, Writing: Emine Çamtosun, Özlem Sangün.

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REVIEW

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Treatment and Follow-up of Non-stress Adrenal Insufficiency

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Abstract

Adrenal insufficiency (AI) is defined as the inability of the adrenal cortex to produce adequate amounts of glucocorticoids and/or mineralocorticoids. As these hormones have important roles in water-salt balance and energy homeostasis, AI is a serious and potentially life-threatening condition. Glucocorticoid replacement therapy is vital in all cases of AI. In children with primary AI (PAI), it is recommended to start glucocorticoid replacement therapy with three or four doses of hydrocortisone and adjust according to individual need. Long-acting glucocorticoids such as prednisolone and dexamethasone are not recommended in children with AI. Mineralocorticoid and salt replacement therapy is also necessary in PAI with aldosterone deficiency. In childhood, it is recommended that patients are monitored at least every three to four months with clinical evaluation including weight gain, growth rate, blood pressure and general well-being of the patient. To prevent adrenal crisis in patients with PAI, glucocorticoid dose adjustment is recommended to patients and/or their families according to the magnitude and severity of the stress situation. This education should include recognition of conditions leading to adrenal crisis, signs of adrenal crisis and how to respond to an impending adrenal crisis. With long-term use of glucocorticoids, the lowest possible dose should be maintained to control the disease to avoid possible side effects. 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 the diagnosis and follow-up of non-stress AI.

Keywords: Adrenal insufficiency, adrenal crisis, glucocorticoid, family education

Introduction

Adrenal insufficiency (AI) is defined as the inability to produce adequate amounts of glucocorticoids and/or mineralocorticoids from the adrenal cortex. Non-stress AI impairs critical functions, such as energy homeostasis, electrolyte balance and immune regulation, leading to symptoms including chronic fatigue, hypotension and increased susceptibility to other illnesses. Effective management of this condition requires early diagnosis and appropriate hormone replacement therapy to prevent serious complications (1).

This evidence-based review with good practice points is developed by the 'Adrenal Working Group' of 'The Turkish Society for Pediatric Endocrinology and Diabetes'. We developed this evidence-based review for 'treatment and follow-up of non-stress AI' in childhood and adolescence. The overall purpose of this evidence-based review is to provide good practice points, with focus on recommendations for daily management.

1. Glucocorticoid Treatment in Adrenal Insufficiency

The basis of treatment in AI is glucocorticoid replacement. The main goals of treatment are to reduce the signs and symptoms of AI, to prevent the development of adrenal crisis by ensuring normal physical and pubertal growth, and also to prevent long-term complications (2,3). Inadequate treatment (in terms of dose or duration) may cause signs

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of AI. Overtreatment is associated with iatrogenic Cushing syndrome (ICS), growth suppression (not necessarily with Cushingoid signs), osteoporosis, increased risk of cardiovascular disease and poor metabolic control (3). Both under- and overtreatment have a negative effect on growth and development in children (4,5).

Long-term glucocorticoid replacement therapy is given in all cases of AI. If aldosterone deficiency is also present in primary AI (PAI), mineralocorticoid and sodium chloride therapy is also needed. Anti-inflammatory and growth suppressive effects of the preparation, mineralocorticoid activity, plasma and biological half-life and route of administration are the key features of the glucocorticoid when choosing which treatment to give (6). Hydrocortisone is the synthetic form of natural cortisol with high oral bioavailability (7), short half-life and less growth suppressive effect (2). It is also the glucocorticoid preparation of choice in childhood because it has fewer side effects compared to synthetic prednisolone and dexamethasone (1,2). Due to the half-life of hydrocortisone of approximately 90 minutes, three or four doses per day are recommended to mimic physiologic cortisol release (1). In addition, hydrocortisone can be titrated more easily than more potent, long-acting glucocorticoids, which reduces the potential for long-term side effects (1).

Hydrocortisone, the first choice glucocorticoid in children, is generally administered orally at a dose of 7.5-15 mg/m^2/day in three or four doses. Hydrocortisone has a high protein binding capacity and its clearance increases at high doses. Hydrocortisone clearance is 26% lower in the evening than in the morning (8). However, it is recommended that the first and highest dose should be given in the morning after waking up, the second dose should be given after lunch and the third dose should be given at least 4-6 hours before sleep and at the lowest dose in order to be compatible with the circadian rhythm and not to disrupt sleep quality and insulin sensitivity (1,9,10). It may also be recommended to divide the total daily dose into three doses, with half the total given in the morning and the other half divided between midday and the evening (1).

There are no published randomized control studies on different treatment regimens in children with PAI (1). The first aim of treatment is to use the lowest dose of glucocorticoid that allows adequate growth and pubertal development and controls the signs of AI. Another aim is to mimic the physiologic release of cortisol and to prevent the side effects of high doses. To better plan the dose of GC, the endogenous cortisol production rate is taken as a basis. A few studies have shown that the physiologic cortisol production rate is 6-8 mg/m^2/day in older children and adults (11,12), but there is insufficient data in children under 5 years of age. While an initial hydrocortisone dose of 8 mg/m^2/day is thought to be sufficient for replacement therapy in non-congenital adrenal hyperplasia (CAH) patients with PAI, supraphysiologic doses of 10-15 mg/m^2/day are needed to suppress adrenocorticotropic hormone (ACTH) secretion, since there is an additional risk of increased adrenal androgen production due to ACTH in patients with CAH.

Children treated with hydrocortisone experience several spikes in cortisol concentrations during the day, often reaching supraphysiologic levels. This is followed by prolonged periods of hypocortisolemia between doses. Therefore, new technologies are being developed to provide more physiologic glucocorticoid replacement therapy, including new glucocorticoid formulations, subcutaneous hydrocortisone pump and some adjuvant therapies (13).

When hydrocortisone is not available and after the epiphyses have closed, glucocorticoid preparations such as prednisone, prednisolone, methylprednisolone, or dexamethasone may be used. As an alternative to hydrocortisone, prednisone may be preferred in adolescents and adults with closed epiphyses with poor treatment compliance (1,14). However, dexamethasone is not preferred because of the high risk of Cushingoid side effects (1). Meta-analyses comparing hydrocortisone and prednisolone treatments have found no significant difference between the treatment groups in terms of 17-hydroxyprogesterone (17-OHP) levels in most studies. Prednisolone treatment has been associated with higher hydrocortisone-equivalent doses and has been found to significantly reduce final height compared to hydrocortisone. Studies comparing hydrocortisone and prednisolone have shown that, despite similar hydrocortisone-equivalent doses, prednisolone is associated with higher values for cardiovascular and metabolic risk markers, including body mass index (BMI), waist-hip ratio, serum insulin during oral glucose tolerance testing, total fat mass, and trunkal fat mass. Prednisolone has also been shown to be associated with higher rates of osteoporosis and fractures. In studies comparing dexamethasone with hydrocortisone/prednisolone, dexamethasone was found to cause significantly more adrenal suppression and was associated with higher values for cardiovascular and metabolic risk markers and lower bone mineral density (BMD), making its use not recommended in children (15,16).

The use of hydrocortisone in three or four doses per day may make it difficult for the patient to comply with treatment. A new generation of long-acting, slow-release, modified hydrocortisone preparations that better mimic physiologic cortisol release and continuous subcutaneous hydrocortisone infusion with a pump are being studied.

There are two modified hydrocortisone formulations; Plenadren® and Chronocort®. Plenadren®, a dual-release hydrocortisone preparation, was designed for single dose use, but failed to provide adequate replacement effect and required an additional glucocorticoid dose in the evening. Studies in adults show that it provided a better cortisol exposure duration profile compared to conventional hydrocortisone formulations, resulting in better metabolic outcomes and quality of life for patients. It is approved for use in adults, but not yet in children (3). Chronocort®, a delayed-release hydrocortisone given in two doses daily, has been reported to be successful in mimicking physiologic cortisol release and controlling androgen synthesis (3).

Continuous subcutaneous hydrocortisone infusion with a pump has been reported to be successful in achieving more normal morning ACTH and cortisol values and 24-hour salivary cortisol curves more in line with circadian rhythm in non-CAH PAI patients. However, in cases with complete glucocorticoid deficiency, the risk of adrenal crisis is high due to the risk of pump malfunction. Moreover, there are high costs, the need for training, and local skin sensitivity. These therapies may be an alternative treatment in cases where classical treatment is not well tolerated (17).

Good practice points:

1. Glucocorticoid replacement therapy is vital in all cases of AI. In PAI accompanied by aldosterone deficiency, mineralocorticoid and salt replacement therapy are also required (1⊕⊕⊕O).

2. In children with PAI other than because of CAH (non-CAH PAI), it is recommended to start glucocorticoid replacement therapy with hydrocortisone, with an initial dose of 8 mg/m^2/day, in three or four doses, and adjust it according to individual needs (2⊕⊕OO).

3. Long-acting glucocorticoids, such as prednisolone and dexamethasone, are not recommended in children with AI (2⊕⊕OO).

2. Mineralocorticoid Treatment in Adrenal Insufficiency

In neonates with proven aldosterone deficiency, fludrocortisone is usually used orally at an initial dose of 100 µg, divided into one or two doses per day. Dose adjustment should be made according to the needs of the patients during follow-up. In children older than 1 year, 50-100 µg/day is usually sufficient. In severely affected patients, mineralocorticoid replacement is provided intravenously with hydrocortisone and sodium chloride (1).

In infants, additional sodium chloride is needed due to mineralocorticoid resistance in immature renal tubules and low sodium content in breast milk and formula. Typically, 1-2 g/day of sodium chloride (17-34 mmol/day) is required in newborns and this need for support may continue for the first 12 months of life (1). The ideal is to use a standard salt solution prepared in the pharmacy or standard sodium chloride tablets (18). Increased secretion of vasopressin and ACTH is prevented by correction of hypovolemia with fludrocortisone and sodium chloride in infancy. Thus, less need for glucocorticoid doses and normal growth may be achieved in cases of CAH-related PAI (15,18).

Up to 20 mg of hydrocortisone used in standard AI treatment has mineralocorticoid activity equivalent to approximately 100 µg of fludrocortisone, 100 µg of fludrocortisone has glucocorticoid activity equivalent to approximately 1-1.5 mg of hydrocortisone (19). Since glucocorticoid absorption and clearance show individual differences, individualization of dose adjustment according to need, with intermittent monitoring after initial doses would be the most appropriate approach (2,3,14).

Good practice point:

1. In all cases with aldosterone deficiency, fludrocortisone is recommended at an initial dose of 100 µg/day, and sodium chloride supplementation is recommended for infants throughout the neonatal period and until the age of 12 months (1⊕⊕⊕O).

3. Treatment of Adrenal Androgen Deficiency

Patients with PAI frequently have adrenal androgen deficit, which can have serious consequences for female patients in particular while they are transitioning from youth to adulthood. Adrenal androgens, including androstenedione and dehydroepiandrosterone (DHEA), are essential for preserving androgen-dependent hair development, bone health, and general wellness. These androgens may also support sexual function and libido in females (20,21).

3.1. Recommendations for Androgen Replacement in Women

It is advised to take into account DHEA replacement medication for female patients who are entering adulthood from adolescence, especially if they are exhibiting signs of adrenal androgen deficit, such as poor energy, decreased libido, and lower quality of life. The initial recommended dose is 25-50 mg/day, which can be changed based on the clinical response and blood androgen levels. Monitoring should be done every six to twelve months, with a focus on

weighing the advantages of a higher quality of life against any possible drawbacks, such as hirsutism or acne (20,21).

Recommendations for Androgen Replacement in Men

Adrenal androgens often have a minor role in men with PAI because gonadal testosterone production is present. Thus, it is not advised to replace DHEA on a regular basis unless there is proof of a combined adrenal and testicular androgen insufficiency. In these situations, testosterone replacement treatment is recommended, with dosage and monitoring in line with accepted practices for the treatment of hypogonadism (1,3).

Men should only think about androgen replacement therapy if symptoms like diminished quality of life, low libido, or decreased muscle mass are evident and low androgen levels are proven (1,3).

Good practice points:

1. While transitioning to adulthood, women with PAI may consider DHEA treatment (25-50 mg/day), especially if they are experiencing symptoms of poor energy or decreased sexual interest (2⊕⊕OO).

2. It is not advised for men with PAI to get regular DHEA medication unless a concomitant testicular androgen deficit has been verified (2⊕⊕OO).

4. Transition from Adolescence to Adulthood

For individuals with AI, the shift from pediatric to adult endocrinology treatment is very important. The dosages of glucocorticoids and mineralocorticoids need to be reviewed and modified in accordance with adult dosing standards during this phase. The particular requirements of this age group, such as bone health, metabolic state, and mental health, should get extra consideration (1).

Glucocorticoid Dosing

Hydrocortisone should be administered at a physiological replacement dose, with modifications to take into consideration changes in body weight and the completion of growth. Adults are usually administered 15-25 mg/day of hydrocortisone in two or three doses (1).

Mineralocorticoid Replacement

To maintain normal blood pressure and serum electrolyte balance in individuals with aldosterone deficit, fludrocortisone should be adjusted. Adult dosage typically varies between 50 and 100 µg/day, split into one or two doses (1).

Support for Transition

To help the patient manage their condition on their own throughout the transition phase, a systematic strategy should be created. This include making sure that the patient is aware of stress dosage, the significance of sticking to their prescription schedule, and emergency response techniques. The patient and family should have a special session on managing adrenal crises, encompassing the following topics:

- Identification of adrenal crisis symptoms.

- The appropriate usage of hydrocortisone injections.

- When to seek medical attention in an emergency.

All things considered, to guarantee the best possible management of AI during the transition from youth to adulthood, meticulous planning and customized therapy modifications are required (1,3).

Good practice points:

1. For glucocorticoid dosing, hydrocortisone should be continued at a physiological replacement dose, with adjustments to account for growth completion and changes in body weight. In adults, hydrocortisone is typically given at 15-25 mg/day divided into two or three doses (1⊕⊕⊕O).

2. For mineralocorticoid replacement in patients with aldosterone deficiency, fludrocortisone should be adjusted to maintain normal blood pressure and serum electrolyte balance. Typical adult dosing ranges from 50-100 µg/day, divided into one or two doses and without restriction of salt intake (1⊕⊕⊕O).

5. Follow-up in Cases of Adrenal Insufficiency

Dose adjustment in glucocorticoid and mineralocorticoid replacement therapy should be adjusted not only according to normal laboratory values but also clinical findings, blood pressure, and serum sodium and potassium values (22). Although dose adjustment is not made according to a single parameter, the most important parameters in dose adjustment are growth rate of height, weight changes and evaluation of general well-being, which should be evaluated at each visit in patients with PAI (1).

Symptoms of cortisol deficiency, such as inadequate weight gain, fatigue, nausea, loss of appetite, hyperpigmentation and headache, indicate that the dose should be increased (1). Doses above 8 mg/m^2/day, which is above physiological

release, may suppress growth. Decreased growth rate with weight gain or other cushingoid findings indicate excessive glucocorticoid use. In addition, weight gain, insomnia and peripheral edema are also signs of glucocorticoid excess. Questioning the daily habits, energy status, mental concentration power, daytime sleepiness, frequency and degree of decreases in energy status of the patients may help in better adjustment of the glucocorticoid dose (1).

The ideal glucocorticoid dose in a growing child is the lowest dose that achieves the desired therapeutic goals (6).

Fludrocortisone treatment monitoring is recommended to be performed primarily according to clinical evaluation and serum electrolyte (sodium and potassium) measurements (1). Inadequate weight gain, salt cravings, dehydration, hyponatremia accompanied by hyperkalemia, and increased renin activity or level indicate inadequate fludrocortisone intake (1). Blood pressure should be routinely monitored, and blood pressure monitoring is especially important because mineralocorticoid sensitivity increases in the first year of life (1). Plasma renin measurement is recommended in case of dose modification and when there is thought to be a problem with treatment compliance (1).

Patients with PAI of unknown autoimmune origin may be evaluated annually in terms of conditions, such as diabetes mellitus, premature ovarian failure, vitamin B12 deficiency due to autoimmune gastritis, and especially thyroid disease, which may be associated with autoimmune diseases (1).

Good practice points:

1. In childhood, it is recommended to evaluate cases at a maximum interval of 3-4 months (ungraded best practice statement).

2. It is recommended that glucocorticoid therapy should be monitored by clinical assessment, including weight gain, growth rate, blood pressure and general well-being of the patient (ungraded best practice statement).

6. Long-term Risks in Treatment

Even if glucocorticoid therapy is optimal, normal circadian rhythm and pulsatile secretion cannot be achieved. Despite adequate glucocorticoid and mineralocorticoid treatment, a significant number of patients continue to have objective or subjective complaints (1). These complaints may be related with decreased function, decreased general perception, feeling unwell, etc., and may be related with under- or overdose of glucocorticoids. Studies into the effects of PAI and long-term glucocorticoid use are generally related to adult CAH cases. Metabolic, cardiovascular, and bone metabolism complications may be observed. It has also been shown that catecholamines and neuropeptides are impaired in PAI (23) and this is associated with cardiovascular variability, hypoglycemia and physical activity in CAH-related PAI (24).

6.1. Growth Suppression and Bone Health

Long-term glucocorticoid usage, especially at supraphysiologic levels, might affect linear development in children and adolescents and may contribute to lower final adult height. In addition, low BMD, an increased risk of osteoporosis, and bone fractures can result because of long-term high-dose glucocorticoid usage. Patients with CAH who are prescribed larger dosages of glucocorticoids to control their adrenal androgen production are at higher risk. Glucocorticoids, which also have a direct resorptive effect on bone, create a negative calcium balance by decreasing calcium absorption from the intestines and increasing calcium excretion from the kidneys. It is important to keep the steroid dose within physiologic limits to ensure normal growth and bone health in children. However, daily glucocorticoid use tends to be higher than total daily endogenous cortisol secretion in healthy people. Most studies of BMD in patients with CAH are limited by small patient numbers, heterogeneous populations and methods, such as age and glucocorticoid regimen. In children and adolescents using glucocorticoids for CAH, there was no evidence of a decrease in height-adjusted BMD measurements regardless of the type of steroid used, duration of use, serum androgen and 17-OHP levels (2,25,26). In a recent cross-sectional randomized controlled study conducted in adults, BMDs of women with CAH and non-CAH PAI were compared after 2 years of glucocorticoid treatment, and it was shown that BMD was lower in those with higher glucocorticoid doses and that glucocorticoid replacement should be performed at the lowest possible dose to maintain bone health (27). Despite the differences between studies, patients with CAH are at risk for osteoporosis at later ages. In adult patients with CAH, it is recommended that BMD measurement be performed in case of higher than average glucocorticoid dose use or non-traumatic bone fracture and then BMD should be measured at 2-5-year intervals (2). To preserve normal development and bone health, it is important to use the lowest effective dose. In high-risk patients, routine monitoring of growth parameters and evaluations of bone health using techniques such as dual-energy X-ray absorptiometry scans may be necessary (1).

6.2. Cardiovascular and Metabolic Risks

Individuals on long-term glucocorticoid medication may experience increased central obesity, dyslipidemia, and

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hypertension, all of which raise the risk of cardiovascular disease. Studies in individuals with CAH have indicated an increased incidence of cardiovascular risk factors, such as high blood pressure and unfavorable lipid profiles, which may contribute to long-term morbidity. In a study including metabolic evaluation, abdominal adiposity was observed in adolescents and young people with CAH in long-term follow-up with a higher rate of proinflammatory visceral adipose tissue increase compared to subcutaneous adipose tissue when compared with age-, gender- and BMI-matched controls (3,28). In a meta-analysis, a higher homeostasis model assessment-insulin resistance (HOMA-IR) value was found in CAH patients compared to controls. However, no significant difference was found in serum fasting blood glucose, insulin levels or lipid levels (3,29). In the same meta-analysis, systolic and diastolic blood pressure were slightly increased (3,29). Although it is difficult to evaluate cardiovascular (CVS) mortality and morbidity in patients, there are a few studies conducted in patients over the age of 50 years (3,30). While normal left ventricular morphology was evaluated in adolescent and adult patients with CAH, mild diastolic dysfunction and impaired exercise performance were found. More studies are needed to evaluate CVS and metabolic side effects (3,31,32).

In the follow-up of patients with PAI, routine monitoring of blood pressure, serum lipid levels, and markers of IR (HOMA-IR and fasting glucose) is advised. To lower these risks, lifestyle interventions including exercise and food adjustments should be promoted.

6.3. Psychological and Cognitive Effects

Long-term exposure to glucocorticoids can affect one's quality of life, mood, and cognitive abilities. Patients on long-term steroid treatment have reported experiencing symptoms such as anxiety, deptression, and trouble concentrating. Although the effects on mental health are frequently underappreciated, they can have a major impact on general wellbeing (3,30). Regular follow-up of patients who have AI should include mental health examination. To treat these symptoms, psychological assistance and, if necessary, pharmaceutical intervention should be taken into account.

6.4. Risk of Adrenal Crisis

The main goal in long-term treatment monitoring should be to use the lowest effective dose of glucocorticoids that prevents adrenal crises, allows adequate growth and adolescent development, and minimizes long-term hazards. Long-term care for children and adolescents with AI should include supportive therapy, customized dose modifications and routine follow-up assessments (3,26).

Patients with AI are nevertheless susceptible to adrenal crisis, even with proper glucocorticoid and mineralocorticoid medication, especially during times of elevated physiological stress, such as illness or surgery. It is important to recognize and treat this potentially fatal situation. It is imperative that patients and caregivers get ongoing education and training on the prevention and management of adrenal crises. In order to notify medical personnel in an emergency, patients should always wear medical identification and patients or their families should be provided with an emergency injection kit (33,34).

Good practice points:

1. In long-term glucocorticoid use, the lowest dose possible to control the disease should be maintained to avoid possible side effects. For bone health, age-appropriate calcium and vitamin D intake and weight-bearing exercises may be recommended in children (ungraded good clinical statement).

2. Chronic use of high-dose glucocorticoids can also lead to bone health complications such as decreased BMD, increased risk of osteoporosis, and bone fractures (2⊕⊕OO).

3. Patients receiving long-term glucocorticoid therapy are at risk for cardiovascular complications, including hypertension, dyslipidemia, and increased central obesity, which may elevate the risk of cardiovascular disease (2⊕⊕OO).

4. Symptoms such as anxiety, depression, and difficulty concentrating have been reported in patients on long-term steroid therapy. The impact on mental health is often under recognized but can significantly affect overall well-being (2⊕⊕OO).

7. Management of Recovery from Adrenal Suppression in Long-term Steroid Use

Synthetic glucocorticoids are widely used in clinical practice for their anti-inflammatory and immunosuppressive effects. One of the possible undesirable side effects of glucocorticoid therapy is the suppression of the hypothalamic-pituitary-adrenal (HPA) axis, corticotrope-releasing hormone (CRH) and ACTH, which may lead to AI. Factors affecting the risk of glucocorticoid-induced AI include the duration, route of administration, dose and strength of glucocorticoid therapy, concomitant drug use affecting metabolism, individual sensitivity and pharmacokinetics of the preparation used. In patients using exogenous glucocorticoids, Cushing syndrome and subsequent glucocorticoid withdrawal syndrome may develop when treatment is reduced (35).

Steroid-related side effects usually require tapering as soon as the disease being treated is under control. To safely terminate long-term steroid therapy, physicians must consider both the recovery of normal cortisol secretion and potential withdrawal symptoms. A careful approach and appropriate patient counseling are necessary during steroid therapy to avoid both recurrent activity of the underlying disease and possible cortisol deficiency due to suppression of the HPA axis. Glucocorticoid therapy should not be completely discontinued until adrenal function is restored. Since it is mainly regulated by the renin-angiotensin system, adrenal glomerulosa function remains normal and salt loss does not occur (35).

The duration of steroid treatment is a critical factor when considering glucocorticoid withdrawal. A few months of treatment will completely suppress the HPA axis but does not cause adrenal atrophy. Years of treatment may result in almost complete atrophy of the adrenal fasciculata/reticularis layers and therefore may cause a withdrawal syndrome lasting months (6).

While adrenal function usually improves rapidly in short-term (< 1 week) high-dose glucocorticoid use, cases of AI have been reported in use lasting more than 7-14 days (36).

Despite the widespread use of steroids, the literature guiding the management of steroid-dependent AI originate from studies that are very heterogeneous in design, patient population, sample size, types and regimens of glucocorticoids used, and assessment of adrenal function. Therefore, the level of evidence is low, leading to differences in management between different centers and physicians (35,36,37,38,39).

Glucocorticoids that enter the systemic circulation directly or survive first-pass metabolism after gastrointestinal absorption cause a negative feedback effect on CRH-producing neurons and corticotrope cells in the pituitary. This leads to decreased adrenal cortisol production and adrenal cortical hypoplasia and atrophy after long-term exposure (35).

Systemic steroids, especially those with longer half-life and higher potency, are more likely to cause AI than other routes of administration due to direct feedback suppression of CRH and ACTH on the HPA axis. Treatment with bedtime glucocorticoid administration and multiple divided doses are more likely to cause AI by affecting circadian ACTH release. The administration of glucocorticoid therapy every other day carries a lower risk of AI than daily high-dose therapy.

A recent analysis of medical records from primary and secondary care in the UK reported an increased incidence of AI and ICS among chronic oral glucocorticoid users (mainly prednisolone) with higher daily and cumulative doses. Although these data provide a good population-based estimate of the risk of ICS associated with glucocorticoid use, it is difficult to determine this risk at the individual level (35,36,37,38). Some studies have suggested a direct relationship between the dose and duration of systemic glucocorticoid treatment and the likelihood of AI, but the evidence has been reported to be limited (36,39).

In a meta-analysis of 10 studies including 298 children with acute lymphoblastic leukemia, it was shown that AI occurred in almost all patients treated with high-dose systemic glucocorticoid therapy for less than two months. In most children, adrenal function returned within a few weeks, but it was reported that AI persisted in 11% of those who underwent ACTH stimulation testing at 12 to 34 weeks (40).

The duration of steroid treatment is critical in the development of glucocorticoid withdrawal syndrome. When tapering pharmacologic doses of steroids, rapidly reducing the dose to "physiologic" maintenance doses can cause problems. Even with physiologic replacement, patients receiving pharmacologic doses of glucocorticoids will experience steroid withdrawal syndrome. Long-term steroid therapy inhibits glucocorticoid receptor synthesis and thus may cause steroid withdrawal syndrome, with a subphysiologic cellular response, even at physiologic concentrations of glucocorticoids. It is therefore necessary to gradually reduce the dose of the drug from the outset. A very important point to be considered is that AI is not clinically significant in patients who do not show obvious signs and symptoms of cortisol deficiency (6,35,37).

In a study evaluating the risk of AI in glucocorticoid users, symptoms consistent with AI were reported in only 2% of patients, but an inadequate cortisol response was obtained in 19% of patients with dynamic testing. Notably, although symptom assessment was not standardized in this study, these data suggest that patients with symptoms are only the tip of the iceberg. Furthermore, patients with AI can often present with non-specific signs and symptoms that can be attributed to other causes. More importantly, in an undiagnosed and untreated patient with AI, events such as infection and surgery may trigger a life-threatening adrenal crisis due to the inability to generate an adequate stress response (41).

Cases of symptomatic glucocorticoid-dependent AI and ICS have also been associated with inhaled glucocorticoids. Most cases have been reported in patients treated with ≥500 µg/day of fluticasone propionate. A retrospective

cohort study in Canada reported 392 hospitalizations for AI over a 15-year period among adults treated with inhaled glucocorticoids. Patients with higher daily doses (≥1000 µg/day) or cumulatively high doses of steroids (>157000 µg/year) were found to have almost twice the risk of hospitalization compared to those with lower exposures (42). In a cohort of 2.4 million people in a review of national medical records in the United Kingdom, only 31 cases of AI associated with inhaled glucocorticoids were identified. Given the widespread use of inhaled glucocorticoids, the low rates of AI observed in these studies suggest that this problem is largely unrecognized or underreported (43).

Steroid tapering protocols are empirical. Their success is determined by the duration and pattern of treatment and individual patient responses. Steroid therapy may be more easily discontinued in patients receiving every other day treatment than in those receiving a long-acting and potent glucocorticoid, particularly dexamethasone, on a daily basis. In patients on long-standing treatment, a 25% reduction, usually weekly, is recommended and a taper protocol of 8 to 10 weeks may be needed. An appropriate tapering scheme should be made based on the size of the tablets available, and treatment should be discontinued after reduction to a dose equivalent to 5 mg/day of hydrocortisone, and adrenal function assessed. In a patient undergoing glucocorticoid taper, the approach is to treat with equivalent hydrocortisone doses of 5 mg for at least 1 to 4 weeks, then discontinue for 24 hours and assess the HPA axis. This assessment is done by measuring morning cortisol levels, synthetic ACTH stimulation tests and, less commonly used, nocturnal metyrapone testing and insulin tolerance tests. Even after successful cessation of treatment, the HPA axis is not completely normal. As in patients successfully treated for Cushing's disease, the HPA axis may fail to respond to severe stress for 6 to 12 months after discontinuation of long-term, high-dose glucocorticoid therapy (6,35).

Methods are described at Part 1 (Clinical, Biochemical and Molecular Characteristics of Congenital Adrenal Hyperplasia Due to 21-hydroxylase Deficiency) of this supplement (44).

Good practice point:

1. In steroid use for more than 14 days due to systemic disease, it is recommended to taper and discontinue the drug (2⊕⊕OO).

Footnotes

Authorship Contributions

Design: Fuat Buğrul, Nurhan Özcan Murat, Data Collection or Processing: Fuat Buğrul, Nurhan Özcan Murat, Analysis or Interpretation: Fuat Buğrul, Nurhan Özcan Murat, Literature Search: Fuat Buğrul, Nurhan Özcan Murat, Writing: Fuat Buğrul, Nurhan Özcan Murat.

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