REVIEW

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

Mehmet İsakoca[1], Şenay Erdeve[1], Semra Çetinkaya[2]

[1]Ankara Etlik City Hospital, Clinic of Pediatric Endocrinology, Ankara, Turkey

[2]University of Health Sciences Turkey, Dr. Sami Ulus Child Health and Diseases Training and Research Hospital, Clinic of Pediatric Endocrinology, Ankara, Turkey

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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Address for Correspondence: Mehmet İsakoca MD, Ankara Etlik City Hospital, Clinic of Pediatric Endocrinology, Ankara, Turkey
E-mail: isakocafatih@yahoo.com **ORCID:** orcid.org/0000-0002-8496-4696

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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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