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Single-Center Experience in Five Patients Diagnosed with Lipoid Congenital Adrenal Hyperplasia due to *Steroidogenic Acute Regulatory Protein (STAR)* Gene Variants: A Rare Cause of Adrenal Insufficiency

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ABSTRACT

Lipoid congenital adrenal hyperplasia (LCAH) is the rarest and most severe form of congenital adrenal hyperplasia (CAH), characterized by impaired adrenal and gonadal steroidogenesis. This case series presents our clinical experience with five pediatric patients diagnosed with LCAH due to mutations in the *steroidogenic acute regulatory protein (STAR)* gene. Clinical and laboratory data from five patients diagnosed with LCAH and followed at the Pediatric Endocrinology Clinic of Akdeniz University Faculty of Medicine Hospital between January 2020 and May 2025 were retrospectively reviewed. The patients, aged 7 days to 6 months, all exhibited a female phenotype and presented with vomiting and feeding difficulties. Three showed hyperpigmentation. Severe hyponatremia, hyperkalemia, elevated adrenocorticotropic hormone and renin activity, and low cortisol were observed. Aldosterone and 17-hydroxyprogesterone were normal; testosterone and precursors were low. Imaging showed bilateral adrenal lipoid infiltration and hyperplasia. Karyotypes included 46,XX (n=3) and 46,XY (n=2). *STAR* gene mutations identified were c.505G>A, c.33del, and c.288G>T. All received hydrocortisone and fludrocortisone and all survived without morbidity. LCAH is a rare genetic disorder that can present with life-threatening adrenal insufficiency. However, as demonstrated in these cases, early diagnosis and appropriate treatment can lead to excellent outcomes.

Keywords: lipoid congenital adrenal hyperplasia, steroidogenic acute regulatory protein, adrenal insufficiency, disorders of sex development

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What is already known on this topic?

Lipoid congenital adrenal hyperplasia (LCAH) represents the most severe and rarest form of congenital adrenal hyperplasia, resulting from mutations in the *steroidogenic acute regulatory protein (STAR)* gene. The disorder is characterized by impaired adrenal and gonadal steroidogenesis, leading to life-threatening adrenal insufficiency and disorders of sex development. Timely diagnosis and glucocorticoid/mineralocorticoid replacement therapy are essential to prevent morbidity and mortality.

What this study adds?

This case series provides detailed clinical, biochemical, radiological, and genetic data from five pediatric patients with genetically-confirmed, classical LCAH followed at a single tertiary care center. It describes the presence of three distinct homozygous pathogenic variants in the *STAR* gene (c.505G>A, c.33del, and c.288G>T), expanding the genotypic spectrum observed in LCAH. The case series illustrates that in LCAH, despite the severity of the condition, early recognition and appropriate hormone replacement therapy can result in favorable clinical outcomes, including survival without morbidity. These cases also reiterate the importance of multidisciplinary care and individualized management, particularly in patients with disorders of sex development.

Introduction

Lipoid congenital adrenal hyperplasia (LCAH, OMIM #201710) is the most severe and rarest form of congenital adrenal hyperplasia (CAH), characterized by impaired synthesis of all adrenal and gonadal steroid hormones (1,2). The most common cause is mutations in the gene encoding the steroidogenic acute regulatory (STAR) protein, which plays a critical role in intracellular cholesterol transport for steroid hormone synthesis.

In classical LCAH, patients typically present with severe adrenal insufficiency within the first few months of life, although symptoms may occasionally appear in later infancy. Common presenting features include vomiting, diarrhea, hyponatremia, hyperkalemia, metabolic acidosis, and hypoglycemia. If left untreated, the condition can be fatal. However, survival into adulthood is possible with early and appropriate mineralocorticoid and glucocorticoid replacement therapy (3,4,5).

Affected 46,XY individuals generally present with female external genitalia due to impaired testicular androgen production (6,7,8). In contrast, 46,XX individuals are born with normal female genitalia and may occasionally experience spontaneous pubertal development. Unlike the adrenal and testicular steroidogenic tissues, the fetal ovary lacks significant steroidogenic enzyme activity and remains unstimulated until puberty. As a result, cholesterol esters do not accumulate during infancy, and ovarian damage is initially avoided (8,9). Consequently, affected 46,XX females may develop secondary sexual characteristics and experience menstrual bleeding. However, over time, progressive accumulation of cholesterol esters in the ovaries leads to the loss of follicular steroidogenic capacity, resulting in anovulatory cycles due to insufficient progesterone synthesis. Eventually, patients develop progressive hypergonadotropic hypogonadism in adolescence or adulthood (10,11).

Defects in either *steroidogenic acute regulatory protein* (*STAR*) or *CYP11A1* (which encodes P450scc) disrupt the initial steps of steroidogenesis, leading to the clinical picture of LCAH (7). Steroid biosynthesis begins with cellular uptake of low-density lipoprotein-derived cholesterol (8,10,12). STAR mediates cholesterol transport into the mitochondria, where it is converted into pregnenolone by the P450scc enzyme (2,6,8,10,12,13). The pathophysiology of LCAH has been explained by a "two-hit" model. The first hit involves impaired cholesterol transport due to STAR mutations. The second hit results from progressive cellular damage caused by the accumulation of cholesterol esters and toxic cholesterol oxidation products within lipid droplets (6,8,13). Decreased cortisol production weakens negative feedback inhibition on the pituitary gland, leading to increased adrenocorticotropic hormone (ACTH) secretion. Elevated ACTH levels contribute to hyperpigmentation and adrenal cortical hyperplasia (14).

The human *STAR* gene is located on chromosome 8p11.2 and consists of seven exons (15,16). Most mutations that cause classical LCAH are located in the C-terminal region, between exons 5 and 7, which encodes the STAR-associated lipid transfer domain. These mutations usually result in no measurable STAR activity and are found in either homozygous or compound heterozygous states involving mutations with similarly reduced function (8). To date, more than 40 pathogenic STAR mutations associated with classical LCAH have been described (8,12,17,18). Although STAR mutations have been identified in diverse ethnic groups, they are more prevalent in Japan, Korea, and certain isolated populations. In Korea and Japan, the most common variant protein is p.Gln258X, accounting for 92.3% and 70% of cases, respectively. The p.Leu260Pro mutation is prevalent in Switzerland, p.Arg182His in Eastern Saudi Arabia, and p.Arg182Leu among Palestinian Arabs (7,8,19,20).

Mutations in *CYP11A1* can also result in a clinical phenotype similar to that of STAR mutations, due to P450scc enzyme deficiency, although adrenal hyperplasia is typically absent in these cases. While adrenal enlargement is a hallmark of classical LCAH, small adrenals have also been reported and are not pathognomonic (18,21).

A milder form of LCAH, referred to as non-classical or atypical LCAH, is associated with STAR mutations that partially preserve protein function (10,22). In such cases, mineralocorticoid secretion is less severely affected, resulting in a milder adrenal insufficiency that manifests later in life. Individuals with a 46, XY karyotype may present with mild disorders of sex development, such as hypospadias and/or micropenis, or even with entirely normal male external genitalia (7,22,23,24,25). Adrenal hyperplasia is typically absent in these patients (22,23).

Early diagnosis, appropriate hormone replacement therapy, close monitoring of sex development, and genetic counseling for the family are essential components of the management of this disorder. This case series presents our experience in the diagnosis, management, and follow-up of five patients with LCAH caused by mutations in the *STAR* gene.

Methods

This retrospective, single-center case series included five patients who were diagnosed with LCAH and followed at the Pediatric Endocrinology Department of Akdeniz University Faculty of Medicine Hospital between January 2020 and May 2025. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine (approval no: KAEK-629, date: 31.07.2025). Written informed consent was obtained from the parents of all participants.

Clinical and laboratory data were retrieved retrospectively through a review of the hospital's electronic medical records system. The collected data included demographic information, presenting symptoms, physical examination findings, hormonal profiles, adrenal imaging results, and genetic analyses.

Laboratory parameters assessed in the study included serum electrolytes, bicarbonate, glucose, blood gas pH, serum cortisol, ACTH, aldosterone, plasma renin activity (PRA), 17-OHP, follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (T), estradiol (E2), dehydroepiandrosterone sulfate (DHEA-S), androstenedione, thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4).

Chromosomal analysis and pathogenic variants of the *STAR* gene were investigated using DNA extracted from peripheral blood samples. Genetic testing was performed using a multi-gene panel targeting exon regions, and analyzed via next-generation sequencing. Variant analysis was conducted using Seq Analysis software (version 15.p; JSI Medical Systems, Ettenheim, Germany) and the Ensembl annotation database (26). The pathogenicity of the variants was evaluated according to the guidelines of the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) (27).

In addition, imaging findings obtained from pelvic ultrasonography (USG) and magnetic resonance imaging (MRI), performed to assess internal genital structures and adrenal morphology, were also included in the study.

Case Reports

Case 1

A 49-day-old infant presented with vomiting, diarrhea, and difficulty in feeding. Blood pressure was low and tachycardia was present (Table 1). System examinations were normal, external genitalia were phenotypically female with separate urethral and vaginal openings. Birth and family histories are given in Table 2. Laboratory tests revealed hyponatremia (Na 125 mEq/L), hypochloremia (Cl 84 mEq/L), hyperkalemia (K 6.5 mEq/L), and hypoglycemia (38 mg/dL). Complete blood count, renal and liver function tests, infection parameters, and urinalysis were within normal limits. ACTH levels and PRA were markedly elevated. Serum cortisol levels were low, while 17-OHP levels were within the normal range. Hormonal values at admission are summarized in Table 3. The patient was admitted to the intensive care unit with a preliminary diagnosis of primary adrenal insufficiency. Treatment included intravenous dextrose bolus, supraphysiological doses of hydrocortisone (100 mg/m²/day), sodium-rich intravenous fluid replacement, and fludrocortisone. USG revealed absence of uterus and ovaries, with a hyperplastic appearance of the adrenal glands (Table 2). Pelvic MRI showed no Müllerian structures or gonads. Chromosomal and fluorescence in situ hybridization (FISH) analysis revealed a 46,XY SRY (+) normal male karyotype. Genetic analysis identified a homozygous pathogenic variant *c.288G>T* (p.Trp96Cys) in the *STAR* gene (Table 1).Multidisciplinary council evaluation led to cystoscopy and vaginoscopy, showing a normal urethra and a vaginal length of 3 cm but the cervix was not visualized. Diagnostic laparoscopy revealed absence of uterus and fallopian tubes, with bilateral vas deferens, epididymis, and testes present. Bilateral gonadal biopsy was consistent with immature testicular tissue. A diagnosis of classic LCAH was established. At the last follow-up at 3.5 years old, the patient's height was 94.1 cm [-1.2 standard devitaion score (SDS)], weight 14 kg (-0.6 SDS), and body mass index (BMI) 15.8 kg/m² (0.26 SDS). The patient remains on hydrocortisone (10 mg/m²/day) and fludrocortisone (0.1 mg/day) treatment with stable clinical status and normal electrolytes. Psychological follow-up is ongoing, and the patient continues to be raised as female. Future multidisciplinary assessments are planned.

Table 1. Genetic and clinical characteristics of five patients with lipoid congenital adrenal hyperplasia

	Case 1	Case 2	Case 3	Case 4	Case 5
City of origin	Silopi/Şırnak/ Türkiye	Yüreğir/Adana/ Türkiye	Elmalı/Antalya/ Türkiye	Yüreğir/Adana/Türkiye	Elmalı/Antalya/ Türkiye
Karyotype	46,XY	46,XX	46,XX	46,XX	46,XY
STAR gene variant	c.288G>T (p.Trp96Cys) homozygous pathological variant	c.505G>A (p.GLu169Lys) homozygous pathological variant	c.33 del (p.Ser12Alafs*9) homozygous pathological variant	c.505G>A (p.GLu169Lys) homozygous pathological variant	c.33 del (p.Ser12Alafs*9) homozygous pathological variant
Age of onset (days)	49	7	60	10	180
Vital signs					
Blood pressure (mmHg)	50/28	35/20	55/34	40/25	50/30
Heart rate (per minute)	162	184	168	190	162
Respiratory rate (per minute)	38	44	40	68	30
Oxygen saturation (%)	99	98	98	85	100
Temperature (C°)	36.5	36.6	38.6	38.2	36.6
Clinical findings	Inadequate oral intake, vomiting, diarrhea	Skin hyperpigmentation, inadequate oral intake, vomiting, icterus	Skin hyperpigmentation, inadequate oral intake, vomiting	Inadequate oral intake, vomiting, dyspnea, tachypnea	Skin hyperpigmentation, inadequate oral intake, vomiting, coma
Genital examination EGS	Normal female EGS: 0	Female genitalia, mild posterior labial synechia EGS: 1.5	Normal female EGS: 0	Normal female EGS: 0	Female genitalia, bilateral inguinal palpable gonads EGS: 1

STAR: steroidogenic acute regulatory; EGS: external genitalia scores

Table 2. Perinatal history, family background, ımaging findings, and treatment characteristics in patients with lipoid congenital adrenal hyperplasia

	Case 1	Case 2	Case 3	Case 4	Case 5
Perinatal history					
Birth weight (g, percentile)	3750 (85^{th})	3000 (40^{th})	2800 (45^{th})	3050 (25^{th})	3530 (45^{th})
Birth length (cm, percentile)	51 (75^{th})	49 (50^{th})	49 (65^{th})	50 (50^{th})	51 (50^{th})
Head circumference (cm, percentile)	36 (85^{th})	34 (40^{th})	34 (60^{th})	35 (60^{th})	35 (45^{th})
Gestational age (w)	38	38	37	40	41
Mode of delivery	NSVY	C/S	C/S	NSVY	NSVY
Newborn CAH screening (Heel prick)	Normal	Normal	Normal	Normal	Normal
Family history					
Parental consanguinity	No	No	No	Second-degree cousins	Second-degree cousins
CAH/SIDS/DSD	None	+/−/−	None	+/−/−	None
Adrenal imaging	Adrenolipoid hyperplasia	Adrenolipoid hyperplasia	Adrenolipoid hyperplasia	Adrenolipoid hyperplasia	Adrenolipoid hyperplasia
Maintenance treatment	Hydrocortisone (10 mg/m^2/d), fludrocortisone (0.1 mg/d)	Hydrocortisone (10 mg/m^2/d), fludrocortisone (0.1 mg/d)	Hydrocortisone (8 mg/m^2/d), fludrocortisone (0.1 mg/d)	Hydrocortisone (8 mg/m^2/d), fludrocortisone (0.1 mg/d)	Hydrocortisone (12 mg/m^2/d), fludrocortisone (0.2 mg/d)

CAH: congenital adrenal hyperplasia; SIDS: sudden infant death syndrome; DSD: disorders of sex development; g: gram; cm: centimeters; w: weeks; d: day; NSVY: normal spontaneous vaginal delivery; C/S: Cesarean section; mg: milligram; m2: square meters; +: present; −: absent

Table 3. Biochemical results and hormonal profiles of patients with lipoid congenital adrenal hyperplasia at ınitial presentation

Laboratory test results	Case 1	Case 2	Case 3	Case 4	Case 5	Reference range
Serum Sodium (mmol/L)	125	126	126	124	95	135-145
Serum Potassium (mmol/L)	6.5	7.0	8.0	7.8	7.2	3.5-5.1
Serum Cloride (mmol/L)	84	88	90	85	68	98-107
Serum Glucose (mg/dL)	38	70	82	76	45	60-100
Hormones						
ACTH (ng/L)	1588	>2000	>2000	>2000	>2000	7.2-63.3
Cortisol (ug/dL)	0.31	0.63	1.0	0.89	0.63	Newborn: 2.0-11 Infant: 2.8-23
PRA (ng/mL/h)	11	18.7	10.9	10.7	7.7	0.1-6.5
17-OHP (ng/mL)	0.1	0.23	0.13	0.80	0.17	0.10-1.78
Aldosterone (ng/dL)	4.2	11.9	6.5	13.1	6.7	7-30
Testosterone (ng/dL)	<0.03	<0.03	<0.03	<0.03	<0.03	0.14-0.76
Androstenedione (ng/mL)	<0.02	1.25	0.26	0.30	<0.02	0.3-3.2
DHEA-S (ug/dL)	<0.2	1.1	5.28	4.83	<0.2	31.6-431
TSH (mIU/L)	2.43	3.70	3.22	2.85	3.64	0.72-11
fT3 (ng/L)	3.42	3.45	3.82	2.96	3.52	1.95-6.04
fT4 (ng/dL)	1.66	1.21	1.53	1.18	1.34	0.89-2.2
LH (IU/liter)	1.25	1.34	1.94	1.26	1.17	
FSH (IU/liter)	9.2	9.5	7.87	6.83	4.27	
Estradiol	<5	<5	<5	<5	<5	

ACTH: adrenocorticotropic hormone; PRA: plasma renin activity; 17-OHP: 17-hydroxyprogesterone; DHEA-S: dehydroepiandrosterones sulfate; TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine.

Case 2

A 7-day-old neonate presented with pathological jaundice, vomiting, and difficulty in feeding. Systemic examinations were normal. The external genitalia were phenotypically female. The patient had significant hyperpigmentation compared to family members. Scleral icterus was evident. Blood pressure was low and tachycardia was noted, with other vital signs within normal limits for age (Table 1). Birth and family histories are given in Table 2. Phototherapy was planned and the patient was admitted to the neonatal intensive care unit. Laboratory tests revealed hyponatremia (Na 126 mEq/L) and hyperkalemia (K 7 mEq/L). Complete blood count, renal and liver function tests, infection parameters, and urinalysis were normal. Both ACTH and PRA were elevated, while serum cortisol was low and 17-OHP was normal. Additional hormone levels are listed in Table 3. Treatment included supraphysiological doses of hydrocortisone, sodium-rich intravenous fluid replacement, and fludrocortisone. USG showed uterus and bilateral ovaries, with bilateral adrenal hyperplasia (Table 2). Chromosomal analysis revealed a 46,XX normal female karyotype. Genetic testing identified a homozygous pathogenic variant *c.505G>A* (p.Glu169Lys) in the *STAR* gene, confirming classic LCAH diagnosis (Table 1). Under hydrocortisone (10 mg/m²/day) and fludrocortisone (0.1 mg/day) treatment, the patient's skin hyperpigmentation significantly decreased. Clinical condition remained stable with regular follow-up.

Case 3

A 2-month-old infant presented to an external center with vomiting and difficulty in feeding and was hospitalized with a preliminary diagnosis of gastroenteritis. The patient appeared severely dehydrated, characterized by dry mucous membranes, prolonged capillary refill time (4 seconds), and decreased skin turgor due to fluid loss. External genitalia were phenotypically female with double openings and mild posterior labial synechia. The patient exhibited significant hyperpigmentation compared to family members. Birth and family histories are given in Table 2. Due to clinical deterioration and resistant hyponatremia (126 mEq/L) and hyperkalemia (8.0 mEq/L), the patient was referred to our center for further evaluation and treatment. Leukocytosis (26,320/mm³) and elevated C-reactive protein (48 mg/L, normal: 0-5) were present. Laboratory results showed ACTH and PRA elevated, low cortisol and normal 17-OHP levels. Additional hormonal values are shown in Table 3. On admission to the intensive care unit, the patient presented with hypotension, tachycardia, and fever, while other vital signs were within normal

limits for age (Table 1). Treatment included supraphysiological doses of hydrocortisone, sodium-rich intravenous fluid replacement, fludrocortisone, and antibiotic therapy (ampicillin and cefotaxime). USG revealed uterus and bilateral ovaries with bilateral adrenal hyperplasia (Table 2). Chromosomal analysis was 46,XX female karyotype. Genetic testing identified a homozygous pathogenic *c.33 deletion* (p.Ser12Alafs*9) variant in the *STAR* gene, confirming LCAH diagnosis (Table 1). The patient continued hydrocortisone (8 mg/m²/day) and fludrocortisone (0.1 mg/day) treatment. Clinical status remained stable with regular follow-up.

Case 4

A 10-day-old neonate presented to the emergency department with fever, tachypnea, dyspnea, desaturation, vomiting, and difficulty in feeding. On physical examination, the patient demonstrated significant intercostal retractions, with rales and rhonchi audible on auscultation. The external genitalia were phenotypically female (Table 1). Birth and family histories are given in Table 2. The patient was admitted to neonatal intensive care with a diagnosis of congenital pneumonia. Hyponatremia (Na 124 mEq/L) and hyperkalemia (K 7.8 mEq/L) were detected. Leukocytosis (24,000/mm³) and elevated C-reactive protein (29 mg/dL, normal: 0-5) were present. Other laboratory results showed ACTH and PRA elevated, low cortisol and normal 17-OHP levels. Additional hormonal values are given in Table 3. Chest X-ray showed bilateral pneumonic infiltrates. The patient developed respiratory failure with severe acidosis on blood gas analysis and received intravenous antibiotics (ampicillin and cefotaxime) and five days of non-invasive mechanical ventilation. Treatment with supraphysiological hydrocortisone, sodium-rich intravenous fluids, and fludrocortisone was started (Table 2). After two weeks of neonatal intensive care, acute phase reactants and electrolyte imbalances improved and the patient was discharged. USG showed uterus and bilateral ovaries, and adrenal glands appeared bilaterally hyperplastic. Chromosomal analysis revealed a 46,XX normal female karyotype. Genetic testing showed a homozygous pathogenic *c.505G>A* (p.Glu169Lys) variant in *STAR* gene, confirming LCAH diagnosis (Table 1). The patient's parents of this case were second degree cousins and were related to the father of Case 2. Segregation analysis revealed heterozygous variants in both parents. The patient is on hydrocortisone (8 mg/m²/day) and fludrocortisone (0.1 mg/day) treatment with normal growth and development at last follow-up at age 5 years. Height was 100.2 cm (0.13 SDS), weight 19 kg (0.16 SDS), BMI 15.6 (0.15 SDS). The patient is actively participating in ballet and regular swimming exercises.

Case 5

A 6-month-old infant was referred to our center with difficulty in feeding, vomiting, and coma. Blood pressure was low and tachycardia was present, while other vital signs were within age-appropriate limits (Table 1). Systemic examinations were unremarkable. The external genitalia were phenotypically female, with palpable bilateral inguinal gonads, presence of two urogenital openings, and skin hyperpigmentation. Birth and family histories are given in Table 2. Laboratory tests showed severe hyponatremia (Na 95 mEq/L), hyperkalemia (K 7.2 mEq/L), and hypoglycemia (45 mg/dL). Complete blood count, renal and hepatic function tests, infection markers, and urinalysis were all within normal limits. Laboratory testing revealed markedly elevated ACTH and PRA levels. Serum cortisol was decreased, while 17-OHP levels remained within the normal range. Hormonal values on admission are summarized in Table 3. Treatment included intravenous dextrose bolus, supraphysiological hydrocortisone, sodium-rich intravenous fluids, and fludrocortisone. USG did not reveal uterus or ovaries, however bilateral inguinal masses consistent with testes were identified. Adrenal MRI showed bilateral adrenal lipoid infiltration and hyperplasia (Table 2). Chromosomal/FISH analysis confirmed 46,XY SRY(+) normal male karyotype. Next-generation sequencing identified a homozygous pathogenic *c.33 deletion* (p.Ser12Alafs*9) variant in the *STAR* gene (Table 1). Classic LCAH diagnosis was made.The patient continued mineralocorticoid and glucocorticoid replacement therapy. Segregation analysis revealed heterozygous variants in both parents. The parents of this case and Case 3 originate from the same district, suggesting a possible founder effect. Vaginoscopy and cystoscopy revealed intact anatomical structures. Diagnostic laparoscopy showed absence of uterus and ovaries. Bilateral inguinal gonads were visualized and biopsy confirmed immature testicular tissue. No significant hormonal response was observed on human chorionic gonadotropin (hCG) stimulation test. The multidisciplinary council decision, based on psychological evaluation and family preference, was to raise the patient as female. Bilateral gonadectomy was performed at 4 years of age. The patient showed no complications during follow-up, with neurodevelopment appropriate for age. At last follow-up at 4.5 years, height was 103.5 cm (-0.55 SDS), weight 17 kg (-0.13 SDS), BMI 15.8 (0.33 SDS). The patient continues hydrocortisone (12 mg/m²/day) and fludrocortisone (0.2 mg/day) treatment and has ongoing psychological monitoring.

Discussion

In this case series, we present the clinical management experience of five pediatric patients diagnosed with LCAH. In order to contribute to the understanding of the natural history of LCAH, the initial presentations, clinical characteristics, diagnostic processes, and treatment courses of these cases are described in detail.

CAH encompasses a group of autosomal recessive disorders characterized by enzymatic defects in steroidogenesis. LCAH represents the most severe form of CAH due to disruption of the initial step of steroid biosynthesis (7). Since all steps of steroidogenesis are affected, accumulation of steroid hormone precursors does not occur. Therefore, as observed in our series, newborn screening results are usually negative (21). Mutations in the *STAR* gene demonstrate a broad clinical spectrum. Consistent with the literature (8,28), all patients in this case series exhibited vomiting and feeding difficulties; one patient presented in a coma, one with jaundice, another with diarrhea, and one with respiratory distress.While some affected infants exhibit immediate signs of mineralocorticoid and glucocorticoid deficiency, others may remain asymptomatic for several months (8,29). In this case series, two patients presented during the neonatal period, whereas the remaining three were admitted with manifestations of adrenal crisis in early infancy. The latest presenting case (Case 5) survived without hormone replacement therapy until six months of age. Similarly, Bose et al. (8) reported a patient remaining asymptomatic up to six months without hormonal intervention. The ability of some LCAH patients to survive for several months without treatment is attributed to the persistence of normal placental steroidogenesis (8). Severe electrolyte disturbances, including hyponatremia, hypochloremia, and hyperkalemia, are commonly observed in patients with classic LCAH, as demonstrated in our series. Signs of adrenal insufficiency, such as hypoglycemia and hypotension, may also be evident (8,28). In this case series, all patients were hypotensive at initial presentation, with two exhibiting hypoglycemia. In non-classic LCAH cases, salt loss is either delayed in onset or minimal to absent (22).

Review of the literature reveals that patients with LCAH, exhibit elevated plasma ACTH and renin levels, similar to our case series, whereas serum cortisol and testosterone levels are variable (1,8). Due to high intrauterine ACTH exposure, hyperpigmentation is an expected finding, though it is not present in all cases (8). Zheng et al. (30) reported hyperpigmentation in 28 of 30 classic LCAH patients. Likewise, the study of Bose et al. (8) which included 15 LCAH cases from 10 countries, documented hyperpigmentation in 13 patients. In contrast, only three patients in our series exhibited notable skin hyperpigmentation compared to their parents. This variation may be attributable to inter-individual differences in melanocyte number and structure, as well as genetic and structural factors.

As expected in classic LCAH, two of our patients with male karyotypes presented with fully female external genitalia. On physical examination, additional findings included mild posterior labial synechia in Case 1 and palpable bilateral inguinal gonads in Case 5. However, in non-classic LCAH patients with a 46,XY karyotype, external genitalia may be completely male-typical or mildly affected (22).

While most LCAH cases are caused by variants in the *STAR* gene, mutations in the *CYP11A1* gene are a much rarer cause (12,31,32). The incidence of this disorder is low, with only approximately 200 cases harboring *STAR* gene variants reported worldwide (33). The *STAR* gene variants identified in our patients have been previously reported as pathogenic in association with LCAH, and all cases were classified as classic LCAH.

The homozygous pathogenic variant *c.288G>T* (p.Trp96Cys) found in Case 1 has also been described in a Portuguese infant presenting with adrenal crisis at two months, normal female genitalia, and a 46,XY karyotype (34). The *c.505G>A* (p.Glu169Lys) variant identified in Cases 2 and 4 has been clearly associated with LCAH in the study by Yüksel et al. (35). The homozygous *c.33 deletion* (p.Ser12Alafs*9) observed in Cases 3 and 5 was included among LCAH-related variants in a national study reporting rare primary adrenal insufficiency cases by Guran et al. (36).

In 46,XY patients harboring pathogenic STAR variants, impaired fetal testicular steroidogenesis results in normal female external genitalia (8). Since Müllerian structures are absent on pelvic imaging, the diagnosis in 46,XY individuals is more likely (1). Consistent with this, pelvic USG performed in Cases 1 and 5 at presentation did not reveal Müllerian structures. Therefore, even prior to genetic results, *STAR* gene mutation, *CYP11A1* mutation, and P450 oxidoreductase deficiency were considered highly probable differential diagnoses.

All cases exhibited adrenal enlargement on imaging, consistent with classic LCAH. Phadte et al. (6) performed a systematic review of 292 cases with classic and non-classic LCAH and demonstrated significantly more pronounced adrenal hyperplasia in classic LCAH patients, who also presented with earlier and more severe clinical features. Thus, the degree of adrenal hyperplasia may serve as a valuable marker of disease severity (6).

In our case series, all patients presented with adrenal crisis and were initially managed with an intravenous bolus of hydrocortisone (100 mg/m²/day) in combination with sodium-rich intravenous fluid replacement. Maintenance therapy was subsequently initiated. All patients received oral fludrocortisone (100-200 µg/day) along with additional supportive measures when clinically indicated. Similar management strategies for adrenal insufficiency in LCAH have been reported in the literature (28,30).

According to the Diagnosis and Treatment of Primary Adrenal Insufficiency guidelines by Bornstein et al. (37), the recommended initial treatment for pediatric patients presenting with adrenal insufficiency consists of intravenous hydrocortisone at 50-100 mg/m²/day, oral fludrocortisone at 100 µg/day, and sodium-rich intravenous fluids containing dextrose. Consistent with this, the Turkish Neonatal and Pediatric Endocrinology and Diabetes Society's consensus statement also advises hydrocortisone

replacement at 50-100 mg/m²/day for infants presenting with adrenal crisis (38).

Zhang et al. (28) described a patient with LCAH who was started on supraphysiological doses of intravenous hydrocortisone, tapered over three days (200 mg/day, 100 mg/day, and 50 mg/day), followed by maintenance therapy with oral prednisone (28). In our series, maintenance therapy consisted of hydrocortisone at 8-12 mg/m²/day, divided into three doses, in combination with 100-200 µg/day of fludrocortisone.

Similarly, in a report of three Chinese patients with LCAH harboring *STAR* gene variants, supraphysiological doses of intravenous hydrocortisone and sodium-rich intravenous fluids were initially administered, followed by hydrocortisone replacement at 10-14 mg/m²/day (7). Çamtosun and Sangün (39) also recommended maintenance hydrocortisone therapy at 8-12 mg/m²/day, divided into three doses. In a case reported by Bizzarri et al. (1) involving an Italian infant with LCAH, high-dose intravenous hydrocortisone and rehydration were provided until clinical stabilization was achieved, after which maintenance therapy with 16 mg/m²/day of hydrocortisone and 100 µg/day of fludrocortisone was continued.

Conclusion

Patients with classical LCAH typically present in early infancy with symptoms of primary adrenal insufficiency and female external genitalia. Due to the defect occurs at the first step of steroidogenesis, cortisol precursors do not accumulate, making detection by CAH newborn screening programs very unlikely. However, when identified early and treated with appropriate hormone replacement therapy, patients typically achieve favorable outcomes, including no recurrent adrenal crises, appropriate growth, development, and neurodevelopment progression. Genetic counseling for families and comprehensive multidisciplinary monitoring of LCAH patients, especially those with a 46,XY karyotype presenting with disorders of sex development, are essential components in effective disease management.

Ethics

Ethics Committee Approval: This study was approved by the by the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine (approval no: KAEK-629, date: 31.07.2025).

Informed Consent: Written informed consent was obtained from the parents of all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Kürşat Çetin, Concept: Kürşat Çetin, Zeynep Donbaloğlu, Hale Tuhan, Design: Kürşat Çetin, Zeynep Donbaloğlu, Hale Tuhan, Data Collection or Processing: Kürşat Çetin, Yasemin Funda Bahar, Ali Tırtar, Mesut Parlak, Analysis or Interpretation: Kürşat Çetin, Zeynep Donbaloğlu, Sezin Yakut Uzuner, Hale Tuhan, Literature Search: Kürşat Çetin, Yasemin Funda Bahar, Ali Tırtar, Mesut Parlak, Writing: Kürşat Çetin, Zeynep Donbaloğlu, Hale Tuhan.

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