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ORIGINAL ARTICLE

Clinical characteristics of female patients diagnosed with congenital adrenal hyperplasia and plastic-esthetic related thoughts: a retrospective study

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Abstract

OBJECTIVES: Congenital adrenal hyperplasia (CAH) is a rare disorder that can cause masculinization of the external genitalia in females, usually evident in neonates. To present a case series of female patients with CAH by summarizing their clinical features and outcomes.

DESIGN: This retrospective study analyzed the clinical data of female patients with CAH admitted to the First Affiliated Hospital of Xiamen University from 1995 to 2019.

MATERIALS AND METHODS: Clinical characteristics, CAH subtype, treatments, and outcomes were summarized from the medical records and analyzed. Follow-up was conducted after drug therapy and surgical treatment and was censored in 2019.

RESULTS: Twenty-one female patients were diagnosed with CAH: 21-hydroxylase deficiency (21-OHD) in 17 patients and 17α-hydroxylase deficiency (17α-OHD) in four patients. The clinical manifestations of 21-OHD were clitoral hypertrophy, pigmentation, male secondary sexual development, genital malformation, sexual precocity, nausea, and vomiting. The clinical manifestations of 17α-OHD were hypertension, feminization, sexual infantilism, and pigmentation. The patients received hormone replacement therapy. When necessary, some patients underwent external genital organ orthomorphia or artificial periodic therapy. Twelve patients were followed up; their sexual development was improved, but seven patients had poor breast development due to late diagnosis and/or poor hormone treatment adherence.

CONCLUSION: Female CAH patients are subject to genital deformities, virilizing signs, breast dysplasia, and other appearance defects. The purpose of this report is to improve plastic and esthetic surgeons' understanding of CAH.

Abbreviations:

11β-OHD	- 11β-hydroxylase deficiency
17α-OHD	- 17α-hydroxylase deficiency
21-OHD	- 21-hydroxylase deficiency
ACTH	- adrenocorticotropic hormone
CAH	- congenital adrenal hyperplasia
CRH	- corticotropin-releasing hormone
CT	- computed tomography
StAR	- steroidogenic acute regulatory protein

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of hereditary diseases caused by various autosomal recessive disorders. CAH is caused by enzyme deficiencies in the adrenal steroidogenesis pathway that results in impaired cortisol biosynthesis, which, depending on the type and severity of the deficiencies, can alter glucocorticoid, mineralocorticoid, and sex steroid production (El-Maouche *et al.* 2017; Claahsen-van der Grinten *et al.* 2022). CAH has an incidence of 1/14,000 to 1/18,000 that varies among regions and races (Speiser *et al.* 2018; Kopacek *et al.* 2017). The most severe form is considered classical CAH, which occurs in two phenotypes: simple virilizing CAH and salt-wasting CAH. Salt-wasting CAH is more severe than simple virilizing and can be life-threatening in newborn infants due to disruption of sodium regulation (Podgórski *et al.* 2018). Girls with classical CAH experience androgen exposure, resulting in masculinization of the external genitalia, usually evident in neonates. Non-classical (or atypical) CAH occurs with lower levels of enzyme impairment, is less severe, and often presents later, even into adulthood (Podgórski *et al.* 2018).

Clinically, CAH is rare and difficult to diagnose due to the different degrees of enzyme deficiency and clinical manifestations. Classical CAH is often identified in neonatal females with ambiguous genitalia, but males show fewer morphological signs at birth (Podgórski *et al.* 2018). Nevertheless, neonatal screening can be effective as the biochemical and genetic background of CAH is well characterized (Török 2019). About 90%-95% of cases are the result of 21-hydroxylase deficiency (21-OHD), while 11β-hydroxylase deficiency (11β-OHD) accounts for up to 8% of cases, and the remaining cases result from 17α-hydroxylase deficiency (17α-OHD), 3β-hydroxysteroid dehydrogenase deficiency, P450 oxidoreductase deficiency, and steroidogenic acute regulatory protein (StAR) deficiencies (Podgórski *et al.* 2018; Merke & Auchus 2020). Both 21-OHD and 11β-OHD influence adrenal steroidogenesis, whereas 3β-hydroxysteroid dehydrogenase or 17α-OHD can also influence gonadal steroidogenesis (Podgórski *et al.* 2018; Claahsen-van der Grinten *et al.* 2022).

Corticosteroid replacement therapy is the primary medical treatment for CAH (Prete *et al.* 2021), while female hermaphroditism can be treated surgically (Sturm *et al.* 2015). Surgical correction of female hermaphroditism is preferred at a young age, before the age of 6 months (Braga & Pippi Salle 2009). If CAH is not treated effectively, sexual development and growth during puberty will be affected, leading to other issues such as female breast dysplasia (Deslauriers *et al.* 2012; Kulshreshtha *et al.* 2012; van de Grift *et al.* 2019). In addition, the requirement for long-term corticosteroid use has many side effects; some of these (such as fat deposits) will influence a patient's appearance, while others (such as slower wound healing, increased bleeding, and venous thrombosis) will increase the surgical risk (Auchus 2015; Prete *et al.* 2021). Therefore, plastic surgeons need to understand the full nature of CAH because they might encounter patients with a need for cosmetic corrections. Any surgical approach needs to be evaluated carefully to ensure that the benefits outweigh the risk of complications.

This report summarizes the clinical characteristics and treatment outcomes of 21 female patients clinically diagnosed with CAH at the First Affiliated Hospital of Xiamen University from 1995 to 2019. The purpose of this report is to improve plastic and esthetic surgeons' understanding of CAH.

MATERIALS AND METHODS

Patients

This retrospective study included female CAH patients admitted to the First Affiliated Hospital of Xiamen University between 1995 and 2019. The inclusion criteria were female inpatients diagnosed with CAH (including patients requiring adjustment of medication type or dose and regular follow-up visits) (Speiser *et al.* 2018). In addition, genetic diagnosis was used to determine the subtype of CAH, including 17α-OHD and 21-OHD (Zhang *et al.* 2009).

Data collection

Patient history, medication history, adrenal computed tomography (CT) scan, and other laboratory tests involved in the diagnosis and treatment of CAH were obtained from the patients' medical records, including hormone levels, genetic analysis, drug therapy (course of treatment, dosage, administration method, *etc.*), and surgical treatment.

Treatment

Patients received hormone therapy (details unknown in most cases). Patients who needed plastic surgery received oral treatment of 25 mg dexamethasone, calcium D1, and Climen (tablets containing estradiol valerate and estradiol valerate in combination with cyproterone) before surgery.

The patients who discontinued drug treatment for 5 days received hydrocortisone per day for one week (50-l00 mg, intravenously): hydrocortisone (l00 mg intravenously) in 250 mL normal saline was given

on day 1; on day 2, the patients received two doses of hydrocortisone (l00 mg intravenously; 60 mg intravenously, 4 p.m.); on days 3-5, the patients received two doses of hydrocortisone (l00 mg intravenously; and 50 mg intravenously, at 4 p.m.); on days 6-7, the patients received hydrocortisone (l00 mg intravenously); from day 8, the patients received dexamethasone (0.375 mg, orally every day, as long-term maintenance dose).

Clinical outcomes

Clinical characteristics, treatment, and outcomes were obtained from the medical records and were summarized. Follow-up was conducted after drug therapy and surgical treatment and was censored in 2019.

Tanner stages were used to evaluate the development of the secondary sexual characteristics (Tanner 1962). Tanner staging was assessed by physicians (including senior physicians with more than 10 years of experience and intermediate physicians with more than 5 years of experience) at initial diagnosis and during follow-up. Tanner stage-breast 1 refers to no breast development; Tanner stage-breast 2 refers to the presence of breast buds (1 or 2); Tanner stage-breast 3 refers to the beginning of the formation of the peripheral mound with an elevation of the breast; Tanner stage-breast 4 refers to a further increase in breast size, with the formation of the so-called "double contour", in which the areola and papilla are both raised off the surface of the whole breast; Tanner stage-breast 5 refers to adult size, with a return to the single contour in which the surface of the areola is again flush with that of the breast. Tanner stage-pubic 1 refers to no pubic hair. Tanner stage-pubic 2 refers to hair appearing in the perineum with sparse, straight, thin pubic hairs that are not pigmented or light brown. Tanner stage-pubic 3 refers to increased pubic hair, spread to the pubic symphysis, curly, blackened. Tanner stage-pubic 4 refers to an enlarged growth area of pubic hair, close to adult characteristics but still concentrated in the upper margin of the ilium and scrotum. Tanner stage-pubic 5 refers to triangles and distributions of pubic hair in adult females, extending to the medialis femoris. Tanner stage-pubic 6 refers to pubic hairs with a fusiform shape and tip to the subumbilical region.

RESULTS

Characteristics of the patients

Of the 21 female patients, 17 were diagnosed with 21-OHD, and four with 17α-OHD. The median age at diagnosis was 21 years and ranged from 7 days to 37 years.

Clinical manifestations

Among the four patients with 17α-OHD (4/21, accounting for 19%), three developed clinical manifestations of hypertension, three had pubertal agenesis, two developed hyperpigmentation, and two reported weakness. Among the 17 patients with 21-OHD (17/21, accounting for 81%), 13 patients developed clinical manifestation of clitoridauxe, six patients developed hyperpigmentation, three had secondary male sexual characteristics (prominentia laryngea protrusion, body hair, and beard), two developed external genital deformity, one had nausea and vomiting, and three suffered from hypokalemia. No 11β-OHD patients were found in this group.

Imaging

According to the adrenal CT scan results of the 21 patients, 12 had bilateral diffuse hyperplasia, one had unilateral diffuse hyperplasia, three had nodular hyperplasia, one had hyperplasia with solid mass, and one had hyperplasia with cystic changes; three patients had no adrenal abnormality.

Treatment and follow-up

Follow-up, lasting 1 to 24 years, was completed for 12 patients, including nine with 21-OHD and three with 17α-OHD (Table 1). Nine patients failed to attend follow-up visits. Among the patients who completed follow-up, six received dexamethasone, three received prednisone, one received cortisone acetate, and one received hydrocortisone. Among those patients, six also underwent clitoral plastic surgery, and one underwent clitoral and vaginal surgery. Table 1 presents detailed treatment information.

After drug treatment, all patients in the follow-up group started to have menstruation and eventually periodic menstruation. Those with virilization gradually noted a reduction in skin hyperpigmentation, increased fat, decreased muscle mass, thinning body hair, and beard disappearance. With menstruation, the breasts of the patients continued to grow. Nevertheless, seven patients diagnosed at an older age or with poor treatment adherence had poor breast growth. Table 1 presents detailed follow-up information.

DISCUSSION

CAH is a group of heritable diseases leading to adrenocortical hyperplasia caused by increased compensatory secretion of corticotropin-releasing hormone (CRH) by the hypothalamus and adrenocorticotropic hormone (ACTH) by the hypophysis because of disordered cortisol synthesis (Claahsen-van der Grinten *et al.* 2022). This case series presents the characteristics of female patients diagnosed with CAH. The cases highlight several issues that should be of interest to clinicians involved in diagnosing and treating CAH.

CAH involves a deficiency of an enzyme required for adrenocortical hormone synthesis, including 21-hydroxylase, 11β-hydroxylase, and 17α-hydroxylase, among which 21-OHD is the most common, observed in 90%-95% of CAH patients (Speiser *et al.* 2018; Török

Tab. 1. Treatment and outcome of 12 female CAH patients

No.	Type	Age of diagnosis/ follow-up visit stop (years)	Drug treatment	Operation	Clinical outcome and marital and childbearing status
1	21-OHD	13/21	Received Dexamethasone treatment at the age of 13 for 8 months, and then discontinued the drug	Received clitoral plastic surgery at the age of 7	Had breast dysplasia, Tanner B2P5, unmarried
2	17α-OHD	24/30	Adhered to Prednisone treatment	None	Developed female secondary sex characteristics, Tanner B3P5, unmarried
3	21-OHD	8/21	Adhered to drug treatment	Received clitoral vaginal surgery at the age of 9	Developed female secondary sex characteristics, Tanner B5P5, unmarried
4	17α-OHD	17/24	Started to receive Dexamethasone treatment at the age of 17	None	Developed female secondary sex characteristics, had external genital development, Tanner B2P5, unmarried
5	21-OHD	25/31	Received Prednisone treatment	None	Tanner B1P5, married, has given birth to one child
6	17α-OHD	24/27	Received Dexamethasone treatment at the age of 24	None	Had hypertension and pubic-hairlessness, Tanner B2P5, married and has given birth to children
7	21-OHD	7/15	Received Dexamethasone treatment at the age of 7 for 3 months, and then discontinued the drug	Received clitoral plastic surgery at the age of 7	Developed virilization, Tanner B2P3, unmarried
8	21-OHD	10/16	Received Cortisone Acetate treatment at the age of 10	Received clitoral plastic surgery at the age of 10	Developed female secondary sex characteristics, had external genital development, Tanner B5P5, of dark skin color, unmarried
9	21-OHD	16/40	Received Prednisone treatment at the age of 16	Received clitoral plastic surgery at the age of 16	Had body hair reduced, developed secondary sex characteristics, had external genital development, Tanner B5P5, married and has given birth to children
10	21-OHD	10/18	Received Hydrocortisone treatment at the age of 10	Received clitoral plastic surgery at the age of 10	Had body hair reduced, developed secondary sex characteristics, had external genital development, Tanner B4P5, unmarried
11	21-OHD	26/27	Received Dexamethasone treatment at the age of 26	None	Had hypertension, public-hairlessness and skin hyperpigmentation, Tanner B2P3, unmarried
12	21-OHD	17/21	Received Dexamethasone treatment at the age of 17	Received clitoral plastic surgery at the age of 17	Had hypertension, body hair reduced, developed secondary sex characteristics, had external genital development, Tanner B4P5, married, has not given birth

CAH, congenital adrenal hyperplasia; 21-OHD, 21-hydroxylase deficiency; 17α-OHD, 17α- hydroxylase deficiency; Tanner BxPx, Tanner breast development stage and pubic hair development stage.

2019; Merke & Auchus 2020; Claahsen-van der Grinten *et al.* 2022). Consistent with the literature, of the 21 female patients in this case series, 17 had 21-OHD. The 21-hydroxylase gene is located in the short arm of chromosome 6 in the human body in the HLA class III gene region and encodes one of the key enzymes for adrenal steroid hormone synthesis (Concolino *et al.* 2013). Mutations in the 21-hydroxylase gene can cause a decrease in cortisol synthesis and weaken the inhibition of the hypothalamus-pituitary-adrenal axis, leading to increased compensatory secretion of ACTH and accumulation of progesterone and 17-hydroxyprogesterone, as well as conversion to the androgen synthesis pathway, eventually resulting in increased testosterone and androstenedione (Huang *et al.* 2008; Claahsen-van der Grinten *et al.* 2022). The degree of enzyme deficiency divides 21-OHD into simple virilizing, salt-wasting, and atypical phenotypes (Hou *et al.* 2019). Patients with the simple virilizing phenotype have incomplete 21-OHD and can synthesize cortisol and aldosterone in small amounts; they mainly develop increased androgens and abnormal external genital development with no electrolyte disturbance (Hou *et al.* 2019). All 12 patients with the simple virilizing phenotype in this group experienced advanced development, age-exceeding skeletal age, breast hypoplasia, pseudohermaphrodism, and virilizing signs such as clitoridauxe and scrotum-like labium majus pudendi. After birth, patients with the salt-wasting phenotype have complete 21-OHD and develop diarrhea, vomiting, dehydration, apastia, hyponatremia, and hyperkalemia. Three patients with salt-wasting phenotype in this group developed recurrent episodes of vomiting. Patients with the atypical phenotype have different clinical manifestations, and child patients do not develop virilizing signs until adolescence, and early diagnosis is difficult (Vos & Bruinse 2010). Two patients with the atypical phenotype in this group developed delayed menarche, acne, hirsuteness, and infertility caused by increased androgens, suggesting that patients with such manifestations should be examined for 21-OHD in clinical practice.

17α-OHD is caused by mutations in exon 5 of the CYP17 gene (Krone *et al.* 2007; Claahsen-van der Grinten *et al.* 2022; Koprulu *et al.* 2022), impairing the synthesis of glucocorticoids and sex hormones, leading to hypertension and hypokalemia and manifestations of undeveloped secondary sexual characteristics and sexual infantilism (John *et al.* 2009; Claahsen-van der Grinten *et al.* 2022). Three patients in the 17α-OHD group had hypokalemia, and two had hypertension; most of the female patients in this group visited the hospital for agenesis.

The clinical manifestations of CAH lack specificity and should be distinguished from hermaphroditism, precocious puberty, polycystic ovary syndrome, and adrenal cortical tumor (Michelle *et al.* 2017; Claahsen-van der Grinten *et al.* 2022). Diagnosis of CAH requires a comprehensive family history, clinical manifestations, laboratory examination results, and adrenal CT results. Due to increased ACTH feedback, CAH patients often have bilateral diffuse hyperplasia or unilateral diffuse hyperplasia in CT findings, while a few are observed with unilateral adrenal tumor-like changes accompanying diffuse hyperplasia (Feng *et al.* 2008; Tsai *et al.* 2020). Most of the 21 female CAH patients in this series had bilateral diffuse hyperplasia, while only a few had unilateral diffuse hyperplasia and nodular hyperplasia. Fewer had hyperplasia with solid mass, and few had hyperplasia with cystic changes. Three patients had no obvious abnormal imaging findings, suggesting that CAH causes various imaging findings and may easily be missed or mistaken in the diagnostic process.

CAH is usually treated with corticosteroid replacement therapy, while surgery is an option for treating female hermaphroditism. It is believed that the best timing for surgery is at 2-6 months after birth, i.e., when the patients have strongly plastic tissues and are subject to a smaller psychological impact (Braga & Pippi Salle 2009; Prete *et al.* 2021). Operation strategies can be designed according to the degree of deformity and characteristics (Claahsen-van der Grinten *et al.* 2022; Shalaby *et al.* 2021). The division of vulvar plastic surgery into two operations, when necessary, will have better efficacy. Clitoral reduction surgery, where the dorsal clitoral vascular bundle is retained as the pedicle, is an ideal method for treating female pseudohermaphroditism-related clitoral hypertrophy (Zhang *et al.* 2011). Although sexual development and fertility are significantly improved for CAH patients after hormone replacement, vulval esthetic surgery, and artificial cycle treatments, some patients will continue to show irregular menstruation, ultimately unsatisfactory body height, and reduced fertility. Among the 12 patients with an available follow-up in this series, seven patients had poor breast growth or undeveloped breasts due to older age at diagnosis or poor treatment compliance.

Several limitations should be acknowledged. First, more detailed information on the patients who underwent drug treatment and surgery, such as treatment outcomes and side effects caused by long-term corticosteroid treatment, could not be collected. In addition, the data on the appearance outcomes or patient satisfaction after surgery were limited. More data related to plastic-esthetic surgery and corticosteroid therapy should be collected in the future.

CONCLUSION

Female CAH patients are subject to genital deformities, virilizing signs, breast dysplasia, and other appearance defects. Therefore, when providing them with treatments to improve their quality of life, plastic surgeons should be vigilant, ask for a detailed medical history

of the patients, and make a defined diagnosis referring to clinical manifestations, laboratory examination results, and adrenal CT results. The author is a plastic surgeon with a practice in patients with CAH and hopes that more plastic surgeons can understand this disease. When they encounter cases of breast dysplasia, external genital dysplasia, etc., CAH should first be excluded to avoid medical errors.

ARTICLE HIGHLIGHTS

Research background

Congenital adrenal hyperplasia (CAH) is a rare disorder that can cause masculinization of the external genitalia in females, usually evident in neonates.

Research motivation

Early diagnosis of CAH can help improve the management of the patients.

Research objectives

To present a case series of female patients with CAH by summarizing its clinical features and outcomes.

Research methods

Clinical data of female patients with CAH admitted to the First Affiliated Hospital of Xiamen University from 1995 to 2019 were retrospectively analyzed.

Research results

Twenty-one patients were included, 17 with 21-OHD and four with 17α-OHD. The patients received hormone replacement therapy, and some patients underwent external genital organ orthomorphia, or artificial periodic therapy if necessary. The sexual development of all 12 follow-up patients was improved, but seven patients had poor breast development that may have resulted from late diagnosis and/or poor adherence to treatments.

Research conclusions

Female CAH patients are subject to genital deformities, virilizing signs, breast dysplasia, and other appearance defects.

Research perspectives

When providing treatments to improve the quality of life in patients with signs of CAH, plastic surgeons should be vigilant, ask for a detailed medical history of the patients, and make a defined diagnosis referring to clinical manifestations, laboratory examination results, and adrenal CT results.

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Informed consent statement

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

Declaration of interest

The authors report no declarations of interest.

Data sharing statement

No additional data are available

Author contributions

Liao L and Sun M carried out the studies, participated in collecting data, and drafted the manuscript. Wang F and Pan S performed the statistical analysis and participated in its design. Wu X and Huang X helped to draft the manuscript. All authors read and approved the final manuscript.

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