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Combination therapy of GnRHa, RhGH and anastrozole to improve final adult height deficit in CAH children with CPP

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Abstract

Background To investigate the clinical and genetic characteristics of classic congenital adrenal hyperplasia (CAH) patients. To determine whether gonadotropin-releasing hormone analogs (GnRHa) + recombinant human growth hormone (rhGH) + Anastrozole combined therapy improves the final adult height of CAH patients with central precocious puberty (CPP).

Methods We described the clinical and genetic characteristics of 16 classic CAH patients, and performed pathogenic analysis and structural modeling of the newly discovered mutation. By using the method of self-before and after control, we statistically analyzed bone age advancement, predicted adult height (PAH) and other indicators of 7 CAH children with CPP before and after combined treatment to observe its effect on adult height.

Results All patients showed high levels of 17-hydroxyprogesterone, testosterone and adrenocorticotropic hormone. All patients had *CYP21A2* gene mutations, and the newly discovered mutation c.79 A > G (p.Ser27Gly) may change the hydrophilicity of the protein and affect its function. Seven CAH patients with CPP were diagnosed at 5.6 (3.5 to 7.3) years. Their target height was 0.18 (-1.2 to 0.78) SD, and the PAH at the start of treatment was −3.01 (-3.75 to -2.89) SD. The ages at which CAH patients with CPP started to be treated with GnRHa, rhGH and Anastrozole were 5.8 (5.5 to 8.7), 7.1 (5.5 to 9.8), 8.7 (7.6 to 10.7) years old, and discontinued them at 8.8 (7.5 to 10.2), 10.4 (9.0 to 12.7), 11.0 (9.7 to 12.7) years old, respectively. The PAH at treatment end was −0.28 (-1.2 to 0.4) SD. The final height was −0.28 (-1 to 1.04) SD, significantly higher than the initial PAH ($P < 0.001$) and similar to the target height ($P = 0.478$).

Conclusion GnRHa + rhGH + Anastrozole therapy can improve the final adult height of CAH patients with CPP. In addition, this study also discovered a new *CYP21A2* gene mutation c.79 A > G.

Keywords 21 Hydroxylase deficiency, *CYP21A2* gene, Central precocious puberty, GnRHa, RhGH, Anastrozole

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Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders, can be classified into two subtypes: classic form and non-classic form. The incidence of classic form is between 1/15,000 to 1/20,000, including salt wasting form (SW) and simple virilizing form (SV) [1]. SW form accounts for approximately 75% of classic cases, while the SV form accounts for 25% [1]0.21-hydroxylase deficiency (21-OHD) is the most common cause of CAH, which is caused by *CYP21A2* gene mutations [2]. 21-OHD leads to the failure of 17-hydroxyprogesterone (17-OHP) to convert into corticosterone and deoxyicorticosl, resulting in a lack of cortisol (Cor) and aldosterone, excessive androgens, manifests as virilization and salt-wasting symptoms.

Currently, the preferred treatment for CAH is adrenocortical hormone replacement therapy, including glucocorticoids and mineralocorticoids, which can replace insufficient adrenocortical hormone secretion, correct water and electrolyte disorders, and inhibit excessive adrenocorticotropic hormone (ACTH) synthesis [3]. Hydrocortisone is a glucocorticoid for growing children with a mean elimination half-life of 58 min, resulting in a return of adrenal steroids to pre-hydrocortisone dose concentrations after 4–5 h [4]. As a result, CAH children are alternately exposed to hyper- and hypocortisolemia, resulting in elevated adrenal androgens. Chronic hyperandrogenism in prepubertal CAH patients may activate the hypothalamic-pituitary-gonadal axis and induce central precocious puberty (CPP) [5]. Affected children often experience accelerated linear growth during childhood with premature epiphyseal fusion, ultimately resulting in adult height below the target height established by their parents [6]. Numerous studies have shown that CAH patients are approximately 10 cm shorter than their parent-based target height [7, 8]. A Chinese study in 2016 showed that the final adult height of classic CAH patients after receiving glucocorticoid and mineralocorticoid replacement therapy was -1.9 ± 1.1 SD lower than that of healthy people [6].

For CAH patients with CPP, conventional treatment combined with gonadotropin-releasing hormone analogs (GnRHa) can effectively inhibit the development of sexual characteristics and slow down the progression of bone age by inhibiting the release of pituitary follicular stimulating hormone (FSH) and luteinizing hormone (LH) [9]. However, this approach is often accompanied by a deceleration in height growth. Recombinant human growth hormone (rhGH) can effectively improve the height of children by stimulating chondrocyte proliferation [10]. The rhGH and GnRHa combined treatment has been shown to effectively improve predicted adult height (PAH) [11, 12]. However, for CPP children who start treatment late, have significantly advanced bone age and impaired height growth potential, the treatment duration is limited. There is currently no ideal solution to improve their problems such as advanced bone age and impaired expected adult height.

In 2000, aromatase inhibitors were first used in CAH patients [13]. By inhibiting the conversion of androgens to estrogens, they were able to inhibit bone age advancement and improve final adult height. In recent years, the advent of third-generation aromatase inhibitors represented by Anastrozole has further improved the inhibition rate of aromatase and reduced the incidence of adverse reactions. Studies have shown that aromatase inhibitors can improve the final adult height of children with short stature who have already started puberty or even in late puberty [14]. Aromatase inhibitors are expected to become a new hope for children who have missed the optimal treatment period of rhGH or GnRHa.

This article retrospectively studied the clinical and genetic characteristics of classic CAH patients. This study aims to investigate the effectiveness of a combined treatment regimen (GnRHa + rhGH + Anastrozole) in enhancing final adult height in children with CAH patients with CPP.

Methods

Participants

We collected clinical data of 16 children who were diagnosed with classical CAH from 2017 to 2024 in the Pediatric Department of the Tianjin Medical University General Hospital. All patients were from northern China. Their medical records were thoroughly reviewed, including clinical manifestations, physical examinations, growth histories, laboratory examinations, treatments, and follow-ups. Inclusion criteria of the patients were: (1) met the diagnostic criteria outlined in the clinical practice guidelines of 21-OHD published by the American Society for Endocrinology in 2018 [15]; (2) follow-up for more than 2 years; (3) the clinical data were complete. Exclusion criteria were: incomplete clinical data or loss of follow-up.

The diagnostic criteria for CPP include: (1) males show secondary sexual characteristics before the age of 9 (testicular volume ≥ 4 mL) and females show secondary sexual characteristics before the age of 8 (breast development); (2) bone age at least 1 year advanced than the chronological age; and (3) pubertal response of LH peak > 5 IU/L or LH/FSH ratio > 0.6 after the GnRHa stimulation test [16].

This study was approved by the Ethics Committee of the Academy of Tianjin Medical University General Hospital (ZYY-IRB-SOP-019(F)-002-02).

Clinical data

Laboratory examinations included measurements of serum sodium (Na^+), potassium (K^+), Cor, aldosterone, ACTH, FSH, LH, estradiol (E2), testosterone (T), etc. These hormones were measured by the chemiluminescence method. Additionally, 17-OHP was measured using high-performance liquid chromatography-tandem mass spectrometry. Testicular or utero-ovarian ultrasound and chromosome karyotype were also conducted. Bone age was determined using the Greulich–Pyle atlas from the non-dominant hand and wrist radiographs of the patients [17]. The Bayley–Pinneau method was used to figure out the PAH [18]. Target height, the genetic potential in stature, is commonly estimated by the corrected midparental height method [19].

Genetic testing was conducted for all participants in the study. Next-generation sequencing and multiplex ligation-dependent probe amplification (MLPA) were used for seeking *CYP21A2* gene mutations. For *CYP21A2* gene mutations analysis, multiple sequence alignments were performed by the UCSC database (http://genome.ucsc.edu/) and Kalign (https://www.ebi.ac.uk/Tools/msa/kalign/) to analyze the conservation of amino acid residues across different species. SWISS (https://swissmodel.expasy.org/interactive) and PyMOL 2.2 (https://pymol.org/2/) were used to analyze the possible change of 21-hydroxylase structure after mutation.

Treatment and follow-up

For CAH patients, conventional treatment includes hydrocortisone 15–20 mg/m^2/d and fludrocortisone 100–150 ug/d. Children with SW < 1 year old can also be treated with sodium chloride 1–2 g/d. For patients with CPP and predicted impaired adult height, GnRHa (3.75 mg, Beijing Biotech) was injected subcutaneously every 4 weeks, rhGH was injected subcutaneously at a daily dose of 0.15–0.20 IU/kg/day (Jinsai, Jilin), and Anastrozole (1 mg/d, Huabang, Chongqing) was taken orally.

Plasma electrolytes, 17-OHP, ACTH, and body weight were monitored monthly for infants before 3 months old, then were monitored every 3 months after that age. Blood samples were taken at around 8 am before daily oral drugs. The dosage of oral hydrocortisone and fludrocortisone should be readjusted according to the examination results. Growth condition was monitored carefully for all patients. Bone age was tested every 6 months after 2 years old.

Table 1 Clinical features of patients with classical CAH

	SW	SV	*P*
Sex (F/M)	4/6	1/5	0.33
Age of diagnosis (y)	0.2(0.1,0.3)	5.3(4.9,7.2)	< 0.001
Na^+ (130–150 mmol/L)	126(124,128)	139(136,140)	0.001
K^+ (3.3–5.5 mmol/L)	5.1(5.8,7.7)	4.2(3.9,4.9)	0.001
Cor (5–25 ug/dl)	2.9(1.4,3.9)	5.8(3.5,19.9)	0.019
ACTH (0–46 pg/ml)	146.6(49.8,248.6)	129.6(93.3,210.9)	0.245
17-OHP (0.3-2.0 ng/ml)	320.75(236.30,1433.00)	231.10(108.37,259.25)	0.03
T (< 10 nmol/L)	209.0(86.2,256.7)	180.7(93.4,297.5)	0.014

Note: The Kruskal-Wallis test was used to analyse continuous clinical variables. Na^+, sodium; K^+, potassium; Cor, cortisol; ACTH, adrenocorticotropic hormone; 17-OHP, 17-hydroxyprogesterone; T, testosterone

Statistical analysis

SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) was used for statistical analysis. Categorical variables were presented as percentages, whereas continuous variables were presented as medians (P25, P75). The Kruskal-Wallis test was used to analyse continuous clinical variables. Chi-square (χ^2) test was used for categorical data. Each time point was compared to the final evaluation by paired t Test. Paired t-test was also used to compare the hormone levels in each treatment period with those at the beginning of combined treatment.

Results

Baseline characteristics

16 CAH patients were included in this study. The chromosome karyotype was consistent with their social gender. All patients did not undergo neonatal screening. The symptoms of SW patients were mainly poor feeding and weight loss. Six patients developed adrenal crisis. Physical examination showed that 2 of the 4 girls had clitoromegaly (Prader 2), the other 2 girls had ambiguous external genitalia (Prader 3), and all 6 boys had scrotal pigmentation. SV patients mainly showed rapid growth and early pubic hair. The only girl diagnosed with SV in this study showed clitoromegaly (Prader 1). Laboratory tests showed that compared with SV patients, SW patients had lower Na^+, higher K^+, Cor, 17-OHP and T ($P < 0.05$), and no significant difference was found in ACTH (Table 1).

CYP21A2 gene mutations were detected by MLPA. All of them were autosomal recessive inherited (Table 2). The mutation sites were scattered in the *CYP21A2* gene (Fig. 1A). Functional change of missense mutation c.79 A > G (p. Ser27Gly) (Fig. 1B) had not been recorded in the Human Gene Mutation Database, Human Cytochrome P450 Allele Nomenclature Committee and 1000 genomes database yet. The patient gained missense mutations c.79 A > G (p. Ser27Gly) and c.518T > A (p.Ile173Asn) from his mother, and obtained the null

Table 2 Mutations of 16 patients in *CYP21A2* gene

Patient	Allele 1	Location in CYP21A2	protein change	Allele 2	Location in CYP21A2	protein change
1	c.293–13 C > G	Intron2	In2G	c.293–13 C > G	Intron2	In2G
2	c.1451-1452delGGinsC	Exon10	Arg484Profs	E1-7 Del	Exon1-7	-
3	c.293–13 C > G	Intron2	In2G	c.293–13 C > G	Intron2	In2G
4	c.949 C > T	Exon8	Arg319*	E1-10 Del	Exon1-10	-
5	c.293–13 C > G	Intron2	In2G	c.293–13 C > G	Intron2	In2G
6	c.293–13 C > G	Intron2	In2G	c.293–13 C > G	Intron2	In2G
7	c.710 T > A	Exon6	I1e237Asn	E1-3 Del	Exon1-3	-
8	c.293–13 C > G	Intron2	In2G	E1-3 Del	Exon1-3	-
9	c.710T > A; c.713T > A; c.719T > A	Exon6	I1e237Asn; Val238Glu; Met240Lys	c.1069 C > T	Exon8	Arg357Trp
10	c.293–13 C > G	Intron2	In2G	c.1069 C > T	Exon8	Arg357Trp
11	c.518T > A	Exon4	Ile173Asn	c.955 C > T	Exon8	Gln319*
12	c.518T > A	Exon4	Ile173Asn	c.606G > A	Exon5	Trp202*
13	c.518T > A; c.79 A > G	Exon4; Exon1	Ile173Asn; Ser27Gly	E4-7 Del	Exon4-7	-
14	c.518T > A	Exon4	Ile173Asn	c.293–13 C > G	Intron2	In2G
15	c.518T > A	Exon4	Ile173Asn	c.1225 C > G	Exon10	Arg409Gly
16	c.518T > A	Exon4	Ile173Asn	c.1306 C > T	Exon10	Arg434Cys

mutation p.E4-6 Del himself (Fig. 1C). We enquired about amino acid sequences around p. Ser27Gly using the UCSC database and Kalign (Fig. 1D) and constructed 3D structures of 21 hydroxylase by PyMol2 software (Fig. 1E). Bioinformatic software was applied to analyze the pathogenicity of p.Ser27Gly. It was located in the N-terminal region, and the hydrophilicity of the protein was changed after mutation, which might affect the anchoring in the cell membrane and reduce the activity of the enzyme.

Complicated with CPP

Seven children have been diagnosed with CPP in this study, including 2 SW (M: F = 1:1) and 5 SV (M: F = 4:1). We observed that the age of diagnosis CPP was 5.6 (3.5 to 7.3) years, representing a group of patients with delayed disease recognition. Ovarian and follicular enlargement occurred before 7.5 years in girls and penile and testicular growth occurred before 9 years in boys. LH and FSH were elevated, and LH peak/FSH peak higher than 0.6. At the time of diagnosis of CPP, the bone age had significantly improved by 6.3 (4.1 to 7.7) years, and PAH was – 3.10 (-3.75 to -2.89) SD.

The data of chronological age and bone age progression observed at each time point during treatment are shown in Table 3. The ages at which CAH patients with CPP started to be treated with GnRHa, rhGH and Anastrozole were 5.8 (5.5 to 8.7), 7.1 (5.5 to 9.8), 8.7 (7.6 to 10.7) years old, and discontinued them at 8.8 (7.5 to 10.2), 10.4 (9.0 to 12.7), 11.0 (9.7 to 12.7) years old, respectively. The duration of single GnRHa treatment was 1.4 (0.1 to 1.7) years, during which no further bone age progression was observed. At 1.4 (0.4 to 3.3) years of GnRHa + rhGH treatment, bone age progression decreased significantly to 4.9 years. At the end of 1.9 (0.3 to 2.7) years of rhGH + Anastrozole treatment, bone age decreased significantly to 4.3 years and remained near this value until the end of clinical evaluation.

The key height indicators of CAH patients with CPP are detailed in supplementary Table 1. Comparison of each time point during treatment with the final height assessment showed a gradual increase in height (Fig. 2). From diagnosis to the end of single GnRHa therapy, predicted height decreased significantly relative to height close to the final level ($P < 0.001$). At the end of GnRHa + rhGH therapy, height decreased significantly relative to height close to the final level ($P = 0.004$). At the end of rhGH + Anastrozole therapy, height still differed relative to final height ($P = 0.011$). There was no difference in height relative to final height at the time of discontinuation of adjuvant therapy ($P = 0.063$). The final height assessment was similar to the target height ($P = 0.478$).

The results of pituitary-gonadal axis hormone levels in male children during different treatment periods are shown in Table 4. During the GnRHa treatment period, FSH and LH decreased (both $P < 0.05$), indicating that GnRHa treatment was effective. At the end of GnRHa treatment, sex hormone status was at puberty levels. During the Anastrozole treatment period, FSH and LH increased slightly, but there was no statistical difference, and the decrease in E2 ($P < 0.01$), which was considered to be related to the addition of Anastrozole. There were only 2 cases in the female group, which were not analyzed. During the treatment period, the children did not experience symptoms such as hirsutism, severe acne, nausea, headache, bone pain, obesity, or hypertension,

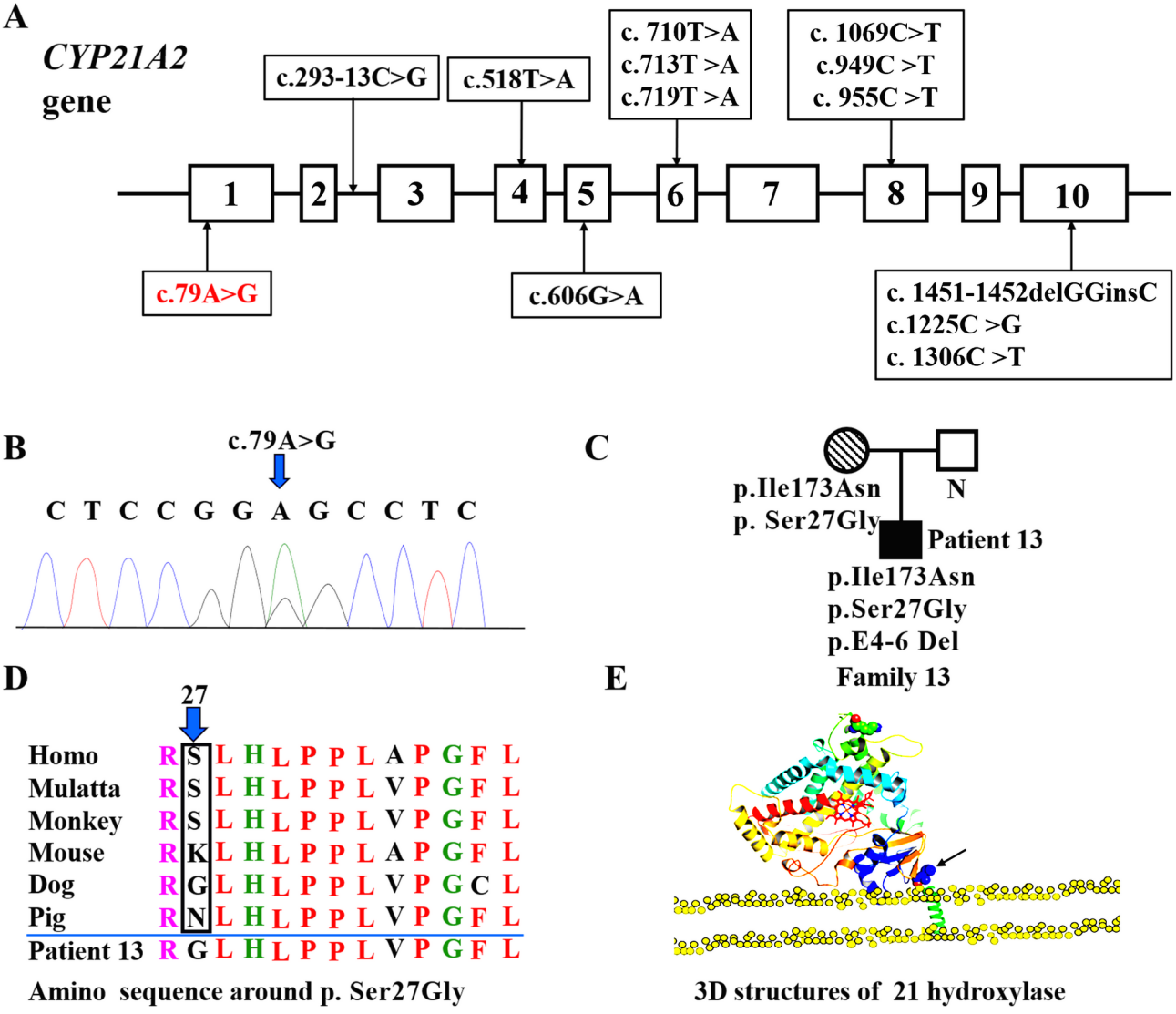

Fig. 1 Point mutations and predicated function change of mutation c.79 A > G. (**A**) Distribution of mutations was identified in the study. (**B**) Missense mutation c.79 A > G in patient 13. (**C**) Pedigree chart of family 13. (**D**) Amino acid sequences around Ser27Gly. (**E**) The position of Ser27Gly in protein structure. Black square represents patient; Slopek circle represents carrier; Blank squares represent healthy. The black arrow shows the site of Ser27

Table 3 Chronological age and bone age advancement (years) in CAH patients

	Chronological age (y)		Bone age advancement (y)	
	Median	Range	Median	Range
Diagnosis	5.6	3.5–7.3	6.1	3.5–7.5
Start of GnRHa	5.8	5.5–8.7	6.3	4.1–7.7
Start of rhGH	7.1	5.5–9.8	5.9	3.3–6.4
Start of Anastrozole	8.7	7.6–10.7	4.8	3.1–6.4
withdrawal GnRHa	8.8	7.5–10.2	4.9	3.0-6.4
withdrawal rhGH	10.4	9.0-12.7	4.5	2.5–4.9
withdrawal Anastrozole	11.0	9.7–12.7	4.3	2.5–5.3
Final height	11.4	11.2–13.9	4.1	2.9–5.1

Note: Bone age advancement (y) = bone age (y) - chronological age (y)

nor did they feel fatigued, regular monitoring of lipid profiles, electrolytes, liver function, kidney function, and coagulation function all yielded normal results.

Discussion

This report is particularly important because it is the first report on the combined treatment regimen (GnRHa + rhGH + Anastrozole) for CAH patients with CPP and follow-up of their final adult height. Through long-term follow-up, the study verified the advantages of this combination therapy in improving patients' final adult height, providing a certain basis for future treatment optimization.

Around 9% of individuals with 21-OHD may experience the development of CPP due to delayed or

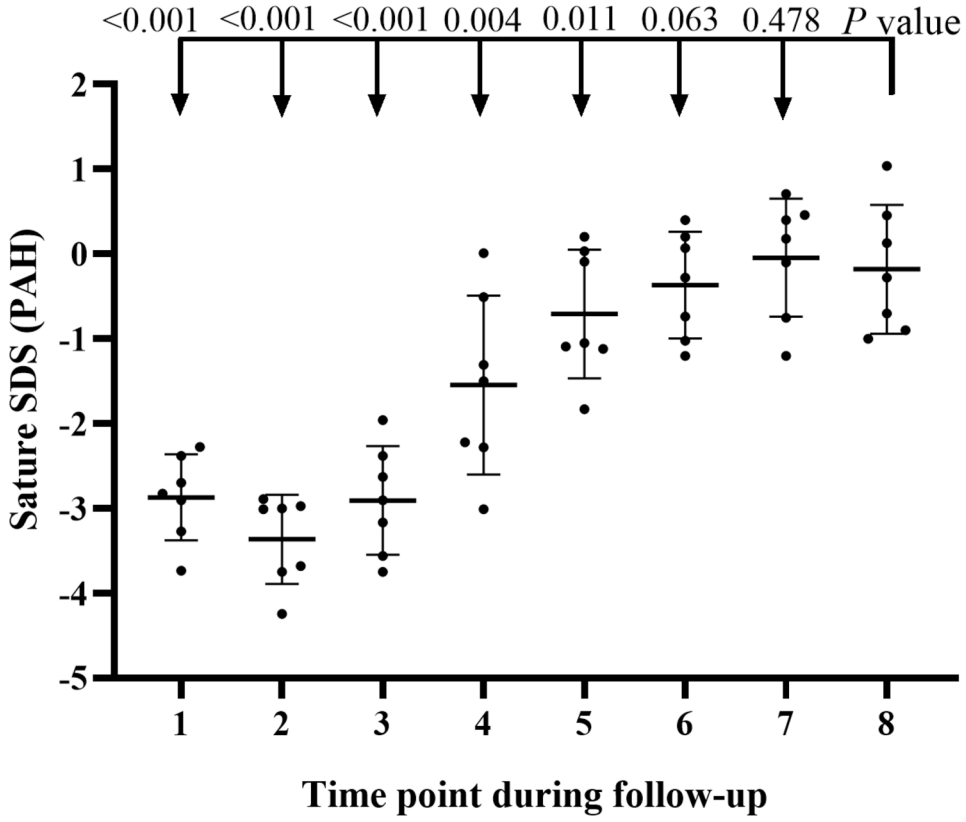

Fig. 2 Stature SDS calculated for PAH. (**1**) Diagnosis of CAH; (**2**) Diagnosis of CPP; (**3**) End of single GnRHa thepary; (**4**) End of combined thepary (GnRHa + rhGH); (**5**) End of combined thepary (rhGH + Anastrozole); (**6**) All treatment withdrawal; (**7**) Target height; (**8**) Final height

Table 4 Changes in sex hormones after treatment note: the paired t-test was used to compare the hormone levels in each treatment period with those at the beginning of combined treatment. *:$P < 0.05$; **:$P < 0.01$. FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; T: testosterone

Treatment period	FSH(U/L)	LH(U/L)	E2(pmol/L)	T(nmol/L)
Diagnosis of CPP	2.1(1.5-3.0)	1.2(0.8–1.4)	13.0(10.3–15.5)	22.0(12.8–50.5)
GnRHa treatment period	0.4(0.1–0.6) *	0.2(0.1–0.4) *	5.5(4.2–15.2)	11.3(11.1–22.1) *
End of GnRHa treatment	1.9(1.6–3.2)	1.1(1.0-1.7)	35.5(25.5–50.3)	17.0(10.7–20.8)
Anastrozole treatment period	2.2(1.7–2.8)	1.2(1.3–1.8)	6.5(5.7–13.6) **	30.3(25.0-60.2)

insufficient treatment [9]. The average age of CAH patients with CPP at diagnosis was 7.6 ± 1.8 years [20, 21]. The 7 CAH patients in this study were diagnosed at 5.6 (3.5 to 7.3) years, and their bone age had advanced by 6.1 (3.5 to 7.5) years at the time of presentation. The age of diagnosis of CPP was 5.8 (5.5 to 8.7) years, and the bone age was further advanced, with a significant impairment of PAH by -3.10 (-3.75 to -2.89) SD. All children with CPP had signs of activation of the hypothalamic-pituitary-gonadal axis, including testicular enlargement in boys, breast development in girls, and gonadotropin response to GnRH stimulation during puberty. Because CPP in these patients was progressive, PAH was impaired. The target audience of this article is CAH patients with CPP who have significantly advanced bone age. In order to achieve greater height growth within a limited height growth time, this article adopts the combined treatment of GnRHa + rhGH + Anastrozole.

GnRHa treatment is effective in regressing secondary sexual characteristics, suppressing the gonadal axis, and slowing skeletal maturation, and this is also true for children with other causes of CPP [22, 23]. In 1997, AT Soliman proposed the first application of GnRHa in CAH patients with CPP [24]. Another study showed that height gain was not significantly correlated with GnRHa treatment duration, but age at the start of GnRHa treatment was significantly negatively correlated [25]. The duration of single GnRHa treatment in this article was 1.4 (0.1 to 1.7) years, and the standard deviation score of height at the end of treatment was − 2.9 (-3.70 to -1.96) SD. Single GnRHa treatment had little benefit on height, which considered to be related to the late start of treatment and

the decreased height growth rate of the children in this article.

rhGH is the most used drug for the treatment of short stature. It can stimulate the liver and other organs to produce insulin-like growth factor-1, and act on chondrocytes in the epiphyseal plate to promote protein synthesis and metabolism, playing an important role in promoting bone growth [26]. In the past two decades, rhGH alone or in combination with GnRHa has been shown to enhance the final adult height of CAH patients [8, 11, 25, 27, 28]. Compared with single GnRHa therapy, rhGH + GnRHa therapy increased the average growth rate from 5 ± 1.9 to 7.8 ± 1.6 cm/y [12]. It has been reported that after 2 years of rhGH + GnRHa treatment, the average PAH increased from 159 ± 11 cm to 170 ± 7.5 cm [12]. This article used rhGH + GnRHa treatment for 1.4 (0.4–3.3) years, with a height growth rate of about 6.3 (5.3–8.8) cm/y, and a height standard deviation score of -1.49 (-3.01 to 0.01) SD at the end of treatment. Compared with the previous situation, both the height growth rate and PAH were improved.

Since estrogen is the primary hormone regulating epiphyseal fusion, the use of aromatase inhibitors is thought to inhibit the conversion of androgens to estrogen, slowing skeletal maturation and allowing for a longer period of growth [29–31]. The third-generation aromatase inhibitors, Letrozole and Anastrozole, have been shown to be safe and effective in treating short stature in children [32, 33]. Anastrozole can delay skeletal maturation and improve final adult height in both classic and non-classic CAH [31, 34]. A 6-year study of Anastrozole treatment for CAH showed that it increased PAH by the average of 13 cm in girls and 17 cm in boys [35]. Aromatase inhibitors can slow skeletal maturation in treating CAH, and this effect is realized without the necessity of raising hydrocortisone doses and without the manifestation of clinical symptoms related to androgen excess. Studies have shown that aromatase inhibitors combined with rhGH treatment have greater benefits in growth velocity and PAH in children and adolescents with short stature [32]. In this article, after rhGH + Anastrozole treatment 1.9 (0.3 to 2.7) years, the standard deviation score of height at the end of treatment bone age was – 1.02 (-1.83 to 0.20) SD. The height was similar to the target height when treatment was stopped. The final adult height score was – 0.28 (-1 to 1.04) SD. During aromatase treatment, liver and kidney function, blood glucose, blood lipids were all at normal levels, similar to previous reports [36, 37].

This study has some limitations. First of all, the study sample size was small, which may have limited the representativeness and statistical significance of the findings. Another point is that a single-center study may limit the generalizability and external validity of the results. Finally, this study did not set up a control group, which may affect the accurate evaluation of CAH patient characteristics and treatment effects.

In summary, the data in this article show that on the basis of conventional treatment, the regimen of rhGH + GnRHa + Anastrozole can be used for CAH children with CPP, especially those with significantly advanced bone age and impaired final adult height, to achieve the therapeutic goal of inhibiting bone age progression and increasing adult height.

Abbreviations

21-OHD	21-hydroxylase deficiency
Cor	Cortisol
CPP	Central Precocious Puberty
GnRHa	Gonadotropin-Releasing Hormone Analogs
rhGH	Recombinant Human Growth Hormone
SV	Simple Virilizing
SW	Salt Wasting
T	Testosterone

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05703-8.

Supplementary Material 1

Supplementary Material 2

Author contributions

RXZ and SFM conceived the idea and design of the article. FL, XXL, YYQ, and XYH performed the literature search, data acquisition, analysis, and/or interpretation. FL, XXL, RXZ, and SFM drafted and critically reviewed the work. All authors reviewed the manuscript.

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Data availability

Due to patient privacy concerns, the data supporting the results of this study are not publicly available but can be obtained from the corresponding author upon reasonable request. The data are stored in a controlled access data repository at Tianjin Medical University General Hospital.Corresponding author email: rzheng@tmu.edu.cn.

Declarations

Ethics approval and consent to participate

This work was approved by Ethics Committee of Academy of Tianjin Medical University General Hospital (ZYY-IRB-SOP-019(F)-002-02). As our study involved a retrospective database analysis, parental consent was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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