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*Case report*

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# Congenital adrenal hyperplasia-induced central precocious puberty: Importance of early recognition and treatment

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## Abstract

One of the commonest causes of peripheral precocious puberty in boys is congenital adrenal hyperplasia (CAH). Hydrocortisone treatment typically prevents peripheral precocity from progressing. However, a small number of patients may develop central precocious puberty while receiving this therapy. In this situation, gonadotropin-releasing hormone analogue (GnRHa) therapy typically arrests subsequent pubertal progression and advancement of bone age. Here, we present a boy with peripheral iso-sexual precocious puberty due to CAH presented at eight years. Since the age of six years, he had a history of the appearance of pubic hair, penile lengthening, offensive behaviour, and gradual darkening of skin. However, his pubertal development and bone age advancement persisted even after conventional treatment with hydrocortisone and fludrocortisone. Conversion to central precocious puberty was subsequently confirmed by clinical and hormonal evaluation. Further, pubertal progression was successfully arrested with a GnRHa in addition to a glucocorticoid and mineralocorticoid regimen. Delayed diagnosis and treatment of CAH may be complicated by true precocious puberty, which can be successfully arrested by treatment with GnRHa along with hydrocortisone and fludrocortisone. *[J Assoc Clin Endocrinol Diabetol Bangladesh,* July 2026; 5 (2): e87119*]*

**Keywords:** Congenital adrenal hyperplasia; Precocious puberty; Gonadotropin-releasing hormone agonist; Testicular microlithiasis

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## Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition of the steroid hormone synthesis pathway. This condition is characterized by inadequate production of key steroid-hydrocortisone due to a deficiency of 21-hydroxylase enzyme, which in turn results in excess adrenocorticotropic hormone (ACTH) secretion. As a result, hypertrophy of adrenal cortex occurs along with increase androgens production.[1] One of the primary clinical manifestations of CAH is peripheral precocious puberty, where the child experiences premature sexual development and the central hypothalamic-pituitary-gonadal (HPG) axis remains inactivated.[2] Increased adrenal androgen production results in premature development of axillary and pubic hair, penile or clitoral enlargement, accelerated height growth, and advanced bone age.

While the cornerstone of treatment for CAH involves glucocorticoid therapy with hydrocortisone and mineralocorticoid therapy with fludrocortisone, which typically suppresses adrenal androgen overproduction, some children continue to show signs of accelerated puberty despite adequate adrenal suppression. Both basal and in response to gonadotropin-releasing hormone analogue (GnRHa), these children may have increased gonadotropin levels, which would indicate a premature activation of the central hypothalamic-pituitary-gonadal axis and a shift toward central

precocious puberty (CPP).[2,3] In CAH, the transition from peripheral to central puberty is still a complicated and difficult phenomenon. GnRHa is frequently used to treat CPP. It effectively inhibits gonadotropin secretion and stops further pubertal growth by persistently stimulating the hypothalamic-pituitary- gonadal axis, providing a crucial tool in the treatment of this distinct and challenging condition.[4]

We present here a unique case of congenital adrenal hyperplasia complicated by CPP, which underpin the challenges in diagnosing and treating such patients.

## Case report

An eight-year-old boy, first issue of non-consanguineous marriage, presented with a history of progressively growing penile size and early morning erections. His pubic and axillary hair first appeared when he was six years old. His family also noticed a masculine change in voice and abrupt height acceleration that was disproportionately greater than that of his classmates. Recently he started to behave aggressively and his academic performance also deteriorated. His parents stated that there was no history of neonatal salt crisis, head trauma, cranial irradiation, meningitis, encephalitis, or sex steroid exposure of their son. He had no significant birth or perinatal history. There was no family history of precocity, ambiguous genitalia, or unexplained neonatal death.

General physical examination was unremarkable, including a normal blood pressure of 90/60 mm-Hg. Anthropometric measurement included a height at +6.6 SD, weight at +8.8 SD, with a sex adjusted mid parental height within target height; his arm span measured 152 cm, and the upper segment to lower segment ratio was normal (1.01). His height age (12 years) was advanced compared to his chronological age **(Figure-1)**. Examination of his genitalia revealed testicular volumes of 6 ml (right) and 5 ml (left), stage 4 pubic hair, presence of axillary hair, and a stretched penile length of 12 cm.

Routine investigations showed a haemoglobin level of 13.4 g/dL and a haematocrit of 38.7%. Urine microscopy was normal. Biochemical investigations revealed a serum creatinine level of 0.6 mg/dL, SGPT of 15 IU/L, and normal serum electrolytes (sodium 140 mEq/L, potassium 4.1 mEq/L). Bone age assessment indicated an age of 10-12 years, which was advanced relative to his chronological age **(Figure-2a)**.

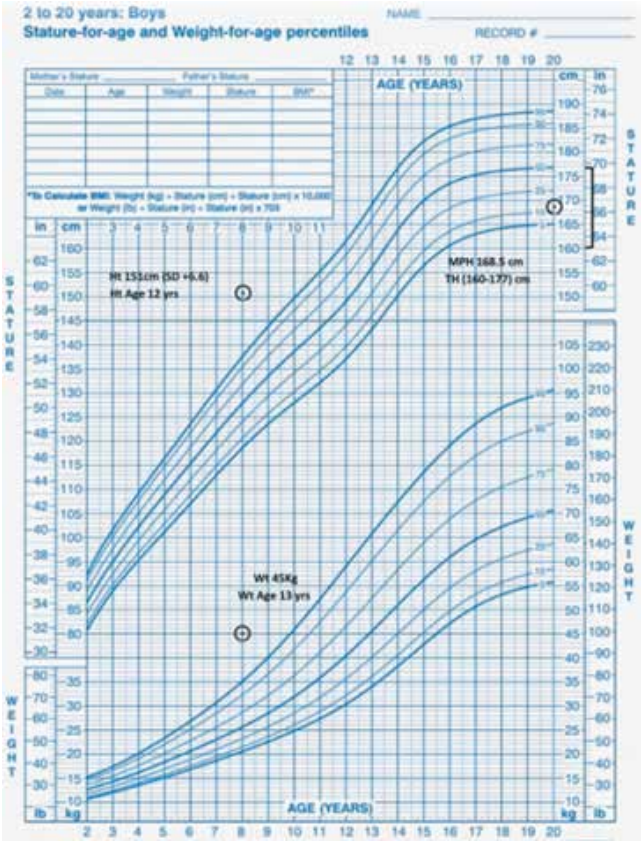


**Figure-1:** Anthropometric measurements of the patient

**Figure-2a:** Bone age (10-12 years) before starting treatment

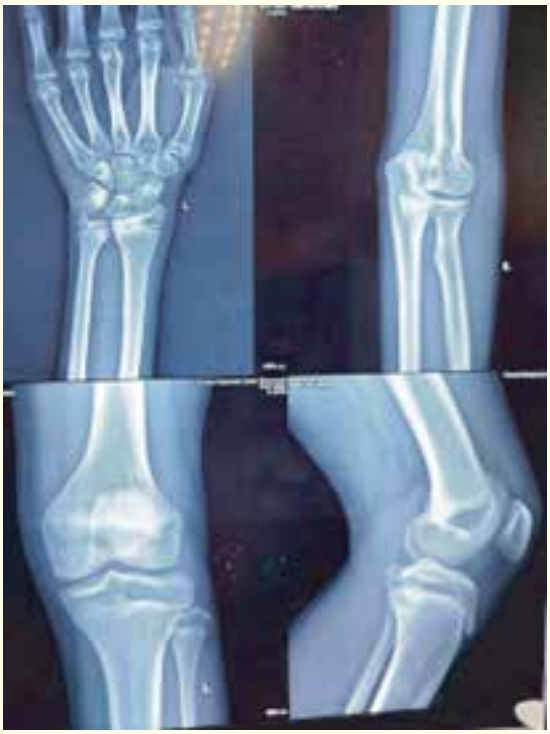

**Figure-2b:** Bone age (16-17 years) after hydrocortisone replacement

Hormonal assay showed normal thyroid function test, suppressed basal luteinizing hormone (LH) & follicle-stimulating hormone (FSH), elevated serum total testosterone, decreased basal cortisol, and elevated adrenocorticotrophic hormone (ACTH), dehydroepiandrostenedione sulfate (DHEA-S) above the upper limit of normal range, elevated 17-hydroxy progesterone (17-OHP), and beta human chorionic gonadotropin (β-HCG) were within normal ranges. A GnRH stimulation test was performed with a 100 mcg subcutaneous triptorelin injection; 60 minutes after stimulation, LH remained suppressed.

Elevated levels of 17-OHP, consistent was with a diagnosis of CAH, and raised serum testosterone levels, indicating precocious puberty. However, basal and stimulated LH levels were suppressed, suggesting a diagnosis of peripheral precocious puberty. Neuroimaging with contrast MRI of the brain was normal, excluding central causes of precocious puberty. An abdominal ultrasound did not reveal adrenal hyperplasia.

The initial treatment plan included hydrocortisone (20 mg daily in three divided doses) and fludrocortisone (0.1 mg daily), aimed at managing the underlying CAH. Despite this treatment, with reasonable compliance to drugs, there was progression of his pubertal development, which was evidenced by a persistent increase in his height, penile length, and testicular volume. Hormonal assessment showed that both LH and testosterone levels had increased into the pubertal range **(Table-I)**, and bone age acceleration continued **(Figure-2b)**.

**Table-I:** Auxological and hormonal data before and during treatment of the patient

| Parameter | Initial | Age match normal range | After hydrocortisone | | After GnRHa | | |
|---|---|---|---|---|---|---|---|
| | | | 1st Follow up after 3 months | 2nd Follow up after 6 months | 1st Follow up after 3 months | 2nd Follow up after 6 months | 3rd Follow up after 12 months |
| Height (cm) | 151 | | 153 | 155 | 155 | 155 | 155 |
| Bone age (years) | 10-12 | | | 16-17 | | 16-17 | 16-17 |
| Testicular volume (ml) | Right-6<br>Left-5 | 0.2- 4.9 | Right- 12<br>Left- 10 | Right- 20<br>Left- 15 | Right- 12<br>Left- 10 | Right- 10<br>Left- 8 | Right- 8<br>Left- 8 |
| LH (basal) (mIU/L) | <0.12 | | | 1.73 | 0.88 | 0.51 | 0.4 |
| LH (stimulated)(mIU/L) | 2.94 | ≤3.0 | | 9.73 | 2.47 | | |
| FSH (mIU/L) | 0.96 | 2-8 | | | 0.59 | | |
| T. testosterone (ng/dl) | 72.9 | ≤0.9 | 173.05 | 327.91 | < 6.92 | < 7.00 | <7.00 |
| 17-OHP (ngl/ml) | >20 | | >20 | 9.95 | | 1.34 | 1.27 |
| Cortisol (nmol/L) | 249 | | | | | | |
| ACTH (pg/ml) | 210 | 13-115 | 196 | 64.07 | | 8.55 | 9.62 |
| DHEAS (ug/dl) | 140 | | | | | | |

LH denotes luteinizing hormone; FSH, follicle stimulating hormone; T. Testosterone, Total testosterone; 17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotrophic hormone; DHEAS, Dehydroepiandrostenedione sulfate

Given this clinical scenario of central pubertal activation despite treatment with hydrocortisone and fludrocortisone, an ultrasonography of the testes was done to exclude testicular adrenal rest tissue (TART) or malignancy, as there was asymmetry in testicular enlargement. In the ultrasonographic assessment, there was a grade 4 varicocele on the right and a grade 2-3 varicocele on the left testis, and bilateral testicular microlithiasis, which raised concern for additional pathology in the gonads.

In light of the advanced pubertal development and hormonal changes, a diagnosis of central precocious puberty (CPP) complicating CAH was established. We started treatment with a GnRHa, leuprolide 3.75 mg, administered intramuscularly every 4 weeks, in conjunction with continued hydrocortisone and fludrocortisone therapy. With this treatment, his aggressive behavior improved, and the patient became comparatively quiet and attentive. Clinically and biochemically, his pubertal signs regressed. The dose of hydrocortisone and fludrocortisone remained the same. There was no adverse reaction to these treatments. Our plan is to continue treatment for 2 years to halt the progression of pubertal development, slow bone age advancement, and achieve his predicted adult height.

## Discussion

CAH is a group of diseases caused by deficiencies of enzymes involved in adrenal steroidogenesis, with 21-hydroxylase deficiency being the most common (in 90% of cases). The 21-hydroxylase is one of the cytochrome P-450 enzymes that mediate the conversion of 17-hydroxyprogesterone into 11-deoxycortisol, a cortisol precursor, and of progesterone into deoxycorticosterone, an aldosterone precursor. As a result, hypocortisolism develops, which subsequently stimulates corticotropin release from the anterior pituitary; as a consequence, adrenal gland hyperplasia occurs, and higher levels of 17-OHP and androgens are produced. In this way, precocious pseudopuberty is caused by CAH due to increased adrenal androgen production.[5,6]

In this instance, an eight-year-old boy with symptoms suggestive of PPP was diagnosed with CAH. In line with PPP, biochemical analyses showed increased testosterone levels and decreased baseline and stimulated LH levels. Furthermore, the diagnosis of CAH due to adrenal androgen overproduction was confirmed by low cortisol, high 17-hydroxyprogesterone, and elevated ACTH values. The hormonal assessment indicated that elevated androgen was the cause of the precocious puberty, and not due to the hypothalamic-pituitary-gonadal axis activation.

Initially, the boy was treated with hydrocortisone and fludrocortisone, and it normalized 17-hydroxyprogesterone and ACTH. Despite this treatment and adequate compliance, acceleration of height, increase in testicular volume, penile length, and androgen levels continued. This change in pubertal signs and hormonal panel, along with advancement in patients' bone age, indicated a shift from peripheral to central precocious puberty.

It is well documented that PPP can transform to CPP in patients with CAH. The primary trigger for this transition, which activates the HPG axis, is high androgen levels rather than the underlying CAH.[7,8] When CAH is inadequately treated or undiagnosed, the persistent exposure to increased androgen results in premature activation of the HPG axis, which causes the initiation of central puberty. These patients frequently exhibit advancement in bone age, which is a reflection of skeletal maturation, and it correlates with the development of central puberty.[9] Our case was delayed diagnosed as CAH at the age of eight years, with advanced bone age. This may be the reason which converted our case from PPP to true precocious puberty.

The importance of early diagnosis and adequate treatment of CAH is highlighted in this case to prevent progression from PPP to CPP and to reduce the risk of early pubertal alterations.

The boy developed asymmetrical testicular enlargement, and ultrasonographic evaluation of the testes revealed testicular microlithiasis (TM) and a varicocele, a unique finding in this case. TM may present in healthy individuals without any testicular pathology. However, TM is more common in CAH than in healthy individuals.[9] In patients with CAH, TM is more prevalent, especially when TART is associated with CAH, and CAH is diagnosed at an advanced age. Varicocele, epididymal cyst, and hydrocele may present in a patient with CAH and TM.[10]

With the diagnosis of CPP in this patient, treatment was modified to include a GnRHa along with hydrocortisone and fludrocortisone. For the management of central precocious puberty, the use of GnRHa is a well-established therapeutic approach. Previous studies have supported its use to suppress gonadotropin

secretion, prevent pubertal progression, and reduce bone age advancement. All of these are critically important for optimizing adult height in patients with CPP.[9,10] The patient exhibits excellent response with the initiation of leuprolide acetate, which stabilizes the pubertal signs, including testicular volume and hormonal parameters. GnRHa therapy effectively arrested the progression of bone age and height acceleration.

## Conclusions

In conclusion, this case highlights the challenges and complexity of managing CAH when it is associated with precocious puberty. The importance of early diagnosis and proper treatment to prevent the transition from peripheral to central precocious puberty is underscored in this case. Additionally, it shows the effectiveness of GnRHa therapy in halting the progression of central puberty, preserving growth potential, and improving sustained outcomes for children with CAH and CPP.

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**Disclosure**

The authors have no conflicts of interest to disclose.

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**Data Availability**

Any queries regarding this study should be directed to the corresponding author, and supporting data are available from the corresponding author upon reasonable request.

**Consent to Participate**

Written informed consent was obtained from the legal guardian of the patient. All methods were performed following the relevant guidelines and regulations



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