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# CENTRAL PRECOCIOUS PUBERTY COMPLICATING CONGENITAL ADRENAL HYPERPLASIA: A CASE REPORT

**Nani Nordin[a], Lim Pei Pei[b], Hasliza Abu Hassan[b] , Hani Ajrina Zulkeflee[c], Siti Nadirah Ab Rahim[a,*]**

[a] Department of Pre-Clinical, Faculty of Medicine and Defence Health, National Defence University of Malaysia, Sg. Besi Camp, 57000 Kuala Lumpur, Malaysia
[b] Department of Clinical, Faculty of Medicine and Defence Health, National Defence University of Malaysia, Sg. Besi Camp, 57000 Kuala Lumpur, Malaysia
[c] Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Bandar Baru Nilai, 71800 Nilai, Negeri Sembilan, Malaysia

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**ABSTRACT**

Congenital adrenal hyperplasia (CAH) is classically known to be responsible for peripheral precocity. It is caused by genetic defects that result in a deficiency of enzymes vital for adrenal steroidogenesis. However, in rare cases, central precocious puberty (CPP) can develop because of chronic hyperandrogenaemia, particularly in late-diagnosed CAH. This condition may develop following prolonged exposure to inadequately suppressed adrenal androgens, particularly in poorly controlled disease. Tanner staging monitoring, bone age determination, and confirmatory GnRH stimulation tests are essential in diagnosing CPP in CAH patients. We describe a case of a girl with simple virilising CAH, initially diagnosed at 3 years old, who subsequently developed CPP at 6 years old due to delayed presentation and poor treatment adherence. This case underscores the critical importance of enhanced patient education on early diagnosis, treatment adherence, and close monitoring of CAH in preventing and allowing the early detection of CPP.

## 1.0 INTRODUCTION

Congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders characterized by enzyme deficiencies that disrupt adrenal steroidogenesis, most commonly the 21-hydroxylase enzyme [1]. This deficiency leads to inadequate cortisol production and the resultant adrenal hyperplasia, causing an overproduction of adrenal androgens [2]. Clinically, CAH is recognized for causing peripheral precocious puberty, where early virilisation presents as clitoromegaly in females [2]. However, in rare cases, central precocious puberty (CPP) can develop due to chronic hyperandrogenaemia, especially in patients with late-diagnosed forms of CAH [3-4]. The pathophysiological mechanism in the development of CPP in CAH is linked to long-term exposure to high levels of androgens. This can reduce the sensitivity of the gonadotrophin–releasing hormone (GnRH) pulse generator to feedback inhibition [5]. Therefore, if CAH is left untreated or diagnosed late, it may lead to premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, which leads to early sexual maturation [6-7]. Although the immediate concern in CAH is early precocity, electrolyte disturbances and hypocortisolism, the long-term health consequences are also equally significant [7-8]. Untreated or poorly managed CAH may result in a compromised adult height due to early epiphyseal closure, and the development of metabolic consequences such as obesity, insulin resistance, hypertension, and psychosocial challenges related to early physical changes and body image issues [8-9]. Effective management of CAH is essential as suboptimal glucocorticoid therapy can accelerate the advancement of CPP [9-10].

This case study reports a 3- year-old girl with a late presentation of CAH (simple virilising form). She later developed CPP at the age of 6 due to the delayed intervention and non-adherence to glucocorticoid therapy. This case highlights the clinical consequences of a late diagnosis and poor compliance with CAH treatment; emphasizing the necessity for enhanced patient education to avert complications such as CPP.

*Corresponding Author | Ab Rahim, S. N. | nadirah@upnm.edu.my

In the following section, we will discuss the patient's clinical presentation, diagnostic processes, and treatment responses to highlight the crucial role of adherence to therapeutic plans and ongoing monitoring in effectively managing CAH.

## 2.0 CASE DESCRIPTION

A 3-year-old girl born out of a non-consanguineous marriage was referred for investigation of ambiguous genitalia. She was noted to have a prominent clitoris by her parents since a few weeks after birth. However, since the patient was well, the parents decided to observe until she had grown older before seeking treatment. She was born via normal vaginal delivery without antenatal and postnatal complications. The patient was well since birth with normal growth and development. On examination, there were no dysmorphic features observed. Her blood pressure was 106/58 mm/Hg (normal for her age and height). Her height and weight were 105 cm (75-90th centile) and 26.5 kg (75 centile), respectively. There was skin hyperpigmentation, especially around the lips and nipples. She had ambiguous genitalia in the form of clitoromegaly. There was no hyperpigmentation observed at the genitalia, and no clinical evidence of pubertal changes, such as pubic hair or axillary hair growth were noted. A serum 17–hydroxyprogesterone (17-OHP) was measured and was determined to be significantly elevated (988 nmol/l, normal range: 0.1-2.7). This confirmed the diagnosis of CAH. Further results are as follows: Serum testosterone 6.9 nmol/L (0.5-2.6), Dihydroepiandrostenedione-sulphate (DHEAS) 11.9 µmol/L (0.9-11.7). Serum cortisol and ACTH levels were normal. Serum electrolyte and renal function tests were also normal. Wrist x-ray demonstrated a bone age of 8 years old (4 years advanced from the chronological age). Cytogenetic study revealed a 46, XX karyotype with no abnormality. Pelvic and abdominal ultrasound revealed the presence of uterus with normal ovaries. No enlargement of adrenal gland was revealed. CAH of 21-hydroxylase deficiency (simple virilising form) was diagnosed.

The patient was started on oral hydrocortisone 12 mg/m²/day. Clitoral reduction with vaginoplasty was performed. She was followed up regularly for assessment of growth and secondary sexual characteristics. 17-OHP and testosterone levels were periodically measured to monitor adrenal suppression, and medication was adjusted accordingly (Table 1) with initiation of oral hydrocortisone 12 mg/m$^2$/day. Baseline and follow-up levels of 17-OHP and testosterone of the patient are depicted in Table 1. Both markers were noted to be markedly reduced compared to the baseline at diagnosis. Testosterone levels were particularly more significantly controlled.

Table 1: Baseline and follow-up levels of 17-OHP and testosterone of the patient starts at 3 years old to 6 years old

| Laboratory parameters | At diagnosis | 3 m | 6 m | 9 m | 12 m | 18 m | 1 y | 2 y | 3 y |
|---|---|---|---|---|---|---|---|---|---|
| 17-OHP nmol/L (normal range: 0.1-2.7nmol/L) | 988.0 | 56.3 | 38.8 | 22.2 | 64.1 | 28.3 | 50.8 | 17.4 | 31.0 |
| Testosterone nmol/L (normal range: 0.8-2.6nmol/L) | 6.9 | 4.2 | 5.1 | 0.6 | 1.4 | 0.4 | 1.5 | 0.4 | 1.2 |

*Abbreviations; month= m. year =y.

Despite the follow-ups, the parents admitted to poor adherence to the medication, especially during vacations. At the age of 6 years, the patient was noted to develop progressive breast enlargement (Tanner stage 2), especially on her left side. An accelerated increase in height (8.5 cm in 11 months) with a bone age of 10 years (4 years advanced from chronological age of 6 years) was noted. These clinical signs of precocious puberty prompted further laboratory workup. A basal gonadotrophin and oestradiol (E2) levels were measured, and the results showed baseline LH of 0.2 IU/L, FSH 7.0 IU/L, and E2 < 37 pmol/L with LH peak post-GnRH of 12 IU/L (more than 5.0 IU/L from baseline), suggestive of CPP. GnRH agonist therapy (Leuprolide acetate) was initiated, with plans for ongoing follow-up and monitoring to assess treatment response. The subsequent GnRH stimulation test, repeated after 2 months of therapy showed no peak in LH after GnRH (Table 2), indicative of a successful response to treatment. The GnRH agonist therapy was maintained until the subsequent follow-up. Subsequently, there was no LH peak of more than 5.0 IU/L from baseline observed after 2 months of initiation of therapy. The result suggests a good treatment response.

*Corresponding Author | Ab Rahim, S. N. | nadirah@upnm.edu.my

Table 2: GnRH stimulation test showed an initial LH peak post-GnRH of 12IU/L

| Time (min) | Before initiation of GnRH agonist | | | | | After 2 months of initiation of GnRH agonist | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 30 | 60 | 90 | 120 | 0 | 30 | 60 | 90 | 120 |
| LH (IU/L) | 0.2 | 12.0 | 10.0 | 7.0 | 6.0 | 0 | 2.0 | 1.0 | 1.0 | |
| FSH (IU/L) | 7.0 | 19.0 | 23.0 | 21.0 | 19.0 | 1.0 | 2.0 | 2.0 | | |
| E2 (pmol/L) | < 37 | | | | < 37 | < 37 | | | | |

## 3.0 DISCUSSION

### 3.1 Central Precocious Puberty (CPP) Complicating Congenital Adrenal Hyperplasia (CAH)

Precocious puberty is defined as the appearance of secondary sexual characteristics before the age of eight in girls and nine in boys [11]. This condition can be divided into two types: CPP and peripheral precocious puberty (PPP). CPP, often referred to as true precocious puberty, is caused by the early activation of the HPG axis before the pubertal age [3]. On the other hand, PPP, also termed as pseudo-precocious puberty, does not involve the HPG axis and can be caused by various factors, including the release of sex steroids from adrenal glands, gonads, exogenous sources, or ectopic gonadotrophin production from germ cell tumour [3, 12]. The patient's clitoromegaly, which appeared at the age of 3 as a sign of peripheral precocity, was determined to be caused by CAH. CAH is a group of autosomal recessive disorders resulting from a deficiency of an enzyme required for the synthesis of cortisol in the adrenal cortex. The most common form of CAH is the nonclassical type, affecting 1 in 200 to 1 in 2000 individuals [1]. While the classical forms are rarer but severe due to complete enzyme deficiency, the non-classical form is less severe with partial enzyme deficiency [1]. The most frequently affected enzyme is 21-hydroxylase, which deficiency accounts for more than 90% of cases [13]. There are several variants of 21-hydroxylase deficiency, namely the classical salt-wasting, the simple virilising, and the non-classical late-onset form [13]. The patient in this report was diagnosed with simple virilising CAH and sought medical attention only at the age of three. The term CAH is used to denote the congenital origin of this disorder (usually at birth) and the adrenocortical hyperplasia that results from the compensatory ACTH response to cortisol deficiency [1]. This diverts the adrenal steroidogenesis pathway to androgen production in zona reticularis, leading to the manifestation of virilisation as in Figure 1. This causes peripheral precocious puberty, which manifests as prepubertal clitoromegaly in females, penile and testicular enlargement in males, and pubic hair development in both [12]. PPP is a well-established sequela of CAH. Nevertheless, in rare cases, children with CAH have been reported to develop CPP [12]. CPP is more commonly developed in the non-classical CAH variant due to its late and prolonged state of hyperandrogenaemia [2].

Neeman et al reported that CPP was the initial clinical presentation in 5% of girls with non-classical CAH [4]. Similarly, Dayal et al. demonstrated that 9.1% of a cohort consisting of 55 children treated for CAH between 2007 and 2016 were diagnosed with CPP [3]. The pathophysiology of CPP in CAH lies in the reduction in the sensitivity of the GnRH pulse generator to sex-steroid inhibition by the prolonged excess pubertal androgens [4]. The late presentation of virilisation in this patient explains the reason for the delayed initiation of medical management of CAH. Meanwhile, both late diagnosis and suboptimal adherence to treatment are the underlying reasons for CPP development in this patient [3-4]. Other than that, the initiation of glucocorticoid treatment itself could lead to CPP in a patient with CAH by induction of a sudden decrease in androgen levels that stimulate the pituitary gland to release gonadotrophins [5]. Therefore, clinicians should also be aware of the potential development of CPP following the initiation of corticosteroid therapy in patients with late-diagnosed CAH [5]. Figure 1 highlights the vital role of 21-hydroxylase (CYP21) enzyme in the adrenal steroidogenesis pathway. It is the most affected enzyme in CAH caused by CYP21A2 gene defect [1]. Partial 21-hydroxylase enzyme deficiency in this patient still allows an adequate aldosterone and cortisol production, thus preventing salt wasting and hypocortisolism. However, the accumulation of the steroid precursors above 21-hydroxylase in the zona glomerulosa and fasciculata will be diverted towards the production of androgens in the zona reticularis, hence the reason for raised 17–hydroxyprogesterone (17-OHP) precursor, androgens, dihydroepiandrostenedione-sulfate (DHEAS), and testosterone level in this patient. The hyperandrogenaemia state is responsible for clitoromegaly in this patient. But prolonged exposure to chronic hyperandrogenaemia leads to reduced sensitivity of GnRH pulse generator towards androgen feedback inhibition, thereby causing CPP [5]. The prolonged exposure to androgens is the key reason for CPP development in an initially peripheral form of precocious puberty.

*Corresponding Author | Ab Rahim, S. N. | nadirah@upnm.edu.my

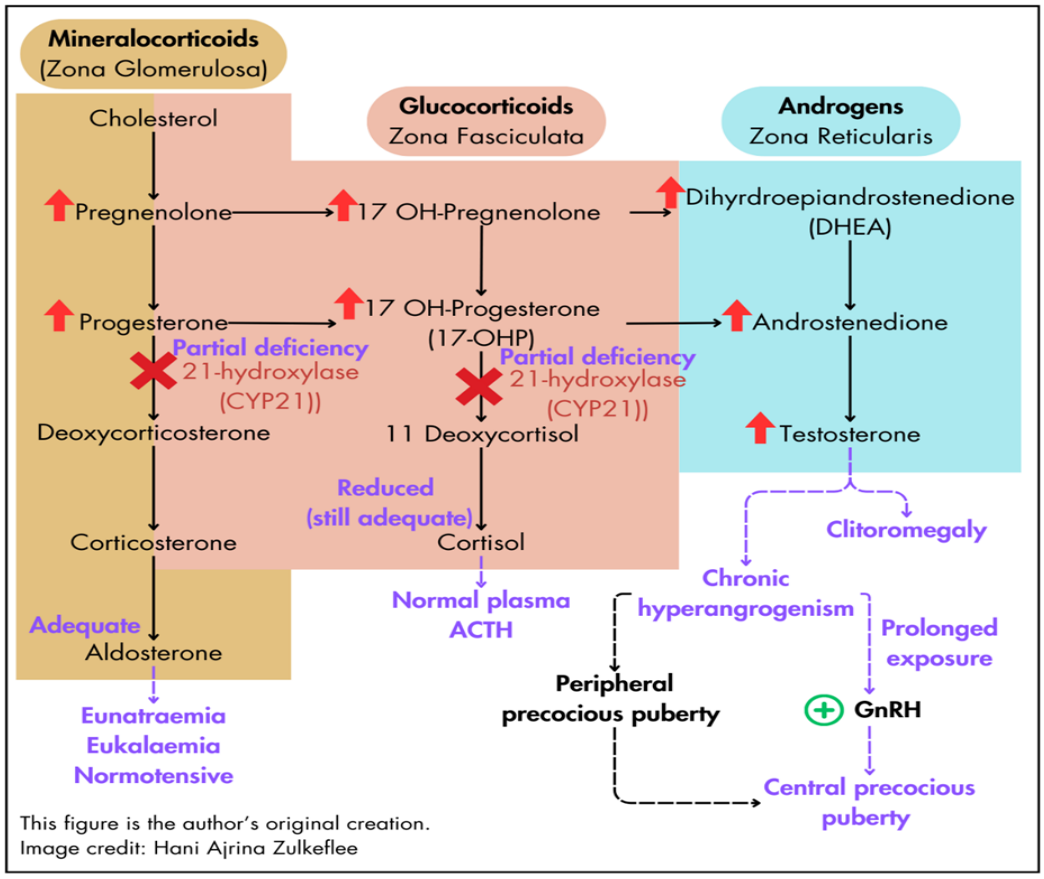


Figure 1. Adrenal steroidogenesis pathway with deficiency in 21-hydroxylase

### 3.2 The Management of CPP in CAH

The diagnosis of CPP relies on the careful detection of clinical features associated with early pubertal changes. Accurate assessment and Tanner staging are essential for identifying the early onset of secondary sexual characteristics in patients with CAH. Additionally, growth velocity should be closely monitored, as accelerated linear growth is a key indicator of early puberty. Bone age is an initial screening test. If the bone age is significantly advanced (greater than two standard deviations) than the chronologic age, additional hormonal testing should follow to distinguish-between peripheral and central causes [12, 14]. A baseline prepubertal LH level of greater than 0.3 IU/L is suggestive of CPP and levels under 0.3 are usually indicative of peripheral causes or benign variants [11-12]. However, baseline levels are usually inconclusive, especially if there is a high suspicion for central causes [6]. Therefore, GnRH stimulation test; the gold standard, should be performed as confirmatory [6, 12]. Luteinizing hormone (LH) increments of ≥4–5 IU/L at 30–60 minutes after GnRH administration are established criteria to diagnose CPP [6, 11]. Values >5 IU/L at both 40- and 45-minute post-GnRH stimulation have shown 98% sensitivity and 100% specificity [6]. Treatment of central precocity in CAH should include adequate glucocorticoids and GnRH agonists. The main goals of treatment are to preserve the adult height and to alleviate the associated psychosocial stress. The glucocorticoids work by suppressing ACTH and normalizing adrenal androgens. GnRH agonists serve as the standard treatment for CPP by inhibiting sex hormone secretion, thereby stabilizing secondary sexual characteristics and preventing bone fusion, which is essential for optimal final adult height. This treatment helps slow down bone age advancement and growth velocity in patients with CAH complicated by CPP, which could assist in improving linear growth [15]. The effectiveness of GnRH agonists in CPP can be observed biochemically through the GnRH stimulation test. This patient's subsequent GnRH stimulation revealed an LH peak of less than 5, indicating a good response. Continuous monitoring of the patient's pubertal progression, growth velocity, and skeletal maturation is crucial during treatment. This surveillance is necessary as untreated precocious puberty can lead to short stature and significant emotional and behavioural issues [8].

Regular assessments allow for timely adjustments to the treatment plan, ensuring optimal outcomes for the patients. Managing CPP in the context of CAH presents unique challenges. One of the primary difficulties

*Corresponding Author | Ab Rahim, S. N. | nadirah@upnm.edu.my

lies in ensuring consistent adherence to glucocorticoid therapy, which is crucial for controlling androgen excess. However, treatment compliance is often hindered by concerns about side effects, misunderstanding of the disease by families, or lack of access to regular follow-up care [15]. Moreover, coordinating care among various healthcare providers is essential to monitor not only the patient's hormonal profile and growth but also their psychosocial development, which may be impacted by early pubertal changes [2]. If CPP remains unrecognized or inadequately treated, several complications may arise. One of the most prominent effects is a compromised adult height due to premature epiphyseal fusion. Additionally, patients are at increased risk of metabolic disturbances, such as obesity and insulin resistance, which can persist into adulthood. More recent studies have demonstrated the link between early menarche with development of certain malignancies, such as breast cancer [16]. Psychosocial consequences are also of great concern, as early physical development may contribute to anxiety, poor self-image, and social difficulties, particularly in young girls [5]. Long-term management of patients with CAH complicated by CPP requires a comprehensive and multidisciplinary approach. Regular follow-up with paediatric endocrinologists is essential to monitor growth patterns, pubertal progression, hormone levels, and bone age, allowing for timely adjustments to treatment. Psychosocial support should be integrated into care plans, particularly for children who may struggle with the emotional impact of early puberty. Collaboration with child psychologists can help address body image concerns and support emotional resilience [4-5]. Parental education plays a vital role in improving treatment adherence. Ensuring that caregivers understand the importance of consistent glucocorticoid therapy and routine monitoring is key to preventing long-term complications [11].

As the patient transitions into adolescence, a structured plan for transfer to adult endocrinology services should be developed to maintain continuity of care. Additionally, the duration and appropriateness of GnRH agonist therapy should be periodically reassessed to avoid overtreatment and to support balanced psychosocial and physical development [15-16]. This case report significantly contributes to the existing knowledge of CPP in the context of CAH by emphasizing the critical need for timely diagnosis and treatment adherence. It highlights the repercussions of delayed timely intervention, reinforcing the importance of effective monitoring plans in mitigating risks associated with CPP. The key lesson learned from this case reveals that proactive management and adherence to treatment protocols are essential to optimizing outcomes for patients with CAH, ultimately enhancing clinical practices and guiding future efforts.

## 4.0 CONCLUSION

This case illustrates that CPP is a rare but significant complication of CAH, especially in late-diagnosed cases due to prolonged androgen exposure from treatment non-adherence. CPP could develop because of inadequate androgen suppression, thereby activating the HPG axis, causing early pubertal development. Regular monitoring of Tanner staging is essential for early detection, which may prompt a bone age assessment and GnRH stimulation test, facilitating the timely diagnosis and management. Emphasizing treatment adherence, educating parents about the importance of compliance, and implementing a multidisciplinary approach, including paediatricians, endocrinologists, and child psychologists, can further enhance holistic patient care and improve health outcomes of affected children. Compliance and monitoring of treatment adequacy in late-diagnosed CAH patients are crucial to prevent complications such as short stature, emotional, and behavioural issues. By focusing on these strategies, the risk of CPP and its associated complications can be reduced through better management of CAH.

## 5.0 CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## 6.0 AUTHOR'S CONTRIBUTION

Nordin, N. (Conceptualization; Literature review; Clinical data collection; Writing of original draft)
Lim, P. P. (Literature review; Writing and critical revision of the article for important intellectual content)
Abu Hassan, H. (Critical revision of the article for important intellectual content)
Zulkeflee, H. A. (Construction of illustration; Critical revision of important intellectual content)
Ab Rahim, S.N. (Literature review; Writing and critical revision of important intellectual content)

*Corresponding Author | Ab Rahim, S. N. | nadirah@upnm.edu.my

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*Corresponding Author | Ab Rahim, S. N. | nadirah@upnm.edu.my 