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Case Report

# A Rare Cause of Precocious Puberty in a 19 Month Old Boy

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**Abstract**

Congenital Adrenal Hyperplasia (CAH) is one of the causes of peripheral precocious puberty in children. We report the case of a 19-month-old boy who presented with increased penile enlargement, prepubertal testes and an advanced bone age. His biochemistry was consistent with a rarer form of CAH, 11-beta-hydroxylase deficiency, and the diagnosis was subsequently confirmed with genetic testing. Treatment includes oral steroids to normalize androgen levels, decrease mineralocorticoid synthesis, and maintain normal growth velocity and skeletal maturation.

**Keywords:** Congenital adrenal hyperplasia; Precocious puberty; 11-Beta-hydroxylase

## Abbreviations

Congenital Adrenal Hyperplasia (CAH); Standard Deviation (SD); Body Mass Index (BMI); Luteinizing Hormone (LH); Follicle Stimulating Hormone (FSH); Thyroid Stimulating Hormone (TSH); 17-Hydroxyprogesterone (17-OHP); Adrenocorticotropic Hormone (ACTH)

## Introduction

Congenital Adrenal Hyperplasia (CAH) is a group of disorders inherited in an autosomal recessive pattern characterized by genetic defects in the enzymes involved in adrenal gland steroid production. Depending on the underlying enzymatic deficiency, patients with CAH may present with a variety of symptoms and signs. The most common cause of CAH is 21-hydroxylase enzyme deficiency, which accounts for 90-95% of cases and results in cortisol and aldosterone deficiency. CAH due to 11-beta-hydroxylase deficiency is much rarer, with a prevalence of 5-8%, affecting 1 in 100,000 live births [1]. Mutations in the CYP11B1 gene, encoding the enzyme 11-beta-hydroxylase, account for its clinical and biochemical presentation of CAH [2].

## Case Report

A 19-month-old boy presented with a one-year history of excessive growth and acne and a two-month history of pubic hair. On exam at his first pediatric visit, he was found to have penile enlargement and small testes. He was referred for urgent assessment with pediatric endocrinology. Here, his height was measured at 100.7 cm (+5.91 standard deviations (SD) or >99.9$^{th}$ percentile), his weight was 20.4 kg (>+3 SD or >99.9$^{th}$ percentile), and his body mass index (BMI) was 20.1 kg/m$^2$ (+2.75 SD or 99.7$^{th}$ percentile). He appeared older than chronologic age and had acne on his face, back and arms. He was Tanner stage 2 for pubic hair and his penile length was 8.7 cm. Testes were <1 mL bilaterally. His blood pressure was initially elevated at 107/59 but subsequently normalized on further measurements. He was previously healthy and there was no exposure to exogenous androgens. Initial investigations included Luteinizing Hormone (LH) <1 IU/L, Follicle Stimulating Hormone (FSH) <1 IU/L, total testosterone 3.9 nmol/L (reference 0-1 nmol/L), DHEAS 1.2 umol/L (reference 0.3-6 umol/L), and androstenedione >35 nmol/L. Thyroid stimulating hormone (TSH) was 9.11 mIU/L (reference 0.2-4 mIU/L) and free T4 was 18 pmol/L (reference 10-25 pmol/L). Electrolytes were normal. Cortisol at 9:45 am was 60 nmol/L and 17-hydoxyprogesterone (17-OHP) was 6.3 nmol/L (reference <1 nmol/L). Bone age was advanced to 6-7 years. Abdominal ultrasound showed no evidence of an adrenal mass. Further results pointed to the underlying etiology.

Adrenocorticotropic hormone (ACTH) returned elevated at 51.1 pmol/L (reference 2-11.5 pmol/L) at the time of the initial low cortisol. A 250 mcg ACTH stimulation test showed a peak cortisol of 79 nmol/L (normal >350 nmol/L). Stimulated 17-OHP values were not able to be obtained due to insufficient samples. Aldosterone was 67 pmol/L (reference 70-1090 pmol/L) and renin was suppressed at <1 mIU/L (reference 4.4-46 mIU/L). These results were consistent with a rare cause of CAH, 11-beta-hydroxylase deficiency.

## Discussion

In the adrenal gland, 11-beta-hydroxylase converts 11-deoxycortisol and 11-deoxycortisocterone to cortisol and corticosterone respectively, and is regulated by ACTH. Deficiencies in 11-beta-hydroxylase expression results in high levels of 11-deoxycortisol and 11-deoxycorticosterone, which are subsequently shifted into adrenal androgen production [2]. Females with this condition are born with virilization [1]. Males may have an increased penile size and can present with precocious puberty, rapid growth and advanced bone ages. They are often not diagnosed at birth as 17-OHP levels are not as high as in CAH caused by 21-hydroxylase deficiency and thus can be missed on the newborn screen [2]. Of note, our patient had an initial slightly positive newborn screen for CAH; when repeated at 19 days of age, 17-OHP was normal. In both sexes, high levels of the mineralocorticoid 11-deoxycorticosterone leads to




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hypertension and hypokalemia in some but not all patients [2].

Our patient was started on oral steroids for this presumed diagnosis. 11-deoxycortisol returned elevated at 43.4 nmol/L (reference <2.6 nmol/L) and genetic testing confirmed the diagnosis of 11-beta-hydroxylase deficiency. With treatment, his sex steroids are normalizing, 11-deoxycortisol is decreasing and renin has normalized. His blood pressure and electrolytes have remained normal but will continue to be followed. Two other important long-term issues will be management of short stature due to his advanced bone age and monitoring for the development of central precocious puberty. Growth hormone and Letrozole have both been reported to improve short stature in this condition [3].

In conclusion, our case demonstrates a rarer cause of peripheral precocious puberty, 11-beta-hydroxylase deficiency CAH, which can be diagnosed biochemically and through genetic testing, and treated with oral steroids to normalize androgen levels, decrease mineralocorticoid synthesis, and maintain normal growth velocity and skeletal maturation.

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