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CASE REPORT

Premature pubarche in a child with abnormal 3β-hydroxysteroid dehydrogenase function and Klinefelter syndrome: the intriguing relationship between androgen deficiency and excess

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Key Clinical Message

Disorders of androgen excess may coexist with disorders of androgen deficiency, such as Klinefelter syndrome, and can create diagnostic and therapeutic challenges.

Keywords

3β-hydroxysteroid dehydrogenase deficiency, Klinefelter syndrome, premature pubarche

Introduction

Congenital adrenal hyperplasia (CAH) is an inherited autosomal recessive disorder of adrenal steroidogenesis. Ninety percent of cases are caused by a defect in 21-hydroxylase. Other less common enzyme deficiencies include 3β-hydroxysteroid dehydrogenase, 11β-hydroxylase, and 17α-hydroxylase. The clinical features of CAH range from classical ambiguous genitalia and salt-wasting crisis in infancy to premature pubarche with bone age advancement and short final height [1, 2].

3β-Hydroxysteroid dehydrogenase (3βHSD) deficiency is caused by a mutation in the HSD3B2 gene and also has a classic and nonclassic form. Laboratory findings suggestive of 3βHSD deficiency include elevated DHEAS and 17α-hydroxypregnenolone, and markedly high ratio of 17α-hydroxypregnenolone to 17α-hydroxyprogesterone [2, 3]. The classic salt-wasting forms are due to point mutations in the type II 3β HSD gene. Nonclassic forms are often due to missense mutations in the type II 3β HSD gene that cause incomplete loss of enzymatic function. However, previous studies that evaluated hormonal phenotype and genotype often found no mutation in either the type I or type II 3βHSD gene [3, 4]. Additionally, there is controversy over the hormonal phenotype for diagnosis of 3βHSD deficiency due to concern for overdiagnosis of the condition. In 2002, Lutfellah et al. suggested revised hormonal criteria for diagnosis to predict more accurately 3βHSD deficiency without genotypic proof [5]. Proposed new hormonal criteria included ACTH-stimulated 17α-hydroxypregnenolone level in children with premature pubarche >72 nmol/L, or greater than 11 standard deviations (SD) above the control mean, and ACTH-stimulated 17α-hydroxypregnenolone-to-cortisol ratio in children with premature pubarche >67 or >5 SD above the mean ratio [5].

Like other children with CAH, children with 3βHSD deficiency have elevated androgen levels secondary to adrenal androgen excess. Conversely, hypoandrogenism is an important feature of Klinefelter syndrome (KS), the most frequent type of sex chromosomal abnormality in males. KS is commonly manifested by hypergonadotropic

hypogonadism, small testes, gynecomastia, infertility, tall stature, and cognitive/learning impairment. The onset of puberty occurs at a normal age but usually does not progress to normal adult stages due to the ensuing testicular failure [6, 7].

In 2002, Mantovani et al. investigated whether the presence of molecular defects in the CYP21 gene was detectable in Turner syndrome and KS and found that the frequency of patients with abnormal 17α-hydroxyprogesterone based on ACTH stimulation testing was significantly higher than that of healthy controls, suggesting that mutation frequency was significantly higher in patients affected by Turner syndrome or KS [7]. To our knowledge, two case reports show a coexistence of 21-hydroxylase deficiency and KS [8, 9], but none with 3βHSD dysfunction and KS. Here, we describe a child with KS and decreased 3β-HSD function.

Case

JR is a now eleven-year-old boy born small for gestational age at 26 weeks with history of developmental delay who presented to the Pediatric Endocrinology Clinic for evaluation of short stature and premature pubarche initially at age 6 years. History revealed facial acne, adult body odor, and axillary and pubic hair since age 4 years. At age six, his height was 104.6 cm (*Z* score = −2.83) (Fig. 1). His midparental target height was 170 ± 10 cm. Physical examination showed prepubertal testes (1 cc bilaterally) and Tanner 2 pubic hair. Initial investigation showed: bone age of 9 years at a chronological age of 6 years 5 months (+3.3 SD), DHEAS 365 μg/dL (42–109 μg/dL), 17α-hydroxyprogesterone 42 ng/dL (<116 ng/dL), and testosterone 43 ng/dL (<3–10 ng/dL). LH was detectable at 0.2 mIU/mL. His TSH, free T4, antitissue transglutaminase antibody, and IGF1 and IGFBP3 were within normal range. A retroperitoneal ultrasound showed normal adrenal glands. Based on these results, an ACTH stimulation test was recommended; however, he was lost to follow-up. He returned at 8 years of age. Growth hormone therapy was initiated due to history of small for gestational age with poor catch-up growth (at time of visit, height *Z* score = −2.91). Examination revealed Tanner 3 pubic hair, 2 cc testes, mild acne, and moderate axillary hair. Repeat bone age was between 9 and 10 years of age (+1.8 SD). An ACTH stimulation test showed the following stimulated levels (1 h after IV cosyntropin 250 mcg): 17α-hydroxypregnenolone 1979 ng/dL (88–675 ng/dL), 17α-hydroxypregnenolone/17α-hydroxyprogesterone ratio 35.3 (0.5–6.3), suggestive of a 3β-HSD dysfunction, and cortisol 36.7 μg/dL (15–36 μg/dL) (Table 1). The stimulated 17α-hydroxypregnenolone (nmol/L)/cortisol (μmol/L) ratio was normal at 53.9 (based on Lutfallah et al. hormonal criteria for 3βHSD) [5].

A diagnosis of 3βHSD dysfunction was made. As he had a normal cortisol response, glucocorticoid replacement was not initiated and growth and maturation were monitored at four-month intervals. At 9 years of age, he was diagnosed with Klinefelter syndrome when evaluation for developmental delay revealed a 47 XXY karyotype. At

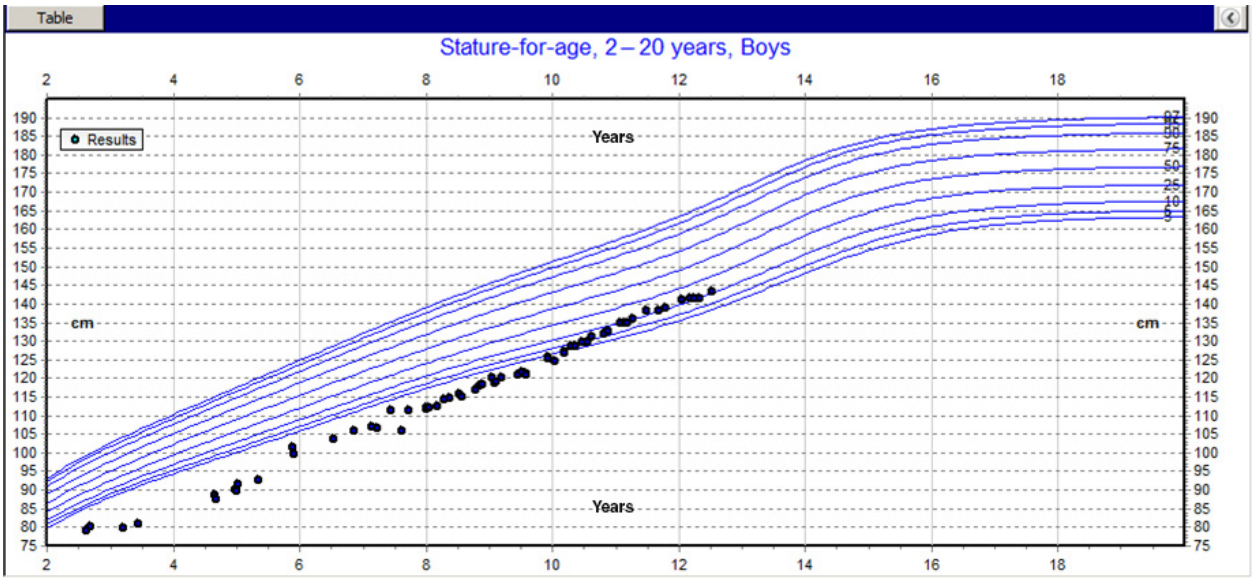

Figure 1. Stature for age of JR. *X*-axis in years and *y*-axis in cm.

a follow-up visit at age 9 years 11 months, his testicular size had increased to 4 cc and gonadotropins were at the pubertal levels of 2.5 mIU/mL (LH) and 6.8 mIU/mL (FSH), with a DHEAS of 417 μg/dL and testosterone of 42 ng/dL (Fig. 2A and B). A bone age completed 3 months later was between 11 years 6 months and 12 years 6 months (+1.8 SD) at chronological age of 10 years 3 months. A diagnosis of early puberty likely secondary to adrenal hyperandrogenism was made. He was started on an aromatase inhibitor to delay epiphyseal fusion. At his most recent visit, at 11 years 2 months, his examination showed good growth velocity on growth hormone, Tanner stage 5 pubic hair, 4 cc testicles, and Tanner 3 phallus. A bone age study performed at chronological age 11 years 2 months was read as 12 years 6 months (+1.5 SD). Laboratory tests at this time revealed FSH of 20.9 mIU/mL, LH of 5.8 mIU/mL, DHEAS of 429 μg/dL, and testosterone of 98 ng/dL. His mother confirmed that he had been taking an aromatase inhibitor at the time.

Discussion

This case describes the consequences of the unusual coexistence between KS and 3βHSD dysfunction leading to a balancing act between androgen excess and insufficiency. These findings were seen in the two previously reported cases of 21-hydroxylase deficiency and KS. One case report describes a Japanese male who was diagnosed with 21-hydroxylase deficiency at birth who had marked acceleration in growth until age 9 years when growth arrested [8]. He initiated steroid treatment after age 10 years and was noted at follow-up to have bilateral, small firm testes. Subsequent chromosomal analysis and testicular biopsy revealed 47 XXY, consistent with KS. It is likely that his short stature, and pubic and axillary hair were attributable to the adrenal androgens from his CAH, but his small testes, arm span (151 cm arm span; 149 cm height), and low testosterone were results of KS [8].

The second case is a 51-year-old man with previously diagnosed idiopathic infertility who presented to an endocrinology clinic with bilateral mastodynia [9]. He was noted on examination to have bilateral gynecomastia and bilateral small, firm testes. Laboratory evaluation revealed hypergonadotropic hypogonadism and altered adrenal function with an elevated ACTH and 17α-hydroxyprogesterone. Karyotype was 47 XXY and he was diagnosed with both CAH and KS. He did not have reported pubertal delay or precocious puberty and his stature was consistent with his genetic target, so was not reduced by high levels of adrenal androgens from CAH or increased due to KS. The hypothesis that adrenal androgen excess masked the KS-related hypogonadism is supported by the quick and progressive deterioration of sexual health with decreased serum testosterone levels when corticosteroid therapy was started. Additionally, the fact that the patient's growth and pubertal onset did not accelerate despite the high levels of circulating androgen supports the concept of defective androgen receptor activity [9].

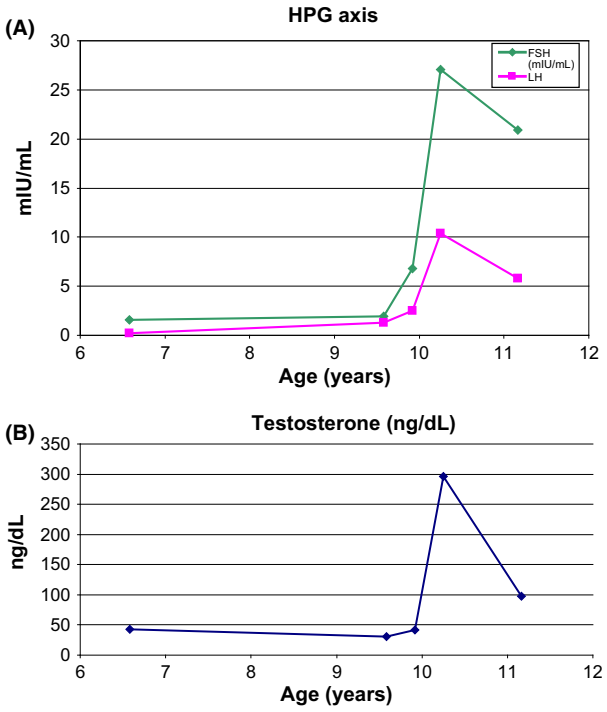

Figure 2. (A) Hypothalamic–Pituitary–Gonadal Axis of JR. *X*-axis is age expressed in years (y). *Y*-axis is mIU/mL of FSH and LH. (B) *X*-axis is age expressed in years (y). *Y*-axis is ng/dL of testosterone.

Table 1. ACTH stimulation test.

	Baseline	Normal values: Mean (range)	Stimulation at 60 min	Normal values: Mean (range)
Cortisol (μg/dL)	5	11 (4–17)	36.7	23 (15–36)
17α-hydroxyprogesterone (ng/dL)	<10	122 (51–240)	56	154 (69–313)
17α-hydroxypregnenolone (ng/dL)	61	95 (20–263)	1979	390 (88–675)
DHEAS (μg/dL)	265	55 (13–119)		

In our patient, a diagnosis of early puberty likely secondary to activation of the hypothalamic–pituitary–gonadal axis following chronic adrenal hyperandrogenism was made, which led to the initiation of an aromatase inhibitor to delay epiphyseal fusion. Subsequent bone age studies showed lessening in his degree of bone age advancement. However, his total testosterone decreased while taking an aromatase inhibitor from 296 to 98 ng/dL. We would expect that his testosterone would be elevated while on an aromatase inhibitor given that the conversion of testosterone to estrogen is inhibited. This is a likely sign that he was entering early testicular failure. If so, we hypothesize that his excess adrenal androgens may be able to compensate for the decreased production in the testes, similar to the adult male described above. It is also possible that if he did require treatment with glucocorticoids and his adrenal androgens decreased, he might have had a clinical course more consistent with KS and not have developed early puberty. We anticipate the need for testosterone replacement therapy in the future.

This is an uncommon combination that clinicians should be aware of, as the evolving testicular failure will influence clinical management. Prepubertally, the adrenal androgen excess predominated in this patient but, as puberty progresses, we speculate that the expected hypoandrogenism from KS will have a greater impact on his phenotypic features. It remains unclear, however, whether there is a true association between KS and a 3βHSD defect or his extreme prematurity and small for gestational age status have also played a role in the abnormal adrenal enzyme system. This case illustrates how the interplay between two disorders with opposing effects on androgen levels can create diagnostic and therapeutic challenges.

Conflict of Interest

None declared.

Authorship

MG and LA: assisted in data gathering for the case report. All authors assisted equally in the writing and editing of the manuscript.

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