

A 46XX Disorder of Sex Development with a Prostate Gland and Increased Level of Prostate-Specific Antigen

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A 5-year-old child with precocious puberty and complete masculinization of the genitalia was diagnosed to have 21-hydroxylase deficiency. The patient was also found to have a prostate gland and increased prostate-specific antigen. The presence of a prostate and its relation to prostate-specific antigen and prostate adenocarcinoma are discussed in the light of the relevant literature.

Key words: prostate ■ prostate specific antigen ■ cancer

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INTRODUCTION

21-hydroxylase deficiency is the most common cause of 46XX disorder of sex development. This enzymatic deficiency decreases cortisol secretion, and the compensatory ACTH increase in turn stimulates the production of adrenal androgens. Increased androgens cause virilization of the external genitalia; however, the internal genitalia are usually normal.¹ On the other hand, development of a prostate gland may ensue again due to increased androgens.² Herein, we report a child with puberty precox who had complete masculinization of the genitalia due to congenital adrenal hyperplasia (CAH). The patient was also found to have a prostate gland and increased prostate-specific antigen (PSA).

CASE REPORT

A 5-year-old child presented to our endocrinology department with pubic hair, deepening of voice and acne development on the back region and the limbs. The child was being reared as a male. The child was born to consanguineous parents, with two healthy sisters and a brother. The family history comprised ambiguous genitalia in one brother, an uncle and the father's uncle—all of whom had died during infancy. Psychometric development was consistent with 3 years of age. Physical exami-

nation was as follows: height 130.4 cm (>97 percentile), weight 35 kg (>97 percentile), height age 9 years, bone age 13.6 years (Greulich and Pyle atlas) and blood pressure 90/60 mmHg. The child had axillary and pubic hair (Tanner stage III). Widespread acne, hoarseness, muscle hypertrophy and genu valgum deformity were also present. The phallus was 8 cm in length and with a normal urethral meatus on the glans. Testicles were not palpable in the scrotum or in the inguinal canals, and the scrotum was hyperpigmented (Figure 1). There was no gynecomastia.

Karyotyping revealed 46,XX chromosome. On biochemical examination, serum electrolytes, glucose, liver and renal function tests were normal. Hormonal tests were as follows; 17 alpha-hydroxyprogesterone 35 ng/mL (0.1–0.9), cortisol 3 µg/dL (5–25), testosterone 23.5 pg/mL (0.15–0.6), ACTH 689 pg/mL (0–60). Based on these findings, a diagnosis of simple virilizing CAH due to 21-hydroxylase deficiency was made and hydrocortisone treatment was initiated. Pelvic ultrasound examination showed the presence of a uterus (23×14×41 mm) and ovaries (23×10, 23×13 with multiple follicular cysts). Testicles could not be visualized by scrotal ultrasound. The prostate was seen below the bladder base both during sonographical and magnetic resonance imaging (32×14×18 mm) (Figure 2). PSA was elevated (290 ng/L, N: 2.236–2.652). Both adrenal glands were found to be hyperplastic on the abdominal ultrasonography. A final diagnosis of genotypic female with CAH due to 21-hydroxylase deficiency was made. The family wanted the child to be reared as a male, and the patient is awaiting hysterosalpingo-oophorectomy and insertion of prosthetic testicles.

DISCUSSION

21-hydroxylase deficiency accounts for 90% of the cases of CAH, which is associated with abnormally low cortisol and high production of androgen precursors, and is the most common cause of ambiguous genitalia. Excessive adrenal androgens in these patients during the 11th week of fetal development lead to hypertrophy of the clitoris, variable virilization of the urethra

and fusion of the labioscrotal folds. But in a female fetus with CAH, normal development of the female internal urogenital tract occurs.^{1,2}

In a female fetus with CAH, the excess adrenal androgens stimulate the paraurethral Skene's gland to develop into a histological and enzymatic homologue of the prostate gland.³ Both timing and the level of adrenal androgens determine whether the prostate gland will develop or not.⁴ For example, a prostate gland develops only in children with severe virilization, i.e., in patients

with Prader type III–V external genitalia or with early androgenic stimulus before the 16th week of development.² Experimentally, exogenous androgen stimulation in the rat model has also revealed the growth of female prostatic glands that are histologically identical to the male prostate.⁵ In the present case, magnetic resonance imaging demonstrated the presence of a uterus, ovaries, urogenital sinus and, additionally, a prostate gland surrounding the posterior urethra.

In children, PSA is produced by male and female periurethral and rectal glands. Periurethral glands in females are considered to be primarily responsible for secreting PSA, as shown by immunohistochemical findings.⁶ Girls generally have undetectable PSA when compared with boys. Keeping in mind the PSA's absolute tissue specificity for the prostate gland, similar to our case, we imply that the presence of PSA can be linked with the presence of the prostate gland.^{7,8} Moreover, reminded of the rare neoplastic development in these patients' prostate glands,⁹ we advocate that such patients should also be followed with respect to prostatic adenocarcinoma. Last but not least, PSA can also be used during the follow-up in this regard.

Figure 1. Examination of the external genitalia revealed complete scrotal fusion with increased pigmentation



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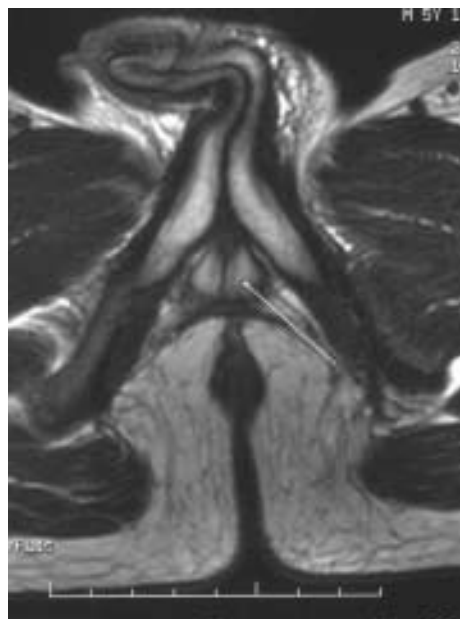
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Figure 2. T2-weighted magnetic resonance imaging (MRI) of the lower pelvis

A. Sagittal view



B. Axial view; white arrows showing the prostate gland



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