Partial androgen insensitivity syndrome presenting as pubertal gynecomastia: clinical and hormonal findings and a novel mutation in the androgen receptor gene

Priya Vaidyanathan and Paul Kaplowitz
Division of Endocrinology, Children’s National Health System, Washington, District of Columbia, USA

Summary

Pubertal gynecomastia is common, can be seen in 65% of the adolescent boys and is considered physiological. It is thought to be due to transient imbalance between the ratio of testosterone and estradiol in the early stages of puberty. It resolves in 1–2 years and requires no treatment. However, more persistent and severe pubertal gynecomastia is less common and can be associated with pathological disorders. These can be due to diminished androgen production, increased estrogen production or androgen resistance. We report a case of persistent pubertal gynecomastia due to partial androgen insensitivity syndrome (PAIS), classical hormone findings and a novel mutation in the androgen receptor (AR) gene.

Learning points:
- Laboratory testing of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone for pubertal gynecomastia is most helpful in the setting of undervirilization.
- The hormonal finding of very high testosterone, elevated LH and estradiol and relatively normal FSH are classical findings of PAIS.
- Gynecomastia due to PAIS will not resolve and surgery for breast reduction should be recommended.

Background

This case describes presentation, diagnosis and treatment of a rare cause of pubertal gynecomastia. The diagnosis was important for proper management of the condition and led to the identification of a novel AR gene mutation.

Case presentation

A healthy, 17-year and 7-month-old male was evaluated for persistent and progressive gynecomastia of 3-year duration. Birth and childhood history was unremarkable. He reported onset of puberty about 4 years ago and had not started shaving. He was not taking any medications. There is no family history of gynecomastia. His height was 178.5 cm, (0.4 s.d.), weight was 63 kg, +0.2 s.d., BMI 20.6, −0.1 s.d. He had a normal general and systemic examination. Distinct features were a lack of facial hair, sparse axillary hair, very little body hair, stretched penile length of 8 cm (<−2.5 s.d.), pubic hair Tanner stage 3 and testicular volume 15 mL. There was bilateral well developed Tanner 3 breast tissue. There was no nipple discharge. Patient denied being sexually active. Laboratory findings are provided in Table 1.
Androgen insensitivity is caused by a defect in the AR, which is a nuclear transcription factor encoded by the AR gene located on the X chromosome at Xq11–12.1. This results in end-organ resistance to androgens resulting in underandrogenization of varying degree despite normal to high levels of androgens. On one end of this spectrum is the total lack of response to androgens as seen in complete androgen insensitivity syndrome (CAIS). CAIS has a prevalence of 1:64 000 (3). The main characteristics are 46, XY karyotype, female external genitalia, a short, blind ending vagina, an intra-abdominal or inguinal gonad, lack of uterus and oviducts, development of gynecomastia and the absence of pubic and axillary hair. Testosterone levels are elevated at the time of puberty, while also elevated LH levels are found.

PAIS has a prevalence of 1:20 000 (4) and results from a milder AR mutation. Phenotypic presentation can vary from ambiguous genitalia to nearly normal male. PAIS with phenotypically normal male external genitalia can be first noted by the appearance of gynecomastia in puberty as seen in our patient and is to be considered in the differential diagnosis of persistent pubertal gynecomastia. At puberty, elevated LH, testosterone and estradiol levels are observed. The proposed mechanism is a dysfunction of the hypothalamic AR that impairs the negative feedback regulation of LH (and FSH) on the hypothalamic–pituitary–gonadal axis (5) resulting in elevated LH levels despite increased testosterone levels. This leads to increased circulating estradiol levels through aromatization and exerts negative feedback on the hypothalamic–pituitary axis resulting in normal FSH levels. Individuals with mild symptoms of undervirization (mild androgen insensitivity syndrome (MAIS)) and infertility have been described as well. Phenotypic variation between individuals in different families has been described for several mutations.

The AR is encoded by an eight exon gene on the X chromosome long arm (4). More than 800 mutations in the AR gene have been reported in AIS patients (www.androgendb.mcgill.ca/) (7). The mutation identified in the AR gene in our patient is a novel one, an A721T missense mutation that has not been reported before. While this mutation has not been previously identified as a cause of AIS, it has been reported as somatic mutation in prostate cancer. Shi et al. (8) have studied 44 mutant ARs from human prostate cancer and reported that this particular mutation is associated with reduced androgen activity. Since AIS results from loss of function alteration in the AR, the A721T missense mutation is a strong candidate for this phenotype. The patient has no known family history of gynecomastia or infertility and one could therefore speculate that it is a de novo mutation.
Persistent pubertal gynecomastia, PAIS

Dr Kaplowitz was not involved in the review or editorial process for this paper, on which he is listed as an author.

---

References


