sexes

MDPI

Case Report

De La Chapelle Syndrome: Clinical and Physical Performance Implications

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Abstract: Gynecomastia in adolescence is a benign condition that mostly disappears spontaneously within approximately two years from onset. When it is associated with hypogonadism, it may suggest a disorder of sexual differentiation. We report the case of a young man (18 years old) with gynecomastia associated with azoospermia, small testes, hyperestrogenism and hypergonadotropic hypogonadism. A karyotype 46,XX was found, and searching for SRY (sex-determining region Y) by fluorescence in situ hybridization (FISH) highlighted the presence of the gene on the terminal region of the short arm, with breakpoints likely in Xp22.3 and Yp11.3. Implications of testosterone replacement therapy with respect to sex differentiation disorder and to physical performance are discussed.

Keywords: gynecomastia; hypogonadism; rare disease; DSD; short stature; physical performance

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1. Introduction

Gynecomastia is an increase in male breast volume. In adolescence, it is a common occurrence affecting two thirds of boys and it is caused by a temporary imbalance in the androgen/estrogen ratio during puberty [1]. In its isolated form, it is a benign condition that appears concurrently with peak height velocity [2] and spontaneously disappears in most cases within approximately two years of onset, when androgen levels rise, without any medical treatment or surgery required [3].

Less often, it represents a pathological condition whose specific cause is rarely identified. When it is associated with the presence of hypergonadotropic hypogonadism, it could be related to tumors or chromosomal abnormalities [4,5].

We describe a case of a young male coming to our attention with the presence of gynecomastia and reduced testosterone levels resulting from a rare and underdiagnosed genetic condition during adolescence.

2. Patient and Methods

An 18-year-old man came to our Andrology Clinic for bilateral long-standing gynecomastia, which was confirmed by ultrasound examination.

The patient had no significant past medical or family history of breast cancer or substance abuse; he reported not having ever attempted sexual intercourse and the absence of any sexual disturbances. At the first clinical evaluation, his height was 166 cm (5th–10th percentile, lower than the mid-parental height of 8 cm, corresponding to −1.0 SDS) with a deflection of the stature growth curve during the pubertal period; he presented mild obesity

(a body mass index of 30 kg/m^2), penile size and body hair distribution appropriate for his age (Tanner stage G1 P4) and testicular volume of 2 mL, as measured by the Prader's orchidometer. He showed normal cognitive and socio-relational development. Phimosis of the prepuce was found with pain at the attempt of retraction. At the scrotal ultrasound, he showed marked bilateral hypoechoic testes, absence of testicular or epididymal focal lesions, and marked atrophy (a volume of 1.5 mL bilaterally).

Hormonal tests documented a condition of primary (subclinical compensated) hypogonadism (reference ranges are reported in brackets): luteinizing hormone (LH), 12.57 mIU/mL (1.5–9.3 mIU/mL); total testosterone, 9.1 nmol/L (8.36–28.7 nmol/L); free testosterone 198 pmol/L (277–1664 pmol/L); and follicle-stimulating hormone (FSH), 26.09 mIU/mL (1.4–18.1 mIU/mL); also found were increased estradiol levels, 52.12 pg/mL (<39.8 pg/mL); low levels of anti-Müllerian hormone (AMH), 4.7 ng/mL (0.57–17.8 ng/mL); and inhibin B (IB), 23.1 pg/mL (25–325 pg/mL). The patient was in a condition of euthyroidism (thyroid-stimulating hormone (TSH), 1.07 uIU/mL (0.55–4.78 uIU/mL), and showed normal levels of prolactin, 6.04 ng/mL (2.1–17.7 ng/mL), and prostate-specific antigen (PSA), 0.8 ng/mL (<4 ng/mL), and normal adrenal function: adrenocorticotropic hormone (ACTH), 11.08 pg/mL (<47 pg/mL); cortisol, 8.02 ug/dL (4.3–22.4 ug/dL); 17α-hydroxyprogesterone (17-OHP), 0.83 ng/mL (0.5–2.1 ng/mL). Hormones measurements were conducted throughout chemiluminescence assays on the Advia Centaur XP ® platform (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA).

A complete sperm analysis showed oligoposia (0.5 mL; normal value > 1.4 mL) and the absence of sperm and germ cells, even after centrifugation of the sample, defining the condition as azoospermia.

Karyotyping was therefore performed, surprisingly showing a 46,XX pattern in all 30 metaphases examined. The subsequent in-depth analysis using fluorescence in situ hybridization (FISH) with SRY (sex-determining region Y) probe highlighted the presence of the gene on the terminal region of the short arm of an X chromosome (Figure 1), probably due to an unbalanced translocation between the short arms of a Y chromosome, with breakpoints likely in Xp22.3 and Yp11.3. Therefore, a diagnosis of testicular disorder of sexual development (DSD) 46,XX was made (identified as De la Chapelle syndrome) [6].

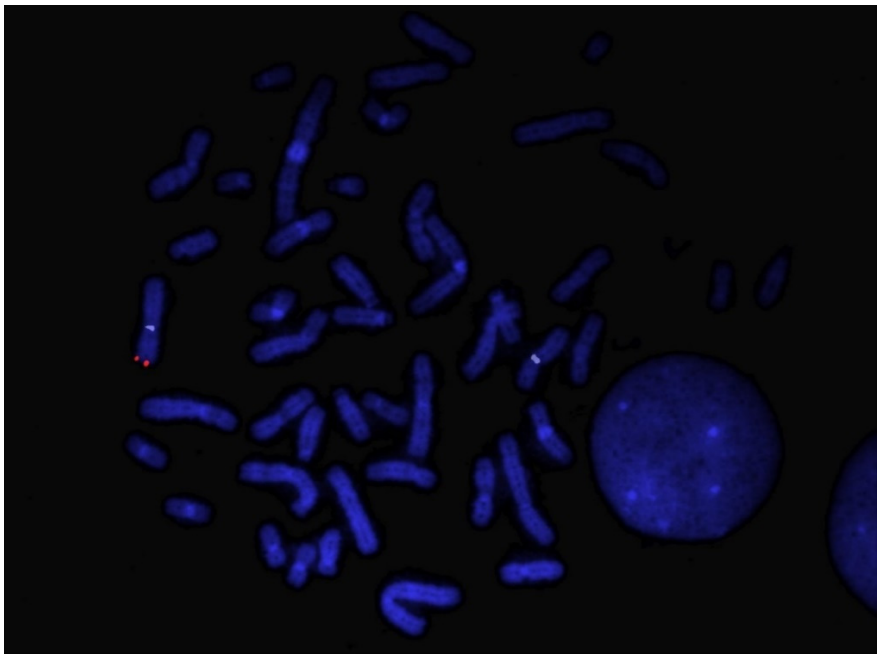

Figure 1. CytoCell SRY FISH probe of the patient. The red signal on the short arm of the X chromosome reveals the presence of the SRY gene. The probe mix also contains control probes for the X centromere (DXZ1), which is labeled in purple.

X-rays of the hand and wrist estimated a bone age of approximately 18 years.

Magnetic resonance imaging (MRI) of the lower abdomen and pelvis showed no residual of female differentiation or Müllerian tissues; moreover, a normal prostate size and the presence of the seminal vesicles were documented.

Before undergoing the circumcision procedure, the patient refused testicular biopsy for conclusive diagnostics of his condition.

Even if the patient reported irregular physical activity (non-professional runner), mainly in the form of unsupervised bi-weekly training, he complained of the incapacity to lose weight and of poor physical performance compared to paired trainees; this prompted us to investigate his physical capacities. He was referred for physical performance battery tests for upper (handgrip strength) and lower limbs (the chair-stand test) in order to compare them with the cisgender population reference values [7,8] (Table 1).

Table 1. Physical performance tests. Reference values are related to the patient's age group.

Test	Patient Results	Cisgender Male Reference Values	Cisgender Female Reference Value
Handgrip strength (kg) [7]	37	43–46	27–28
30-s chair-stand test (repetitions) [8]	23	25.5 ± 5.7	24.3 ± 5.9

The patient finally started therapy with testosterone transdermal gel at the initial dose of 20 mg/day and the follow-up is still ongoing.

3. Discussion

The definition of "disorders of sex development" represents a container of heterogeneous congenital conditions whereas the chromosomal, gonadal or anatomical sex does not pair with the usual development of gonadal embryonic and/or external genitalia. According to the new classification developed in the Chicago Consensus, DSD are divided into three classes based on the karyotype analysis: 46,XY DSD, sex chromosomal DSD and 46,XX DSD. Moreover, 46,XX DSD are classified into three groups: disorders of androgen excess, unclassified disorders and disorders of gonadal development. Amongst the latter, the disorders of gonadal development are divided into three groups: 46,XX (Ovo)testicular DSD, monogenic forms of primary ovarian insufficiency and syndromic forms [9,10].

The 46,XX testicular DSD is a rare disorder of sexual differentiation with a prevalence of 1/20,000 newborns [6]. Approximately 90% of XX males are SRY-positive and present a male phenotype and psychosexual identification due to normal testicular differentiation during fetal development. Gonadal size is normal during childhood due to a normal Sertoli cell number, and this makes the diagnosis difficult in infancy [11]. Considering that male differentiation is supported by the sex-determining region of the Y chromosome (SRY), in the SRY-positive 46,XX testicular DSD, the inactivation of an X chromosome and the complete expression of the X chromosome containing the SRY gene determines the complete development of the testes, virilization with a male phenotype and the regression of Müllerian structures [12,13].

Sometimes, these patients are subjected to clinical evaluation for gynecomastia and short stature during puberty. Usually, in the late stages of puberty, the testes are found to be smaller because of altered germ cell proliferation, as is presented herein [11]. Furthermore, the determination of normal values of 17-OHP in a 46,XX karyotype leads to a rapid exclusion of a girl with virilized external genitalia presenting with congenital adrenal hyperplasia. The lack of gonadal histopathological analysis did not allow us to rule out the presence of ovarian tissue within the testicles, although the presence of AMH values at the lower limit for the male range, but higher than the female ranges, together with the complete androgenization of the patient and the absence of Müllerian structures, oriented us towards the diagnosis of a testicular DSD [14,15]. FSH and LH were elevated with a mild hypotestosteronemia and IB was very low, due to Sertoli cell failure.

We assume that the patient's moderate hyperestrogenism might have been determined by either increased aromatase activity caused by excess fat or by the increased levels of LH that can stimulate Leydig cells to increase estrogen production [16]; this finding is in accordance with data in the literature in similar cases [11]. Generally, the final diagnosis is made during adulthood, when the patient has difficulty becoming a father.

The treatment of these patients is aimed to compensate hormonal failure, through testosterone replacement therapy (TRT), favoring the complete pubertal development and the improvement of gynecomastia. However, this may also have implications for physical performance. Clinical concerns about sex steroid variability in cisgender and transgender athletes is a major issue especially in competitive sports [17]. Our patient's grip strength and lower limb physical performance were lower when compared to cisgender controls (male and female) [7,8]. Specifically, our patient's physical performance resulted in intermediate responses compared to controls (cisgender). This may determine alarming expectations in the engagement of future agonistic sport activities that will require advertisement by the physician in the management of these conditions. We believe that the physical performance of male patients suffering from rare DSD diseases is currently poorly evaluated, so we encourage physicians to include physical performance investigations during the diagnostic workup.

In the present case, the deflection of stature growth during puberty was suggestive of the absence of the physiological spurt due to the lack of testosterone secretion, and the misdiagnosis during puberty resulted in a subsequent lower stature than expected. Adrenarche and testosterone levels, even if in the lower quartile, accounted for the development of secondary sexual characteristics until Tanner stage G1, P4 was reached, making the detection of the underlying pathology difficult.

Finally, a variable risk of developing a gonadal germ cell cancer has been reported in DSD, considering that the presence of Y materials and dysgenetic gonads increases the risk. Rare cases of a testicular tumor with 46,XX SRY-positive testicular DSD have been reported [18–22]. There are no specific investigations that allow for the early recognition of precursor lesions, and biopsies are recommended to exclude its presence in undescended testes [10]. In our case, we submitted the patient to standard tumor markers and periodic testicular ultrasound surveillance.

4. Conclusions

The 46,XX SRY-positive male syndrome is rare. An adult diagnosis represents a challenge for different specialists such as pediatricians and endocrinologists but also for uro-andrologists; it is therefore important to consider all possible organic causes of gynecomastia to avoid the underdiagnosis of comparable rare genetic disorders.

Also, physical performance and quality of life may be partially compromised as a result [23]. When TRT is promptly instituted, it is expected that physical performance may approach that of a cisgender man [24]; any attempt to use nutraceuticals or supplements to increase testosterone levels in male subclinical compensated hypogonadism has proven unsuccessful [25]. For this reason, we conclude that physical performance of these patients should be investigated more extensively before initiating replacement therapy.

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