



Complete Androgen Insensitivity Syndrome (CAIS) and Karyotype 47, XXY, with Sertoli-Leydig Cell Tumor: Description of a Rare Case

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Abstract

Objective: To report the rare case of a patient with Complete Androgen Insensitivity Syndrome (CAIS) with Klinefelter Syndrome (KS) (47, XXY) presenting a Sertoli/Leydig cell tumor discovered during the gonadectomy.

Materials and Methods: Patient(s): Patient with 36 years-old seeking assistance with decreased libido.

Intervention(s): Adequate hormone replacement therapy, which had not previously been instituted.

Result: The patient had improved secondary sexual characteristics but only partially improved libido.

Conclusion: The clinical case described shows a rare phenomenon such as the association between CAIS and KS, associated with the finding of Sertoli/Leydig cell tumor after gonadectomy.

Keywords: Androgen Insensitivity Syndrome; Klinefelter syndrome; Sertoli/Leydig cell tumor; Hormone Replacement therapy; Endocrinology

Introduction

There are few reported cases of Androgen Insensitivity Syndrome (AIS) and karyotype 47, XXY. We describe the case of a 36-year-old patient who sought us for treatment of decreased libido and who was using injectable testosterone every 10 days as a treatment after bilateral gonadectomy. She presented a family history of CAIS and was the only who carried a 47, XXY karyotype.

Materials and Methods

Description of a clinical case of rare presentation for publication purposes we obtained the Formal Informed Consent signed by the patient, which allowed us to do so, and according to the Institution ethics committee.

Androgen insensitivity syndrome

Androgenic insensitivity syndrome is the most common cause of disorders of sexual differentiation in 46, XY individuals. It results from alterations in the androgen receptor gene, leading to a frame of hormonal resistance, which may present clinically under 3 phenotypes: complete (CAIS), partial (PAIS) or mild (MAIS) [1]. It is a rare X-linked genetic disease with a pattern of recessive inheritance, with several mutations in the androgen receptor gene (Xq11-12), which leads to absent or attenuated response to androgens [2,3]. CAIS prevalence in 46, XY is estimated from 1 in 20,400 to 1 in 99,100 [4,5].

The phenotype ranges from normal female external genitalia in the complete form (CAIS) to normal male external genitalia associated with infertility and/or gynecomastia in the mild form (MAIS). A large spectrum of under virilized male external genitalia is observed in the partial form (PAIS) [6].

CAIS is diagnosed in three scenarios: in fetal life when prenatal sex determination disclosed a 46, XY karyotype in a fetus with female external genitalia; in childhood in a girl with inguinal hernia or at puberty; in females with primary amenorrhea [7]. Tissue response to estrogen is present and breast development and other signs of feminization occur. Female internal reproductive organs are missing or vestigial and Wolffian duct derivatives persist [8]. Menstrual cycles do not appear

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Received Date: 26 Jul 2019

Accepted Date: 29 Aug 2019

Published Date: 03 Sep 2019

Citation:

Weber Silva DM, Bagatin de Souza Moreira B. Complete Androgen Insensitivity Syndrome (CAIS) and Karyotype 47, XXY, with Sertoli-Leydig Cell Tumor: Description of a Rare Case. *Ann Clin Diabetes Endocrinol.* 2019; 2(1): 1011.

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since normal production of Anti-Müllerian Hormone (AMH) by the testis impeded uterus, cervix and proximal vagina to development. A shortened blind-ending vagina is observed in almost all patients. Pubic and axillary hair are sparse or absent [4,7]. Final height in CAIS is above normal mean female height [1].

Typically, in AIS, basal testosterone and LH levels are elevated demonstrating the impairment of androgen negative feedback on the anterior pituitary. In contrast, FSH levels are usually normal in AIS. In post puberal patient estradiol levels are normal or slightly elevated for a male individual [9].

Klinefelter syndrome

Klinefelter's syndrome is defined by the 47, XXY karyotype resulting from aneuploidy of the sex chromosomes, with a prevalence of 1 to 650 men [10]. The suspicion is clinical, the syndrome should be considered in cases of physical examination demonstrating a testosterone deficiency, mainly with reduction of testicular volume. Diagnostic confirmation is by cytogenetics, through karyotyping [11]. An optimal treatment for this syndrome has not yet been established. Usually the treatment is to use exogenous testosterone to supply the deficiency of this hormone [12]. The clinic of the syndrome is marked in patients with high body stature, small testes, late gynecomastia at puberty, gynoid aspect in the hips, signs of androgen deficiency related to low testosterone levels, high gonadotrophins, oligospermia with hyalinization, azoospermia and consequent fibrosis of the seminiferous tubules demonstrating the characteristic phenotype of hypogonadism [13].

With respect to the classical phenotype of the syndrome, hypogonadism manifests itself in only a few patients with evident signs (shortage of body, axillary and facial hair, and decrease of muscular mass). Most present with symptoms of sub-virilization and/or delayed puberty [14].

Hypogonadism is usually associated with elevated gonadotrophins, presenting as hypergonadotropic hypogonadism, in which case the latter are higher than normal, even in patients with serum testosterone in the physiological range [13,14]. Estradiol may be normal or elevated, with the proportion of testosterone in patients with the disease being higher than in normal men. This may explain the clinic of gynecomastia of the disease [15]. In addition, due to the tubular damage presented in the syndrome, the serum concentration of inhibin B may be undetectable and the anti-Müllerian hormone may be below normal [16,17].

Reduction of muscle strength may also be present. Studies indicate that the finding of lower than normal bone mineral density is prevalent in patients with Klinefelter's syndrome but does not seem directly related to low serum testosterone [18].

Results

A 36-year-old Caucasian female patient came to consult because she had decreased libido, especially after a few years of removal of gonads. She had already used estrogen in low doses without adequate response. The use of intramuscular testosterone was indicated every 10 days, where it felt a little better.

Fourth daughter of five, she reports that her older sister after sexual intercourse had hemorrhage, and on examination had about one-third of the vagina on a blindfold. When investigated, 46, XY karyotype was detected, confirming the diagnosis of AIS. The second and third sisters do not present the picture, but the second one has

three daughters with androgenic resistance (46, XY). The fifth sister also has AIS. In the family investigation two twin sisters of the mother had the same phenotype.

The patient had spontaneous thelarche at age 15, but there was no menstruation. Normal intellectual development, she was submitted to gonadectomy at the age of 18, after diagnosis of AIS in the family. Video-laparoscopy showed a missing uterus with fibrous cord in the anatomical region. The surgery report was right testicle measuring 4.0 cm × 3.0 cm × 2.8 cm with Sertoli-Leydig cell tumor measuring 2.0 cm × 2.0 cm × 2.0 cm. Adjacent testicular tissue showing aplasia of germ cells. The left testis measured 4.5 cm × 2.0 cm × 1.5 cm and showed germinal cell aplasia.

At physical examination she had a weight of 57.4 kg, height 180 cm and BMI (Body Mass Index) =17.7 kg/m². The limbs were long, almost absent from the axillary and genital hairs, breasts stage Tanner III, female external genitalia, blind-ending vagina. No further changes.

Using testosterone, tests showed: Total testosterone =499.0 ng/dl, Free Testosterone =18.4 pg/ml, LH=35.4 mIU/ml; FSH=3.5 mIU/ml; E2<15.0 pg/ml (radioimmunoassay).

Testosterone was suspended and appropriate replacement of estrogen started.

Discussion

This is the description of yet another rare case of CAIS and karyotype 47, XXY. As Girardin et al. published in 2009, the estimated prevalence of the 47, XXY karyotype is approximately 1 in 1400 births, and the prevalence of CAIS is estimated to be at most 1 in 20.000 births. Thus, the probability of having the 2 conditions by chance is about 1 in 28.000.000 births since 1966 there have been only 7 cases described in the literature, including theirs [19].

There is no record of genetic mutation in this case because the family has no interest in the investigation, although the mutation compatible with CAIS is present in at least 3 generations. The patient under discussion, however, presents karyotype 47, XXY. There is no alteration of the intellectual function, but the longilite biotype and long limbs are characteristic of the Klinefelter Syndrome. Little stimulated breasts with female genitalia and few hairs reveal the familiar CAIS, but also the effect of the lower production of testosterone that is common in Klinefelter syndrome. In the other 7 published cases there is only one described as having low intellectual level. Clinical presentations are also varied, mostly showing the scarce pubic and axillary hair, clitoromegaly in two of them, small breast, and one with blind-ending vagina. The internal genitalia showed small testis and no presence of uterus and ovaries [19].

In this case, gonadectomy revealed a tumor present at 18 years of age. The finding of Sertoli-Leydig cell tumor in this patient occurred at random on the resection of the gonads. In patients with infertility Walsh et al. [20] found an incidence three times higher than those without (HR 2.8, 95% CI 1.3-6.0).

Shaw et al. [21] review and report that the rate of testicular cancer, and particularly Leydig cell tumor, has not been shown to be elevated in KS. The treatment of choice in cases of Leydig cell tumor has been orchiectomy [22]. In this case, after gonadectomy the testosterone levels drop in and in turn the conversion to estrogen decreased, to the point of seeking us to present a complaint of decreased libido.

Estrogen replacement was started (1.5 mg of estradiol hemihydrate) and a secondary sexual character has been well developed, but partially libido.

As the patient was evaluated at another treatment center initially, we did not get the results of the tests from the beginning of the clinical picture. On testosterone treatment FSH was still elevated. In the cases of CAIS and KS found in the literature, patients had slightly decreased or normal levels of testosterone associated with elevated FSH (and sometimes LH) levels [18].

Bone mineral density in KS may be low, with a diagnosis of osteoporosis present in about 40% of cases [23]. In this case the patient present's normal bone mass for age.

Conclusion

We describe a rare case of a patient who has a genetic mutation that has led to CAIS, seen in at least three generations, and which has a 47, XXY, KS karyotype present. The removal of the gonads showed a unilateral Sertoli-Leydig cell tumor and alerts us to the possibility of these patients progressing with a testicular tumor. The main complaint is to present decreased libido, making life difficult. Replacement of 1.5 mg of estradiol hemihydrate resulted in partial relief of the complaint. Unfortunately, the family did not want to proceed with genetic evaluation.

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