

Complete Androgen Insensitivity Syndrome

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ABSTRACT

The incidence of Complete Androgen Insensitivity Syndrome (CAIS) is about 1 in 20,000. People with CAIS are normal appearing females, despite the presence of testes and a 46, XY chromosome constitution. We came across a case in which a 17 years old girl presented with the complaint of inguinal hernia and amenorrhea. Subsequent investigations were done revealing absence of female internal genitalia and the presence of abdominal mass, possibly testes. Syndrome has been linked to mutations in AR, the gene for the human Androgen Receptor, located at Xq11-12 leading to the insensitivity of the receptor to testosterone. Gonadectomy was performed and life long Hormone replacement therapy was advised.

Key words: *Androgen insensitivity syndrome (AIS). Complete androgen insensitivity syndrome (CAIS). Partial androgen insensitivity syndrome (PAIS). Testicular feminization. Androgen receptor deficiency. Androgen resistance syndrome.*

INTRODUCTION

Complete Androgen Insensitivity Syndrome (CAIS) is a rare X-linked recessive disorder, which affects one in 20,000 live male births only.¹ The affected individuals exhibit female phenotype in conjunction with a 46 XY genotype. This genetic disorder formerly known as testicular feminization syndrome² is caused by the mutation of the Androgen Receptor gene located on the X chromosome resulting in a complete loss of the ability of the androgen to bind to its receptor.³ In these individuals, failure of masculinization occurs as a result of resistance to the action of testosterone at the cellular level. This insensitivity allows the estrogen to take over hence the female appearance and development of female external genitalia.

The CAIS sufferers come into notice only when they seek medical help mainly for two complaints namely inguinal hernia and amenorrhea and despite a major discrepancy in their genetic make up, these XY females stand out among their peers with their exceptional height⁴ and striking features.

CASE REPORT

A 17-year-old female patient was admitted in Civil Hospital, Karachi, on 23rd April 2007. She came with the complaints of swelling in the left inguinal region and amenorrhea. According to the patient, the size of the

swelling had been static since birth. Also the patient did not encounter any pain in the swelling unless she exerted herself.

On general physical examination, the patient was lean figured with normal vitals and sub-vitals. Significant findings included scanty body hair, small breasts with rudimentary areola and nipples. The external genitalia was normal but with small labia. On pervaginal examination, a 2" long vagina with intact hymen was seen.

On examination, the size was about 3 x 4 cm, firm in consistency and was irreducible. Cough impulse was negative.

Ultrasound revealed the absence of uterus, (Figure 1), ambiguity in the presence of ovaries, blind ending vagina and bilateral cyst (right: 8.9 x 5.5 cms and left 7.9 x 5.8 cms) in the inguinal region, possibly testes (Figure 2).

Serum FSH and LH values were 31.16 mIU/ml and 51.91 mIU/ml respectively. Serum Testosterone was 4.79 ng/ml.

Laparoscopy confirmed the absence of uterus and ovaries. Bilateral mass was visualized, the left one being extra-abdominal while the right remained intra-abdominal. the left mass was excised during the procedure and was sent for biopsy.

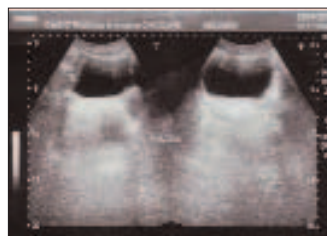


Figure 1: showing the absence of uterus, fallopian tube and cervix.

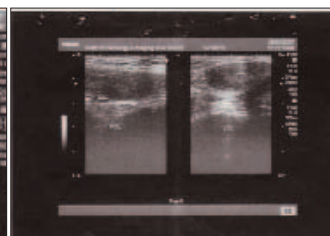


Figure 2: showing the presence of bilateral cryptorchid testes.

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Histopathological section showed testicular tissue composing of immature seminiferous tubules along with benign epithelial cyst favouring epididymal cyst. No spermatogenesis was seen and there was no evidence of malignancy. After confirmation, the right testis was also removed.

DISCUSSION

During the fetal period, the testes of these individuals produce the regular hormones including the Mullerian Inhibitory Substance (MIS). This hormone suppresses the development of the Mullerian duct derivatives, i.e., uterus, fallopian tubes, cervix and the upper part of vagina. However, the lower vagina does develop since it is not a Mullerian duct derivative and thus is not suppressed by MIS, although it is blind ending.

The presence of the SRY gene induces testes to form on the genital ridges in the fetal abdomen a few weeks after conception. Then by the 7th week, fetal testes begin to produce testosterone and release it into the blood. But due to the defective receptor testosterone cannot exert its effects, so the Wolffian duct also degenerates, and thus, the absence of vas deferens. There is also no penis or scrotum and the testes remain in the abdomen (where they originate).

These individuals reach puberty at a later stage than average girls. The hypothalamus and the pituitary gland continue to stimulate testes to produce testosterone till it reaches levels as that in an average boy. This testosterone is converted to estradiol but this estradiol is not secreted in a cyclic manner.

The sensitivity of the patients to estrogen seems 10 times greater than that of normal males. This is appreciated by the fact that even small amounts of estrogen in the body results in the development of female phenotype.⁵

The presence of estradiol and insensitivity to the action of testosterone leads to CAIS. A typical case presents with normal reshaping of the pelvis and redistribution of body fat, little or no appearance of pubic or other androgenic hair, scalp hair being fuller than average, without recession of scalp or thinning with age, normal breast development with juvenile nipples. In addition, a female external genitalia with small labia and a blind ending vagina, rudimentary or absent internal genitalia, cryptorchid testes producing estrogen and testosterone is found.^{6,7}

Two other features that are frequently encountered are the rare appearance of facial acne and increased height⁴ compared to average females. The reason for tallness appears to be the presence of Y chromosome. Some researchers in the field have suggested that genes on the Y chromosome have an effect on growth, independently of hormonal changes, as shown by increased growth in boys with an extra Y chromosome.⁸

Another study states that these individuals are on average tall and also show an increase in head and face dimensions relative to normal females. A size increase is likewise evident in permanent tooth crowns, thus it is obvious that this excess root growth conceivably would develop independently of the possible androgen influence and it is suggested that the increase results from the direct effect of the genes on the Y chromosome. It is possible that these genes on the Y chromosome are the same that promote tooth crown growth.⁹

Studies show that Androgens are of direct importance in the development and/or maintenance of Bone Mineral Density (BMD), therefore, It has been observed that in CAIS patients, there is decreased (BMD), specially in the hip and spine region.⁹

Women with one mutated AR gene will not exhibit the syndrome but instead will be carriers, whose male children have a 50 percent risk of inheriting the mutant gene. Since affected individuals are sterile, they cannot pass it on to offspring. It is believed that about one-third of all cases are due to new mutations, which are not present in the mother's genes but arise in the development of the early embryo.

Gonadectomy: Optimal timing of removal of the testes has been the management issue, most often debated by physicians, whether it is necessary has been questioned as well. The advantage of leaving testes till puberty allows pubertal changes to happen "naturally," without hormone replacement. The primary argument for removal is that testes remaining in the abdomen throughout life may develop benign or malignant tumors and confer little benefit. The testicular cancer risk in CAIS appears to be higher than that which occurs with men whose testes have remained in the abdomen, and rare cases of testicular cancer occurring in adolescents with CAIS have been reported. Unfortunately, the uncommonness of CAIS and the small number of women who have not had testes removed make cancer risk difficult to quantify. The best evidence suggests that women with CAIS and PAIS retaining their testes after puberty have a 25% chance of developing benign tumors and a 4-9% chance of malignancy. The only known benefit provided by testes in CAIS is to produce the estradiol from testosterone, which may be provided pharmaceutically.

For the treatment of vaginal hypoplasia, dilation should be the first approach. It is done by applying pressure to expand the tissue over an extended period of time. Plastic surgical techniques to construct a new vagina from donor sites should only be resorted to, once the dilation is ruled out.

Estrogen replacement: Once testes have been removed, estrogen is required to be taken in order to support pubertal development, bone development, and

completion of growth. Usually estrogen is given orally, but transdermal patches are gaining popularity. Since there is no uterus, progesterone is not considered necessary.

Females with CAIS possess customary feminine appearance and their proper management can give them a normal life, despite a major chromosomal discrepancy. This case is presented in view of the rarity of the condition and the importance of early diagnosis and management considering the social and personal implications of this condition.

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