Case Report

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Androgen Insensitivy Syndrome: Case Report

Kamlesh[1], **Kushla Pathania**[1], **Rama Thakur**[1], **Anoop Sharma**[1], **Varsha Sapehia**[2]

[1]Department of Obstetrics and Gynecology, Kamla Nehru Hospital, Shimla, Himachal Pradesh, India, [2]Department of Anesthesia, Civil Hospital Nagrota Bagwan, Kangra, Himachal Pradesh, India.

Abstract

Androgen insensitivity syndrome (AIS), also known as testicular feminization, caused by different mutations in the androgen receptor gene. AIS is an X-linked recessive disorder. AIS classified as complete, partial, or mild based on the phenotypic presentation. The clinical findings include a female type of external genitalia, 46-XY karyotype, absence of Müllerian structures, presence of Wolffian structures to various degree, and normal to high testosterone and gonadotropin levels. The syndrome is illustrated by a 17year-old phenotypic female who presented with amenorrhoea, infantile external genitalia, clitoromegaly, an absent uterus and ovaries, and bilateral testes at the level of the internal inguinal ring. Management includes counseling, gonadectomy to prevent primary malignancy in undescended gonad, and hormone replacement.

Keywords: Androgen Insensitivity Syndrome, Androgen Receptor Gene, Testicular Feminization Syndrome, Gonadectomy.

Corresponding Author: Varsha Sapehia, Department of Anesthesia, Civil Hospital Nagrota Bagwan, Kangra, Himachal Pradesh, India.
E-mail: varshasapehia@gmail.com

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Introduction

Androgen Insensitivity Syndrome (AIS) causes resistance to androgens actions, influencing both the morphogenesis and differentiation of the body structures in which this hormone exerts its effects. It depends on X-linked mutations in the Androgen Receptor (AR) gene. The first who described this syndrome was John Morris, but we have to wait until 1989 to define the exact location of the human AR gene.[1,2]

The androgen receptor (AR) gene is located on the X-chromosome at Xq11–12 and codes for a protein with a molecular mass of approximately 110 kDa. The androgen receptor belongs to the family of steroid thyroid hormone-retinoid nuclear receptors. It contains 3 major domains: a hormone-binding region, a DNA-binding region, and an amino-terminal region.

AR is expressed from 8 weeks of gestation: in male embryo, testes begin to secrete testosterone at 9 and peak at 11 and 18 weeks, stimulating differentiation of the Wolffian duct system into epididymis, vas deferens, and seminal vesicles. A more powerful androgen, dihydrotestosterone, originates from action of the enzyme 5alpha-reductase type 2 on testosterone and stimulates differentiation of the masculine primordial external genitalia.[3]

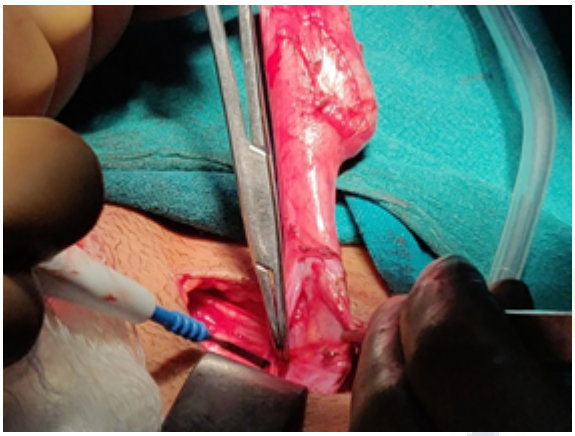
In the AR gene, 4 different types of mutations have been detected in DNA from individuals with AIS: (1) single point mutations resulting in amino acid substitutions or premature stop codons; (2) nucleotide insertions or deletions most often leading to a frame shift and premature termination; (3) complete or partial gene deletions; and (4) intronic mutations in either splice donor or acceptor sites, which affect the splicing of AR ribonucleic acid.[3,4]

It is the third most common cause of primary amenorrhea after gonadal dysgenesis and Müllerian agenesis.[4] The syndrome is usually detected on evaluation of a phenotypic female with primary amenorrhea. We report one such case.

Case Report

A 17 years old, phenotypic female presented to the OPD of the obstetrics and gynecology department with complaints of amenorrhea. On general physical examination, we found hypotrophic breasts, sparse pubic and axillary hair. The gynecological examination evidenced infantile external genitalia, blind ending vagina and clitoromegaly present. Cervix could not be visualized on speculum examination. An ultrasound of the abdomen and pelvis revealed an absent uterus and ovaries. Karyotyping revealed a 46, XY pattern. Follicle stimulating hormone (FSH) was elevated with a value of 68 mIU/mL. Luteinizing hormone (LH) was also elevated with a value of 26 mIU/mL. However, serum testosterone level was 130 ng/dL (adult female20-80ng/dl). Diagnostic laparoscopy revealed

bilateral testes approximately 2 cm x 1.5 cm x 1 cm in size, located at the level of the internal inguinal ring. Bilateral gonadectomy done and sent for histopathological examination. Histopathology revealed Sertoli cell hyperplasia with absent lumen in the seminiferous tubules and an absence of spermatogonia. Histopathology did not reveal any evidence of malignancy. The patient was put on estradiol oral replacement therapy after counseling.



Discussion

In androgen insensitivity syndrome there occur feminization (undermasculinization) of the external genitalia at birth, abnormal secondary sexual development in puberty, with a 46, XY karyotype. It subdivided into 3 broad phenotypes: (1) complete androgen insensitivity syndrome (CAIS) with typical female genitalia; (2) partial androgen insensitivity syndrome (PAIS) with predominantly female, predominantly male, or ambiguous genitalia; and (3) mild androgen insensitivity syndrome (MAIS) with typical male genitalia.[5] The incidence of androgen insensitivity syndrome is estimated to be 1:20,000- 64,000 male births.[6] The present case is a partial androgen insensitivity syndrome because there is female phenotype with clitoromegaly.

Definition of CAIS itself is controversial, with different authors expressing different views. Griffin et defines CAIS as completely female external genitalia, paucity of axillary and pubic hair, and absent Wolffian duct derivatives. Quigley defines CAIS as completely female external genitalia without pubic hair, but states that remnants of Wolffian duct derivatives may be found.[7,8]

According to Quigley et al, there are five grades of PAIS: in the first one there is normal female genital phenotype, with androgen-dependent pubic and/or axillary hair development at puberty; in the second grade, there is a female phenotype with mild clitoromegaly or small degree of posterior labial fusion; in the third grade, there are undifferentiated phallic structures intermediate between clitoris and penis, and the urogenital sinus presents perineal orifice and labioscrotal folds; the fourth grade is a predominantly male phenotype with perineal hypospadias, small penis, cryptorchidism or bifid scrotum; the fifth and last grade presents isolated hypospadias and/or micropenis.[9]

The diagnosis of AIS in individuals with a 46,XY karyotype is based on the following clinical findings: undermasculinization of the external genitalia, impaired spermatogenesis with otherwise normal testes, absent or rudimentary Müllerian structures, evidence of normal or increased synthesis of testosterone and its normal conversion to dihydrotestosterone, normal or increased LH production by the pituitary gland, and deficient or defective androgen-binding activity of genital skin fibroblasts.[3,5] In the present case, the diagnosis was established by undermusculinized external genitalia,clitoromegaly, intraabdominal testis without any spermatogenesis, increased testosterone levels, and raised gonadotropin levels.

To prevent testicular malignancy, Treatment of CAIS includes either removal of the testes after puberty or prepubertal gonadectomy accompanied by estrogen replacement therapy. The laparoscopy can be used to locate as well as remove the gonads.[10] Additional treatment for CAIS may include vaginal dilatation to avoid dyspareunia.

Treatment of PAIS in individuals with predominantly female genitalia is similar to treatment of CAIS, but is more likely to include prepubertal gonadectomy to help avoid clitoromegaly. Individuals with PAIS who are living as males may undergo surgery such as orchiopexy and hypospadias repair. Individuals with Males with MAIS may require mammoplasty for gynecomastia.[11]

AIS are associated with numerous psychosexual issues. Therefore, systematic disclosure of the diagnosis of AIS should be done in an empathic environment, with both professional and family support.[12]

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