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Complete Androgen Insufficiency Syndrome in Siblings with Normal Androgen Receptor Gene

Amit Varma*, Bhagwan Singh Yadav, Santosh Agarwal***, Ravindra Kumar****, Gaurav Pawar*******

Abstract

Androgen Insensitivity Syndrome occurs as the genetic defects determine a resistance to the actions of the androgen hormones, which in turn switches the development towards the aspect of a woman. Mutations in the AR located on the X chromosome are responsible for the disease. Here, we describe two siblings affected with CAIS with normal AR gene.

Keywords: AIS; Testicular feminization syndrome; AR gene.

Introduction

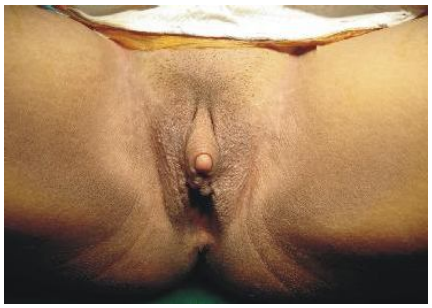
Testicular feminization syndrome or androgen insensitivity syndrome(AIS) is a rare disorder with an incidence of 1:20,000-64,000 male births.[1] Two forms of AIS are described: complete androgen insensitivity syndrome (CAIS) and partial androgen insensitivity syndrome (PAIS). Patients with CAIS are genotypically male (XY) but phenotypically and psychologically female[2], usually present with primary amenorrhoea or infertility with well developed breast, but absent axillary and pubic hair, normal external genitalia and short and blind vagina. The upper two-thirds of vagina, uterus and tubes are absent. Testes are normally developed but abnormally positioned; either placed in the labia, or inguinal canal or intra-abdominal. The phenotype of individuals with partial androgen insensitivity syndrome may range from mildly virilized female external genitalia (clitorimegaly without other external anomalies) to mildly undervirilized male external genitalia.

CAIS is inherited in an X-linked recessive manner and characterized by resistance to androgen due to a mutation in the AR gene. AR gene is a protein coding gene located at Xq11.2-q12, and codes for a protein that functions as a steroid hormone-activated transcription factor. Mutation in the AR gene causes androgen unresponsiveness which then affects transactivation of androgen-responsive genes in peripheral target cells.Here we are reporting two siblings affected with CAIS with normal AR gene.

Case 1

A 19-year-old girl was admitted to Department of Gynaecology with the

Figure 1: Clinical Picture of a Case 1 Showing Well Developed Labia and Vagina with a Small Penis

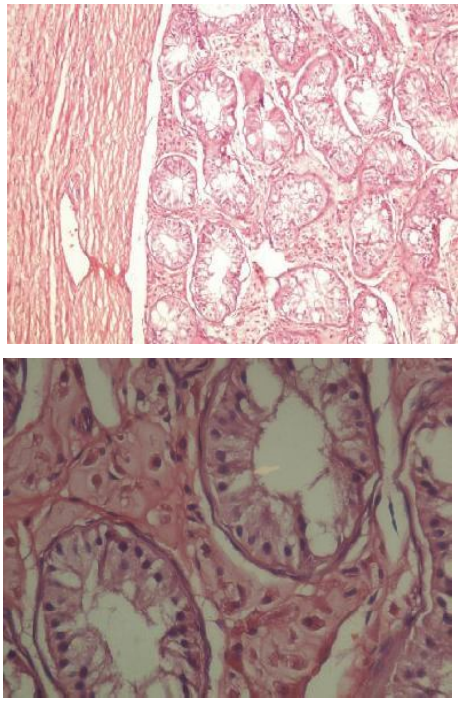


Author's Affiliation: *Professor and Head, Department of Pathology, **P.G. Resident, Department of Pathoogy, ***Associate Professor,Department of Urology,****Scientist,Central Research Lab,*****P.G. Resident, Department of Pathoogy, Sri Aurobindo Medical College and PG Institute, Indore, Madhya Pradesh, India.

Corresponding Author: Dr. Amit Varma, Professor and Head, Department of Pathology, Sri Aurobindo Medical College and PG Institute, Indore, Madhya Pradesh, India.

E-mail: dravvarma@rediffmail.com

Figure 2: H&E Stained Section (10x) Showing Fibrous Thickening of Capsule with Increase Interstitial Tissue. Seminiferous Tubules Lined with only Sertoli Cells (A). H&E Stained Section (40x) Showing Seminiferous Tubules Having Single Epithelial Lining of Sertoli Cells.Interstitium Showing Prominent Leydig Cells [B].



complaint of primary amenorrhea. During examination it was found that breast development stage 2 and pubertal hair stage was 4+ and axillary hair was present. Labia were well developed with only vaginal pit. Urethral opening was in introitus with small size penis (Figure 1). Ultrasound examination suggested that there is absence of uterus and ovary and presence of testis at both side in inguinal canal.

Her routine blood chemistries were within normal limits, with serum testosterone levels of 9.2ng/ml. Cytogenetic analysis showed a 46, XY karyotype. Provisional diagnosis was made as CAIS. The patient was referred to Department of Urology for bilateral gonadectomy. Orchiectomy was accomplished on both sides and the patient was discharged without complication on third postoperative day. Histopathological examination of both the removed gonads showed seminiferous tubules with only sertoli cells. Increased number of leydig cells in interstitial tissue made the diagnosis compatible with CAIS (Figure 2).

Blood sample was sent to genetic lab for the mutational analysis of Androgen Receptor(AR) Gene. However we did not found any mutation in all the eight exons.

Case 2

A 17 year old woman referred to department of Gynaecology, SAIMS soon after the operation on her elder sister. Her medical history was similar to that of her sister with the symptom of primary amenorrhea.She had well developed breast stage was -4, pubic hair development stage was - 4 and axillary hair present. There were well developed labia with normal introital opening of urethra with small penis. Ultrasound examination showed the same result as elder sibling. Her karyotype was 46, XY and the level of testosterone in peripheral blood was 5.0ng/ml. AR gene mutation was not found on genotype analysis in her sample.

Bilateral inguinal orchiectomy was performed in urology department and she was discharged at second postoperative day without complication. Histopathologic report of surgical specimen showed seminiferous tubules lined by sertoli cells. Germinal cells were not observed. There was hyperplasia of leydig cells in interstitial tissue.

Discussion

Androgen insensitivity syndrome is a set of disorders of sexual differentiation caused by mutations of the gene encoding the androgen receptor.[3] This alteration in the gene blocks the body's response to masculinizing hormones (androgen) during fetal development and after birth. It makes the body insensitive to androgen, and masculine

development that would occur in the presence of a normal gene is impossible.

The first problem with Complete Androgen Insensitivity Syndrome is the diagnosis. It requires many tests, some quite rare and frequently unavailable, so therefore it is often uncertain. Still, if everything can be performed, there are 5% of patients without an androgen receptor gene mutation as in our case, various other genetic abnormalities are ruled out through karyotyping. Exom sequencing should be performed in such cases to rule out the other possible causes.

Conclusion

Androgen insensitivity syndrome is a rare disorder that must be diagnosed and treated through close work between gynecologists, endocrinologists, geneticists, urologists, anatomic , pathologists and psychiatrists.

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