International Journal of Reproduction, Contraception, Obstetrics and Gynecology
*Varma D et al. Int J Reprod Contracept Obstet Gynecol. 2023 May;12(5):1497-1499*
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20231250

**Case Report**

# A case of partial androgen insensitivity syndrome with undescended testis and clitoromegaly

**Dixit Varma*, Sangita Mahela, Ibrahim Khalil Ullah, Sharath C. Mouli, Kritika Sharma, Gaurav Singh, Nirupam K. Baishya, Jyotishmita Pathak**

Department of Radiology, Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta, Assam, India

**Received:** 06 March 2023
**Accepted:** 04 April 2023

***Correspondence:**
Dr. Dixit Varma,
E-mail: dixitvarma95@gmail.com



## ABSTRACT

Androgen insensitivity syndrome is a rare disorder of sex development that results from genetic mutations affecting the androgen receptor. Recently, we encountered a case of a 13-year-old individual who had been raised as female and sought medical attention for primary amenorrhea, which led to the discovery of partial androgen insensitivity syndrome. Early detection and gonad removal are necessary to mitigate the risk of cancer. Additional management steps such as corrective surgery and psychological support can also be valuable.

**Keywords:** Androgen insensitivity syndrome, Disorder of sexual development, Management

## INTRODUCTION

Androgen insensitivity syndrome (AIS) is an uncommon X-linked disorder of sexual development that is caused by mutations in the androgen receptor (AR) gene.[1] This results in a range of changes in individuals who are genetically XY males, depending on severity of androgen resistance, from a partial to a complete female phenotype. The sensitivity of androgen receptor (AR) is an important determinant in the full expression of male characteristics in XY individuals during intrauterine development and puberty. Early diagnosis and treatment are critical, given the rarity and underreporting of the condition, and we present a case of a 13-year-old patient with partial androgen insensitivity syndrome (CAIS) who was raised as female and presented with primary amenorrhea.

## CASE REPORT

We examined a 13-year-old Caucasian individual who was raised as female for evaluation of primary amenorrhoea. The patient displayed typical feminine characteristics, with breast development and pubic hair growth at Tanner stage 3, and was found to have soft tissue masses in both inguinal regions. (Figure 1) On gynaecological examination, we observed small labia, an enlarged clitoris, and a short vagina (4 cm) with a blind-ended pouch. Speculum examination did not reveal the cervix, and the patient had a positive family history of androgen insensitivity syndrome in an older sibling. Ultrasound examination showed testicular echotexture gonads in the bilateral inguinal canals s/o undescended testis, with no other visible internal genitalia such as fallopian tubes, uterus, seminal vesicles, or epididymis.

**Figure 1: Local examination reveals bilateral inguinal masses (undescended testis), sparse pubic hair (Tanner stage 3) and enlarged clitoris.**

MRI confirmed these findings and absence of internal female or male genitalia (Figures 2 and 3). The patient exhibited normal intellectual function and feminine habitus and voice.

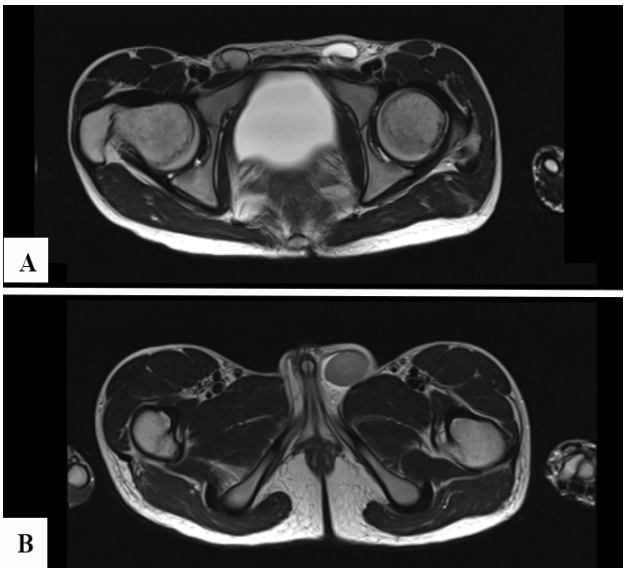


**Figure 2 (A and B): Axial T2WI of the pelvic region reveals right and left testis in inguinal canal bilaterally.**

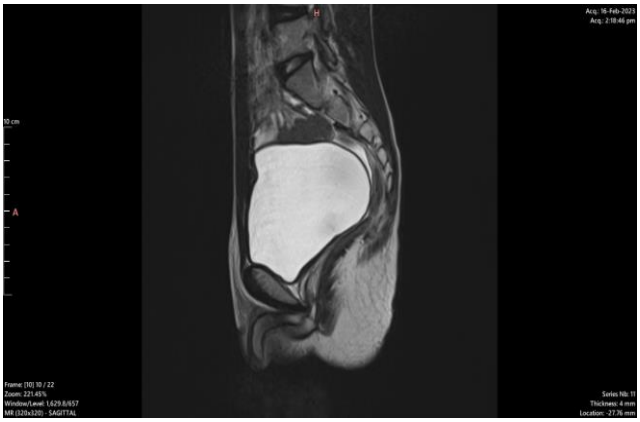

**Figure 3: Sagittal T2WI of the pelvic region reveals absent internal male/female genitalia.**

## DISCUSSION

AIS is a genetic disorder that affects an individual's development of sex characteristics. It is caused by mutations in the AR gene located on chromosome Xq11.12, and there have been over 1000 identified mutations in patients with AIS.[1] These mutations can be found throughout the coding region of the gene.[2] Despite the presence of testes and normal testosterone levels in genetically XY males with these mutations, they do not undergo typical male virilization.[3] AIS is a range of disorders that vary in the degree of receptor insensitivity. There are three basic phenotypes: Complete androgen insensitivity syndrome (CAIS), with typical female external genitalia, partial androgen insensitivity syndrome (PAIS) with predominantly female, predominantly male, or ambiguous external genitalia and mild androgen insensitivity syndrome (MAIS) with typical male external genitalia.[4]

Individuals in all instances have typical testicles that generate testosterone and successfully convert it to dihydrotestosterone. Despite producing a normal quantity of Müllerian-inhibiting factor, individuals affected are not equipped with fallopian tubes, a uterus, or a proximal vagina.[5] Therefore, the testicles provide natural levels of oestrogens by converting testosterone. The estimated prevalence of complete androgen insensitivity syndrome (CAIS) is one in 20,400 XY births, while the incidence of PAIS is one in 130,000 births.[6,7]

The human gonads emerge from the intermediate mesoderm. During 4 to 6 weeks of gestation, the urogenital ridges form as paired outgrowths of coelomic epithelium (mesothelium). The urogenital ridge gives rise to the gonads, adrenal cortex, kidney, and reproductive tract. The Sex determining region Y gene (SRY) present in the XY karyotype determines the fate of the gonad and whether it will develop into a testis or ovary.[8] SRY induces the formation of testis if present and ovarian development if absent. In cases of androgen insensitivity syndrome, where the karyotype is XY, testis are formed. The testis contains Leydig's cells, responsible for producing testosterone. Normally, testosterone induces the formation of internal male genitalia such as the epididymis, vas deferens, seminal vesicles, and external male genitalia, including the penis and scrotum. However, in AIS cases, internal and external male genitalia fail to develop due to defective testosterone receptor function. Sertoli cells produce the mullerian inhibiting factor which inhibits the formation of mullerian duct structures such as the fallopian tubes, uterus, and upper vagina.[9] As no testosterone is available to inhibit their formation, the external female genitalia, including the labia, clitoris, and lower vagina, develop.

To diagnose AIS, a 46,XY individual must present with underdeveloped external genitalia, deficient sperm production, and a lack of Mullerian structures, along with typical or elevated testosterone synthesis and conversion to dihydrotestosterone, as well as normal or increased pituitary gland production of luteinizing hormone (LH), or a single harmful variant in the AR gene detected via molecular genetic testing.[4] Whole-exome sequencing is a valuable tool for identifying Mendelian diseases such as CAIS.[3]

Gonadectomy is recommended after puberty to reduce the risk of testicular tumours, and hormone replacement therapy is initiated after, or at the time of, expected puberty if gonadectomy was performed prepubertally. Patients with a female phenotype or raised as females can benefit from corrective surgery of the urogenital tract, vaginal dilator therapy, or vaginoplasty before active sexual life is contemplated. Providing patients and their families with

psychological support and appropriate education about the condition as soon as the diagnosis is made is essential, as recommended by current practice guidelines.[10,11] Such disclosure prevents unintended consequences of a patient learning of the diagnosis later.

## CONCLUSION

The patient, reared as female, was referred to obstetrics and gynaecology department to undergo laparoscopic removal of the undescended testes to avoid the risk of malignancy. Children with PAIS may present with ambiguous genitalia at birth, which requires a thorough and careful evaluation to confirm the diagnosis. If raised as females, these children may experience virilization during male puberty, as in the case presented. While most professionals recommend raising them as males, it is important to take a multidisciplinary approach and customize the treatment plan for each case to achieve the best possible outcome for a psychologically fulfilling adulthood.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: Not required*

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**Cite this article as:** Varma D, Mahela S, Ullah IK, Mouli SC, Sharma K, Singh G et al. A case of partial androgen insensitivity syndrome with undescended testis and clitoromegaly. Int J Reprod Contracept Obstet Gynecol 2023;12:1497-9.