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CASE REPORT
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A CASE OF MALE GENOTYPE WITH PREDOMINANTLY FEMALE PHENOTYPE AND PARTIAL ANDROGEN INSENSITIVITY SYNDROME: A CASE REPORT

Muhammad Uzair Ishaq[1*], Muhammad Yasir Abbas[2], Muhammad Shahwaiz Lund[3], Moeen Nawaz[4], Mubashir Riaz[5], Muhammad Zeeshan[6], Javeeria Arshad[7], Muhammad Shees Raza[8], Dr. Shabbir Hussain Chaudhry[9]

[1]Department of Medicine, Allama Iqbal Medical College, Lahore - Pakistan
Email: uzairishaqm@gmail.com, ORCID: 0009-0000-3432-9101
[2]Department of Medicine, Allama Iqbal Medical College, Lahore - Pakistan
Email: myasirabbas7@gmail.com, ORCID:0009-0005-9196-5012
[3]Department of Medicine, Allama Iqbal Medical College, Lahore - Pakistan
Email: drshahwaiz2019@gmail.com, ORCID: 0009-0003-6698-3249
[4]Department of Medicine, Allama Iqbal Medical College, Lahore - Pakistan
Email: moeennawaz931@gmail.com, ORCID: 0009-0006-5001-5181
[5]Department of Medicine, Allama Iqbal Medical College, Lahore - Pakistan
Email: mubashir.riazhussain@gmail.com, ORCID: 0009-0001-7992-9618
[6]Department of Medicine, Allama Iqbal Medical College, Lahore - Pakistan
Email: zeeshan98ch@gmail.com, ORCID: 0009-0001-8160-8389
[7]Department of Medicine, Allama Iqbal Medical College, Lahore - Pakistan
Email: javeriaarshadaimc@gmail.com, ORCID: 0009-0008-7979-1429
[8]Department of Medicine, Allama Iqbal Medical College, Lahore - Pakistan
Email: sheesraza1@gmail.com, ORCID: 0009-0002-1517-8808
[9]Assistant Professor, Urology and Renal Transplant Surgery, Jinnah Hospital, Lahore - Pakistan
Email: dr.shchaudhry@yahoo.com, ORCID: 0000-0003-4011-9746

***Corresponding Author:** Muhammad Uzair Ishaq
*Email: uzairishaqm@gmail.com

Abstract
Androgen insensitivity syndrome (AIS) is an X-linked disorder caused by mutations in the Androgen Receptor (AR) gene in which individuals with normal male karyotype 46XY and gonads can have partial to complete insensitivity to androgens, thus resulting in undescended testes and the development of a female phenotype. We present a case with partial androgen insensitivity syndrome with a female phenotype that explores the unique and diverse nature of phenotypic manifestations of this rare condition and emphasises the need for further research into the genetics of PAIS to fill the knowledge gap in the future.

Keywords: Androgen Receptor Insensitivity, Antrogen Receptors, Partial Androgen Receptor Insensitivity, PAIS

Introduction
Androgen receptor (AR) sensitivity is an important factor that determines the full expression of male

phenotype in an individual with XY genotype at two stages of life, such as intrauterine life and puberty. (1) Androgen insensitivity syndrome (AIS) or Morris' syndrome (MS) is an X-linked disorder caused by mutations in the Androgen Receptor (AR) gene,(2),(3) in which individuals with normal male karyotype 46XY and gonads can have partial to complete insensitivity to androgens, thus results in undescended testes and the development of a female phenotype. (4) Complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS) are the three phenotypes of AIS that can be differentiated based on the degree of androgen receptor failure. (5) Individuals with MAIS are phenotypically males with male sterility, azoospermia, and gynecomastia,(3). In contrast, individuals with CAIS are tall, phenotypically females with well-developed breasts along with absent or scanty axillary as well as pubic hair and blind vaginas. (3)**,**(5) However, individuals with PAIS are the most difficult to diagnose,(5) because of various phenotypes of PAIS,(3) such as individuals with predominantly female phenotype present with mild clitoromegaly, the fusion of the labia and development of pubic hair at puberty, while, those having predominantly male phenotype exhibit micropenis, perineal hypospadias, and cryptorchidism. However, individuals with ambiguous phenotypes present with severely limited masculinization, phallic structure intermediate between clitoris and penis; urogenital sinus with perineal orifice, and labio-scrotal fold**.** (3)

We present a case of partial androgen insensitivity syndrome, who was born with female genitalia and developed ambiguous genitalia with no features of gynecomastia and was raised as female. The mother of this child had all 4 elder male children with normal primary and secondary sexual characteristics. The mother took Oral Contraceptive Pills (OCPs) and then conceived after a gap of a few years, the child was born after that and presented to us with a history of amenorrhea.

Case Presentation

An 18-years young, phenotypically female, presented in the outpatient department on September 2023 with primary amenorrhoea and gradual onset of features of masculinization over the past 4 years. She was fifth in order of birth among 6 siblings and was of average height compared to her siblings. A detailed history revealed that she was born with a female phenotype without any ambiguous genitalia.

On examination, she was of average height and weight (height: 169 cm, weight: 63 Kg, BMI: 22.05). However, she had a masculine body contour. **(figure 1)**

Figure: 1

Hirsutism was evident and breast development was at Tanner's stage I. Axillary and pubic hair were developed to Tanner's stage III. A lump was palpable in the left inguinal region on abdominal examination. The right labia majora was raised, resembling a stretched scrotal shape with a palpable

mass. (**Figure 2**)

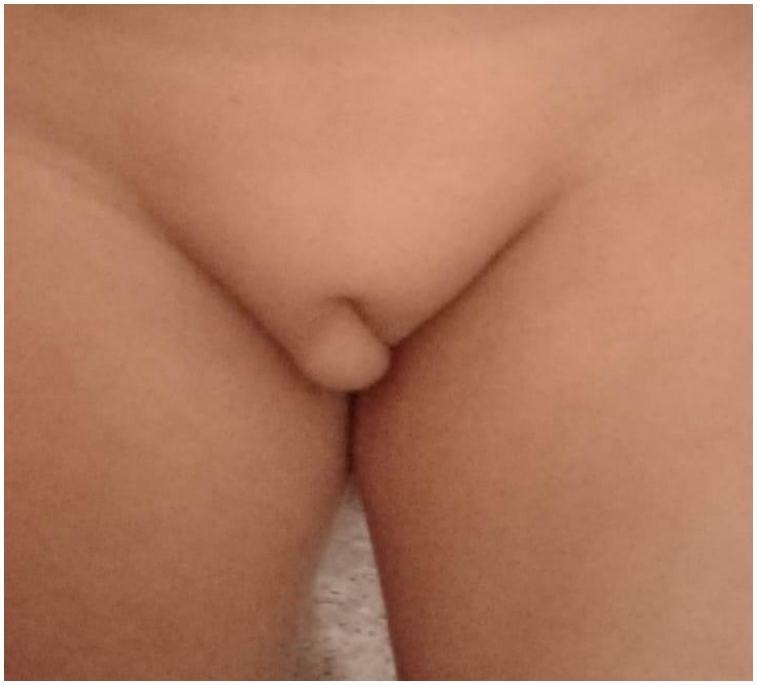

Figure: 2

However, the left labia majora was normal in size with no palpable mass. The urethral opening was seen in the perineum rather than the tip of the clitoris and the vagina was just an inch long and ended blindly. On rectal examination, the uterus was not palpable. Ultrasound of the pelvis shows a right testis measuring 45 x 20 mm with intact vascularity in the right hemi-scrotal region while the left testis measures 31 x 12 mm with intact vascularity in the left inguinal region. However, the uterus and adnexa were not visualised. Magnetic Resonant Imaging of the pelvis without contrast revealed evidence of intra-abdominal gonads, measuring 40 x 23.4 mm on the right side and 33.7 x 14.9 mm on the left side. **(figure 3)**.

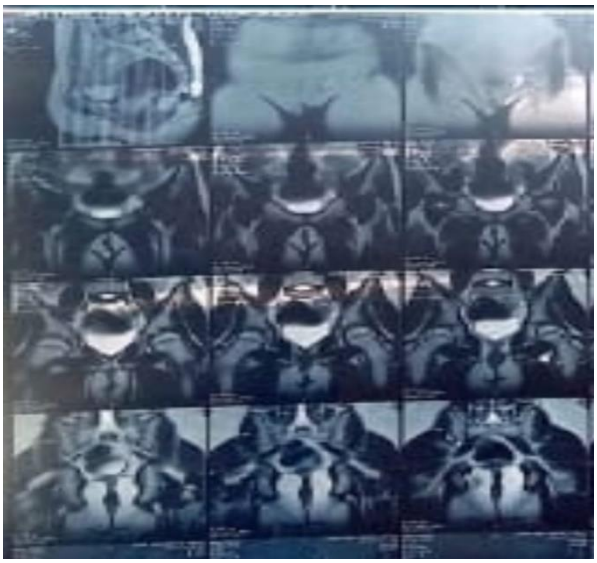

Figure: 3

A Cytogenetic Study of the patient reveals a chromosomal pattern of 46XY indicating a male genetic pattern despite her female phenotype. Her preoperative hormone profile revealed normal serum progesterone, LH, FSH, and prolactin (0.11 ng/mL, 3.63 mIU/mL, 4.30 IU/L, and 7.44 ng/ml respectively). However, her serum testosterone level (1.06 ng/dL) was low for an adult male. Hence, a diagnosis of “PAIS with predominantly female phenotype” was made and management options

such as sex assignment, genitoplasty, gonadectomy, and hormonal therapy were discussed with the patient and her family.

Discussion

Partial or incomplete forms of AIS comprise a wide variety of phenotypes that are difficult to diagnose. (5) It can be classified into predominantly male, ambiguous, and predominantly female phenotypes. (3) The presented case explores a scenario of partial androgen insensitivity syndrome (PAIS) with a predominantly female phenotype in a child, which is a rare occurrence. In addition to the unique nature of the case, she presented with unique similar features as well, such as raised labia majora with right testicular descent at the onset of puberty and the left testicular location in the inguinal region along with no breast development even after the onset of puberty, thus exploring the complex nature of diagnosing PAIS.

Androgen insensitivity syndrome (AIS) is an X-linked disorder caused by mutations in the Androgen Receptor (AR) gene. (2),(3), however, the fact that the child is affected by PAIS with a predominantly female phenotype showed a potential genetic or familial pattern, which is demanding a need for further research into the genetics of PAIS. Moreover, this study can be helpful for clinicians, residents, and medical students to diagnose and manage rare presentations of the PAIS. In addition, the presented case can be beneficial for researchers to illustrate the variety of presentations and clinical manifestations of PAIS, which can help them fill the knowledge gap in the future.

Conclusion

In conclusion, the presented case of partial androgen insensitivity syndrome (PAIS) with a predominantly female phenotype in a child explores the diverse nature of phenotypic manifestations of this rare condition. Moreover, the familial presentation of the disease in this case emphasises the need for further research into the genetics of PAIS to fill the knowledge gap in the future.

Abbreviations:

AR (Androgen receptors)
AIS (Androgen insensitivity syndrome)
MS (Morris syndrome)
CAIS (Complete androgen insensitivity syndrome)
PAIS (Partial androgen insensitivity syndrome)
MAIS (Mild androgen insensitivity syndrome)
OCPs (Oral contraceptive pills)

Declaration

Ethical approval: Ethics approval for this case report manuscript was obtained from the Institutional Ethics Committee.

Consent for publication: Informed consent was obtained from the patient/parents for their participation and publication of this case report, ensuring confidentiality and anonymity.

Availability of data: Online sources (PubMed, Google Scholar)

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