Partial Androgen Insensitivity Syndrome

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Abstract
Androgen insensitivity syndrome (AIS) present at several differentiation from genetic defects to end organ resistance thereby producing gender dilemma dispelled by sex hormones signature. It is quite traumatic for the patients and family of the affected baby. Extreme sensitivity and awareness on the part of the caring doctor is necessary for early diagnosis of case of AIS & for successful outcome.

Key Words
AIS, PAIS, Androgen, Ambiguous Genitalia

Introduction
Androgen insensitivity syndrome (AIS) is typically characterized by evidence of undermasculization (i.e. feminization) of the external genitalia at birth, abnormal secondary sexual development in puberty, and infertility in individuals with a 46, XY Karyotype (1). The incidence of AIS is estimated to be 1:20,000 to 64,000 male births (2). AIS represents a spectrum of defects in androgen action and can be subdivided into three broad phenotypes: complete androgen insensitivity syndrome (CAIS), with typical female genitalia; partial androgen insensitivity (PAIS) with predominantly female, predominantly male, or ambiguous genitalia; and mild androgen insensitivity syndrome (MAIS) with typical male genitalia. We present a case of 19 year old phenotypic male patient who was diagnosed as a case of partial androgen insensitivity syndrome with ambiguous genitalia (1). Awareness of this entity is important as with early diagnosis such disorder can be managed appropriately and accurate information can be given to parents regarding long term issues of hormone replacement therapy and fertility.

By definition PAIS is an intersex condition marked by genital ambiguity in any individual whose biology includes an identifiable mixture of male and female characteristics, regardless of the appearance of the genitalia at birth. It has been estimated that in US the incidence of Intersex conditions with ambiguous genitalia is about 1 in 2000 (3). Lawson Wilkins was one of the pioneers or founder of pediatric endocrinology in establishing the criterias for

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intersex patients (4). In the group of PAIS individuals, Wolffian duct derived structures can be partially to fully
developed, depending on the biochemical phenotype of
the Androgen Receptor (AR) mutation (5). At puberty,
elevated LH, testosterone, and Oestradiol levels are
observed, but in general, the degree of feminization is
less as compared to individuals with CAIS. Individuals
with mild symptoms of undervirilization and infertility have
been described as well. Phenotypic variation between
individuals in different families has been described
(6). Deciding gender assignment for infants with the
diagnosis of PAIS remains challenging (7). Diamond and
Sigmundson (1997) proposed to base gender assignment
of infants with PAIS on the degree of virilization of
external genitalia, which is presumed to be marker of
androgen imprinting in the brain (8). However, the status
of masculization of the external genitalia is, at best, a
crude estimate of such prenatal androgenization (3).

**Case Report**

Nineteen year old student Mr. M presented in the
outpatient's department of Surgery with complaints of
occasional pain in both sides of inguinal region with
radiation to urethral region. He was short statured (as
compared to his brother and sisters being 4th in birth
order) and of normal built. There was history of
appearance of pubic hair at around 13-14 years of age
and followed by axillary and later on facial hair (beard).
The systemic and abdominal examinations were normal.
External genitalia showed maldeveloped penis covered
partially with prepuce and bifid maldeveloped scrotum
having absent testes bilaterally. Urethral opening was at
perinoscrotal position. Pubic hairs were present but not
having male pattern and monspubis contained excess of
fat. Ultrasonography of pelvic organs showed uterus
measuring 52 X 16 X 23 mm in size, anteverted with
uniformly normal myometral echotexture, endometrial
thickness normal and both side ovaries normal in size
and echotexture (**Fig 1**). The ultrasonography was
performed with 11 Mhz linear transducer in supine position
with direct contact scanning technique even then, both
scrotal sacs were found empty. The testes were not
located in the scrotal sacs as well as in the inguinal canal
region. Karyotype analysis was 46 XY (**Fig 2**). Diagnostic
laprotomy was done for acute pain abdomen. Midline
normal size uterus with bilateral fallopian tubes attached
to its cornu and two large sized ovaries were found.
Biopsy was taken from right ovary and was received in
the Department of Pathology, GMC Jammu for
histopathological examination. Grossly a soft tissue piece
measuring 4 X 2 cms, grey white in colour and on cut
section - 2-3 small cystic cavities each ranging in diameter

![Fig 2. Karyotype of the Individual Showing Well Spread Metaphase Plate with Normal Male 46, XY Chromosomes](image1)

![Fig 3. Microphotograph of the Gonadal Biopsy Showing Normal Ovarian Stroma. 10X](image2)

![Fig 4. Microphotograph Showing Developing Follicle (Graffian follicle) within the Ovarian Stroma. 10X](image3)
from 0.2 to 0.3 cm were seen. Whole of the tissue was processed. Microscopic examination of the multiple sections showed normal ovarian histomorphology. Graffian follicle and two follicular cysts were seen. No testicular tissue was identified in the multiple sections studied (Fig 3 & 4). Levels of the different hormones were assessed. DHEA-S (Dehydroepiandrosterone-Sulphate) - 835 μg/dl (was markedly raised). While FSH - 5.84 mIU/ml; LH - 4.91 mIU/ml; Prolactin - 29.49 ng/ml; total testosterone - 3.65 ng/ml and Progesterase II - 1.2 ng/ml (all were within normal limits).

**Discussion**

Partial androgen insensitivity syndrome is a rare disorder, especially PAIS with ambiguous genitalia. Such patient may present with microphallus (< 1 cm) with clitoris like underdeveloped glans; labia majora like bifid scrotum, descended or undescended testes; perinosrotal hypospadias or urogenital sinus; gynaecomastia (development of breasts) in puberty (1). PAIS like CAIS is transmitted as an X-linked trait and is related to the mutations in Androgen Receptor gene. Though more than 95% of individuals with CAIS show such mutations; these are seen in < 50% of PAIS patients. The laboratory findings required for diagnosis include 46 XY karyotype; as well as evidence of normal or increased synthesis of testosterone (T) by the testes and its normal conversion to Dehydrotestosterone. Measurement of serum 17-Hydroxy progesterone and its sulphate can be done to detect testosterone biosynthetic defects. In case of PAIS besides clinical and laboratory findings, the family history of other affected individuals related to each other in a pattern consistent with X-linked recessive inheritance should be sought (4). The affected individuals are almost always infertile. AIS are prone to testicular neoplasms. Hamartomas develop in 63% of cases of AIS and Sertoli cell Adenomas in 23%. Malignant tumours occur in about 9% of these patients (9). Ultrasonography and laproscopy should be done in all such patients to examine internal genital organs and to detect any neoplastic growth.

Management of AIS includes removal of testes after puberty when feminization is complete to prevent testicular malignancy or prepubertal gonadectomy accompanied by estrogen replacement therapy. Additional treatment include vaginal dilatation to avoid dyspareunia. In individuals with PAIS and ambiguous or predominantly male genitalia, parents and healthcare professionals should assign sex of rearing as early as possible in infancy. Those individuals with PAIS who are raised as males may undergo urologic surgery such as orchipexy and hypospadias repair. A trial of androgen pharmacotherapy may help improve virilization in infancy. In some mammoplasty for gynecomastia can be done. Systematic disclosure of the diagnosis of AIS is an empathic environment with both professional and family support, is encouraged. Surveillance includes periodic reevaluation for gynecomastia during puberty in individuals which have been assigned a male sex. Genetic counseling always has a role to play. Since carrier females have a 50% chance of transmitting the AR gene mutation; therefore, carrier testing in affected family members and prenatal molecular genetic testing is possible for pregnancies of women (1).

**Conclusion**

AIS constitutes one of the most common cause of ambiguous genitalia. A coordinated approach by physician, surgeon, pathologist and a good lab test set up help to arrive at a quick diagnosis.

**References**