Partial Androgen Insensitivity Syndrome- XY Female (Male Pseudohermaphroditism)

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Abstract

Disorders of androgen receptor function represent the most common definable cause of the undervirilized male. These patients characteristically have a 46, XY karyotype and testes and present with a spectrum of phenotypic abnormalities that vary from complete external feminization (syndrome of complete androgen insensitivity), to ambiguous genitalia (partial androgen insensitivity), to the phenotypically infertile male. The clinical presentations may vary according to the severity of the disorder but the pathophysiology is similar.

Introduction

Androgen Insensitivity Syndrome (previously known as XY female or testicular feminization syndrome or Morris syndrome) is an intersexual condition having genetic sex of male karyotype (46XY) with cryptorchid testes and female phenotype. The end organs are insensitive to androgens due to abnormality of androgen receptor (AR). There is loss of function mutation in AR gene located on long arm of X chromosome Xq 11-12. AIS is said to be complete AIS (CAIS) when there is no response to androgens. The incidence of CAIS is about 1 in 40,000 to 60,000 births. Partial AIS (PAIS) occurs when androgen receptors can partially respond to androgen stimulation.

The syndrome of partial androgen resistance includes syndromes that were once thought to represent separate entities: Reifenstein’s, Gilbert-Dreyfus, Rosewater’s, and Lubs’ syndromes. These are X-linked disorders of incomplete masculinization that represent a spectrum of phenotypic abnormalities. The major finding is ambiguity of the external genitalia to varying degrees. The classic phenotype is that of a male with perineoscrotal hypospadias, cryptorchidism, rudimentary Wolffian duct structures, gynecomastia, and infertility. The endocrine profile of partial androgen insensitivity syndrome is similar to that of the complete androgen insensitivity syndrome. To date, over 300 mutations in the androgen receptor gene have been discovered. It has been well recognised in partial androgen insensitivity syndrome that these mutations produce a diversity of phenotypes between and within affected families, consistent with additional factors that modulate responsiveness to androgen. This seems consistent with prior studies in the 1980s on genital skin fibroblasts, demonstrating two forms of receptor defect in the partial androgen insensitivity syndrome: (1) a reduced number of normally functioning androgen receptors and (2) a normal receptor number but decreased binding affinity.

Case Reports

24 years old unmarried female presented with complaints of failure to menstruate.

Family history: Not significant.

On examination: General examination: NAD Breast development was present, scanty axillary and pubic hairs.

Abdominal examination: Both sides swelling present at the superficial inguinal ring, firm on palpation, non-tender (illustration 1).

Vulval examination: Clitoromegaly seen along with ambiguous external genitalia in the form of absence of labia majora and labia minora with male impression of scrotal sac (illustration 2). There was blind vaginal pouch of approx. 2cm in length (illustration 3).

P/R examination revealed no uterus and ultrasound pelvis confirmed absent uterus and ovaries.

A buccal smear disclosed a male chromatin pattern. A vaginal smear revealed precornified cells in sufficient quantity to indicate a moderately good estrogen effect. Chromosomal analyses revealed 46XY karyotype. MRI revealed presence of testes in the inguinal canal at the superficial inguinal ring on both sides.

Endocrine evaluation revealed normal levels of testosterone and gonadotropin.

Patient and parents were explained regarding diagnosis and future prospects of the condition.
Patient’s marriage was decided within three months from date of admission to hospital. The cryptorchid testes at the superficial inguinal ring were removed on both sides and sent for histopathological examination (illustration 4). Vaginoplasty operation was performed to create neovagina using amnion as the source of graft material (illustration 5). The neovagina was kept patent with the help of vaginal moulds. After orchidectomy and vaginoplasty to establish coitally functional vagina was done, patient was kept on long term estrogen replacement therapy along with psychological support and follow up.

The histopathological examination report excluded malignancy in testes. The patient was married after 3 months of discharge from hospital.

Discussion

Phenotypic females with congenital androgen insensitivity (previously called testicular feminization) develop secondary sexual characteristics but do not have menses. These patients are male pseudohermaphrodites. Genotypically, they are male (XY) but have a defect that prevents normal androgen receptor function, leading to the development of the female phenotype. Defects in the androgen receptor gene located on the X chromosome include absence of the gene that encodes for the androgen receptor and abnormalities in the binding domains of the receptor. Postreceptor defects also exist. Total serum testosterone concentration is in the range of normal males. Because antimullerian hormone is present and functions normally in these patients, internal female (mullerian) structures such as a uterus, vagina, and fallopian tubes are absent. Testes rather than ovaries are present in the abdomen or in inguinal hernias because of the presence of normally functioning genes on the Y chromosome. Patients have a blind vaginal pouch and scant or absent axillary and pubic hair. These patients experience abundant breast development at puberty; however, the nipples are immature and the areolae are pale. Testosterone is not present during development to suppress the formation of breast tissues; at puberty, the conversion of testosterone to estrogen stimulates breast growth. Patients are unusually tall with eunuchoidal tendency (long arms with big hands and feet).

The diagnosis of partial androgen insensitivity syndrome can be difficult. In the newborn period, it may be made in the setting of a 46,XY karyotype, ambiguous external genitalia, and absent mullerian structures on pelvic ultrasound. Endocrine evaluation confirms normal testosterone and gonadotropin levels and a normal testosterone/DHT ratio. An hCG stimulation test and characterization of the androgen receptor gene in serum DNA by PCR should confirm the diagnosis. A family history consistent with X-linked inheritance of ambiguous genitalia is of great significance.

Management must be individualized depending on the degree of genital ambiguity. In patients assigned a female gender, gonadectomy and surgical reconstruction of the external genitalia are indicated; at puberty, estrogen/ progesterin replacement is instituted. Those individuals raised as males would require treatment of their cryptorchidism, reduction of gynecomastia, and genitalia reconstruction. Phallic size remains small, however, and the effects of supraphysiologic doses of testosterone have been disappointing. Of importance in considering gender assignment in patients with partial androgen insensitivity is the recognition that the receptor defect affecting the external genitalia appears to affect brain receptors for testosterone similarly. Unfortunately, because of the distinct phenotypic variability, even within families, gender assignment of patients with partial androgen insensitivity syndrome cannot be based on the specifically identified androgen receptor gene. The study by Melo and colleagues (2003) of 11 patients with partial androgen insensitivity syndrome (5 raised female, 6 raised male) demonstrated gender of rearing to be consistent with adult gender role. This suggests the possibility that in the setting of inadequate androgen imprinting of the fetal brain, sex of rearing may predominate in determination of gender identity. Unfortunately, this has not consistently proven to be the case.

The current recommendation with partial androgen insensitivity syndrome is to allow virilization of the external genitalia to serve as a guide in gender assignment, in that this may be the best means of assessing androgen imprinting of the brain, for lack of a more precise marker.

Intersex conditions can present in wide variety of ways. Therefore, thorough review and investigations by experienced multi disciplinary teams is essential for optimal diagnosis and management. Management includes making correct diagnosis by history, examination and investigations, communicating the diagnosis to both patient and parents along with psychological support, counseling for future gender assignment and surgical treatment in the form of genital and gonadal surgery according to gender selected.

If female gender selected—- treatment is gonadectomy
followed by long term hormone replacement therapy (HRT) and later on vaginoplasty for vaginal hypoplasia to establish coitally functional vagina, along with psychological support and follow up.

If male gender selected--- multistep surgery in the form of:

I. Releasing chordee followed by hormonal treatment.
II. Vaginal closure.
III. Construction of urethral tube (Urethroplasty).
IV. Penile surgery (Phalloplasty).

Conclusion

Incidence of intersex condition is 1:2000 births and multitude of aetiologies can lead to XY female. These intersex conditions are complex with many management areas remaining highly controversial. Sensitive, pacing information be given to allow young women and their families to make informed decision about treatment and a realistic adaptation to life with AIS. The Clinical services regarding management of intersex condition need to be multi disciplinary and aim to optimize the patient physical and psychological health.

References

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Illustrations

Illustration 1

UNDESCENDED TESTES

Illustration 2

AMBIGUOUS EXTERNAL GENITALIA
Illustration 3

BLIND VAGINAL POUCH

Illustration 4

ORCHIDECTOMY OF UNDESCENDED TESTES
Illustration 5

PHOTOGRAPH SHOWING VAGINOPLASTY
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