

Partial Androgen Insensitivity Syndrome: A rare disease

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Abstract: Androgen insensitivity syndrome is a rare disease, manifested as normal female external phenotype to infertile male with 46 XY karyotype due to different level of resistance of androgen receptor. Androgen insensitivity syndrome is classified as complete, partial and mild androgen insensitivity. Partial androgen insensitivity syndrome is further sub-classified according to morphogenesis as predominant female phenotype, ambiguous genitalia and predominant male phenotype. Partial androgen insensitivity syndrome usually presents in early month of life but this can present rarely at puberty with primary amenorrhea as complete androgen insensitivity syndrome. Our case is predominantly female phenotype partial androgen insensitivity and presented with primary amenorrhea.

Keywords: Androgen insensitivity syndrome, primary amenorrhea.

INTRODUCTION

Androgen insensitivity syndrome (AIS) is a disorder of androgen receptor (AR) function resulting in resistance to androgen action. It is characterized by spectrum of phenotypic abnormality of genetically male (XY) from normal female phenotype to infertile male depending upon level of resistance of androgen receptor. Androgen receptor gene is located on long arm of X chromosome (Xq 11-12), mutation of AR gene leads to resistance. Variable mutation of AR gene (around 600) leads to variable spectrum of expression of AR in presence of androgen [1]. Hereditary form of AIS predominant but around 30 % case occurs as sporadic form [2]. AIS is classified as complete androgen insensitivity (CAIS), Partial androgen insensitivity syndrome (PAIS) and mild androgen insensitivity syndrome (MAIS). CAIS is characterized by phenotypical normal female appearing external genital but short blind end vagina, undescended testis and absence of müllerian structure (i.e. uterus, fallopian tube and cervix) as well as wolffian structure (epididymis, vas deferens and seminal vesicle). PAIS's characteristics ranges from mainly normal female like features with clitoromegaly and partial fusion of the labia to those mainly male external genitalia with small penis, hypospadias and cryptorchidism unilaterally or bilaterally. Wolffian duct derivative (epididymis, vas deferens and seminal vesicle) and prostate partially or completely developed. MAIS is characterized by normal male phenotype with defective spermatogenesis and infertility with or without gynecomastia [1]. The estimated incidence of CAIS is one in 20400 XY births

while the incidence of PAIS is one in 130000 births [3]. PAIS patients usually presents in early month of life with ambiguous genitalia [4]. We present a case of 15 year old PAIS patient with predominantly female phenotype presented with primary amenorrhea.

CASE HISTORY

A 15 years old female phenotype presented with primary amenorrhea in gynecology department and she was referred to urology department. On examination she was average height and obese (height: 163 cm, weight: 79 kg, BMI: 29.7). She had female type of body contour. Breast was developed to Tanner's stage 3. Axillary and pubic hair was present. On abdominal examination no hernia or lump present. External genitalia examination showed clitoromegaly with short and blind vagina (Fig.- 1). Labia majora and minora were well developed. Urethral and vaginal opening were separated. Routine blood examination, urine routine and microscopy was normal. She had high serum testosterone level 3.28 nmol/l (normal range 0.38-1.97 nmol/l), high serum androstenedione level 5.99 ng/ml (normal range 0.2-2.2 ng/ml), high serum LH level 15.61 mIU/ml (normal range :2-12 mIU/ml), high anti müllerian hormone 9.22 ng/ml (normal range: 2.1-6.8 ng/ml), high S.Prolactin level 30.44 ng/ml (normal range :1.9-25.0 ng/ml), normal Thyroid function and normal FSH level.



Fig-1: Photograph showing clitoromegaly with well developed labia majora and minora.

On USG abdomen: uterus and bilateral ovaries were not visualized. Prostate was seen (Fig.-2).



Fig-2: USG pelvis showing prostate with absent uterus

Bilaterally ovoid structures seen in inguinal region suggestive of ectopic gonads. On MRI bilateral gonads seen in inguinal region. No uterus and bilateral ovaries were seen. On family history no such abnormality was found. Karyotyping was done, which shows 46+XY chromosome (Fig.-3).

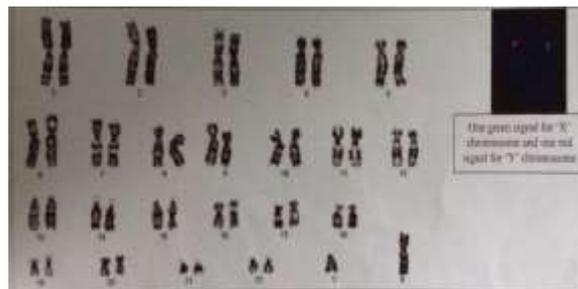


Fig-3: Karyotyping showing 46+XY chromosome

Due to risk of testicular carcinoma bilateral open orchidectomy done. Per operatively bilateral testis with cord seen, no hernia seen. HPE examination showed seminiferous tubule and leydig cells, no ovarian tissue or neoplasia were seen, which further confirms testis (Fig.- 4).

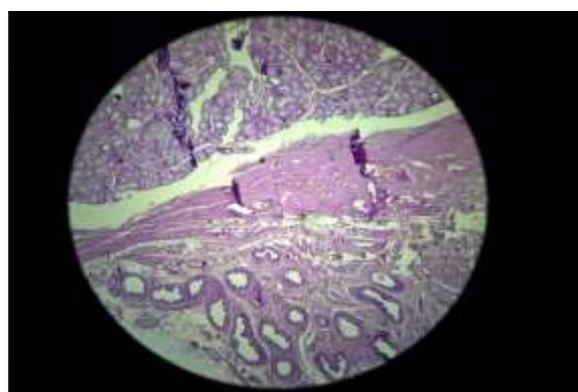


Fig-4: Microphotograph showing seminiferous tubule and leydig cells (H & E X40)

Patient mentally seeing herself as female so the decision of telling regarding her disorder was left to her parent's. Postoperatively she was referred to endocrinologist for hormonal supplement and plastic surgeon for clitoroplasty.

DISCUSSION

Partial androgen insensitivity syndrome is rare disorder with variable spectrum of phenotypes ranging from predominantly female phenotype to male predominant type. PAIS usually presents as ambiguous genitalia in early month of life [4]. Its characteristics and phenotypes are best understood by following subdivision [5].

1. PAIS with predominant female phenotype: Inguinal or labial testes, Clitoromegaly or labial fusion and distinct urethral as well as vaginal openings or a urogenital sinus.
2. Partial AIS with ambiguous genitalia: Micro phallus (<1 cm) with clitoris-like underdeveloped glans; labia majora like bifid scrotum, descended or undescended testes, perineoscrotal hypospadias or urogenital sinus, Gynecomastia (development of breasts) in puberty.

3. Predominantly male genitalia: Simple (glandular or penile) or severe (perineal) "isolated" hypospadias with a normal-sized penis and descended testes or severe hypospadias with micropenis, bifid scrotum, and either descended or undescended testes, gynecomastia in puberty.

Diagnosis of PAIS require clinical, hormonal, genetics and radiological investigation [6]. Genetically 46 XY karyotype is present. Clinically PAIS predominant female phenotype is similar to CAIS but presence of clitoromegaly, pubic and axillary hair differentiates it from CAIS. Hormonal investigations are similar in PAIS and CAIS. Evidence of normal or increased synthesis of testosterone (T) by the testes, evidence of normal conversion of testosterone to dihydrotestosterone (DHT), evidence of normal or increased luteinizing hormone (LH) production by the pituitary gland are seen. In PAIS higher-than-normal levels of anti-müllerian hormone (AMH) during the first year of life or after puberty are seen. Radiological investigations help in locating gonads (ectopic/ undescended), absence of müllerian structure (fallopian tube, uterus and cervix), presence of prostate and or any wolffian structures/remnants.

In our patient's case: 46 XY karyotype, absent müllerian structure, increased testosterone suggestive of AIS and clitoromegaly, distinct urethral and vaginal openings, female body contour, bilateral inguinal testis, presence of pubic and axillary hair, prostate seen in USG and increased testosterone and anti müllerian hormone is suggestive of partial androgen insensitivity syndrome with female phenotype.

The patients with CAIS are usually managed with bilateral orchiectomy for risk of testicular cancer, estrogen supplementation and vaginal dilatation. Orchiectomy should be done after puberty when feminization of individual is complete as it occurs by peripheral conversion of androgen to estrogen. Risk of testicular cancer is low in prepubertal age [6], so gonadectomy is preferred in postpubertal age [7]. Patients with PAIS and ambiguous genitalia or predominantly male type are managed with multidisciplinary approach. Gender is reassigned and further management depends upon gender reassignment. Main consideration involved in assigning gender include external look of genitalia [4], extent to which child can virilise at puberty [8], surgical option and post-operative sexual function of the genitalia [9, 10], genitoplasty complexity [9] and projected gender identity of child.

Patients with PAIS predominantly female type are managed similarly as CAIS except prepubertal gonadectomy, which helps avoid the emotional discomfort of increasing clitoromegaly at the time of puberty [5]. Our patient presented after puberty as PAIS

with predominant female phenotype, she was managed with bilateral orchiectomy for risk of development of testicular cancer. She was referred to plastic surgeon for clitoroplasty and endocrinologist for hormone supplementation.

CONCLUSION

Partial androgen insensitivity syndrome cases are rare and generally presents with ambiguous genitalia in early months of life. A detailed evaluation is required to confirm the diagnosis and multidisciplinary approach is done for the management of such cases. As our patient reported at puberty so immediate bilateral gonadectomy was done and she was assumed herself as female.

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