CASE REPORT

Partial Androgen Insensitivity Syndrome

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Abstarct

Androgen insensitivity syndrome (AIS) present at several differentiation from genetic defects to end organ resistance thereby producing gender dilema 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

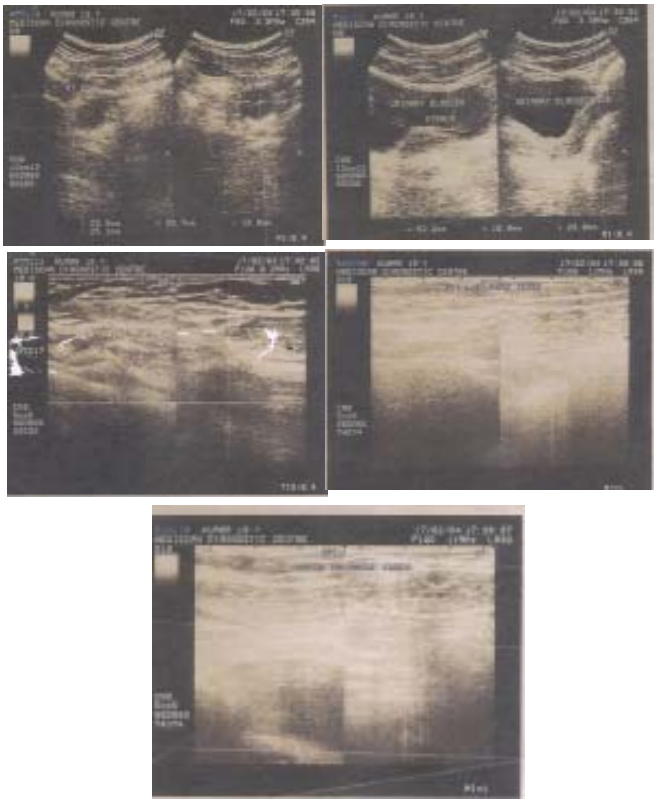

Fig 1. Ultrasonography of Pelvis Showing Presence of Uterus & Bilateral Tubes, Ovaries & of Inguinal Canal Showing Absence of Testes Both Sides

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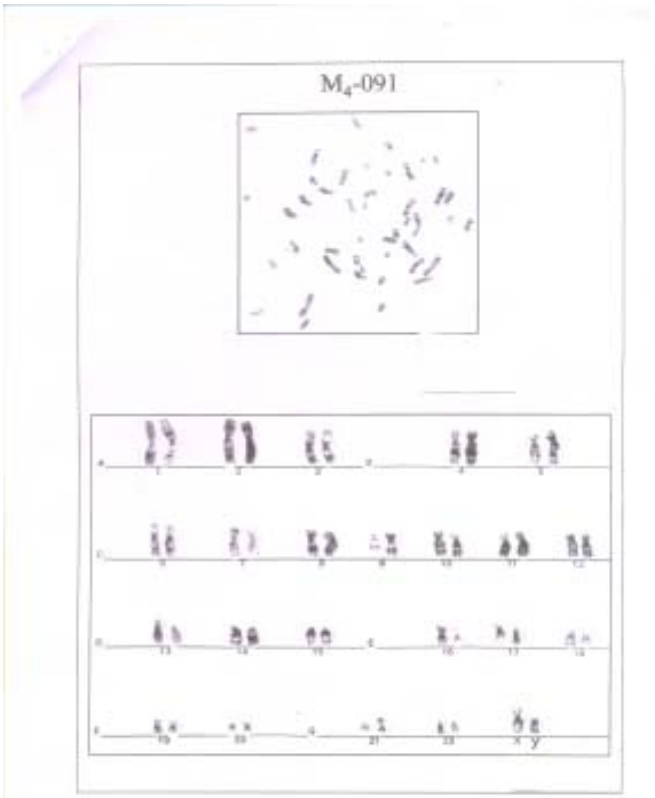

Fig 2. Karyotype of the Individual Showing Well Spread Metaphase Plate with nNormal Male 46, XY Chromosomes

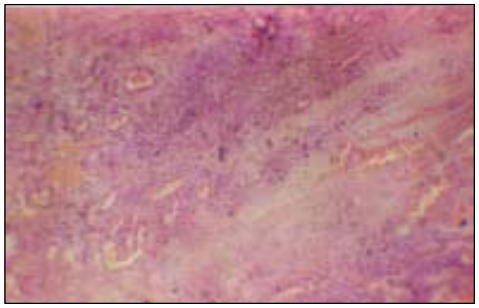

Fig 3. Microphotograph of the gonadal biopsy showing Normal ovarian stroma. 10X

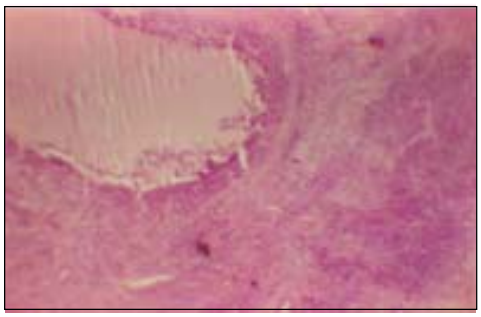

Fig 4. Microphotograph showing developing follicle (Graffian follicle) within the ovarian stroma. 10X

intersex patients (4). In the group of PAIS individuals, Wolfian 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 myometrial 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

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 (Dehydoepiandrosterone-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 for(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 gentalia, 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 gynaecomastia 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

1. Gottlieb B, Beitel LK, Trifiro MA. Androgen Insensitivity Syndome; Gene Reviews. [Initial posting 24 March 1999 and Revised 24 May 2007]. Available from: http://www.geneclinics.org/ profiles/androgen/detail.html.
2. Kour V, Abrol A. Testicular Feminization Syndrome; *JK Science* 2005; 7(1).
3. Diamond M. Sex gender and identity over the years: a changing perspective. *Child & Adolescent Psychiatric Clin North Am.*2004;13: 591-607.
4. Migeon CJ. 46, XY Intersex Individuals: Phenotypic and Etiologic Classification, Knowledge of Condition, and Satisfaction with Knowledge in Adulthood; Pediatrics Vol. 110 No. 3, September 2002. pp. e 32.
5. Mendez JP. Mixed Gonadal Dysgenesis: Clinical, Cytogenetic, Endocrinological, and Histopathological findings in 16 patients. *Am J Med Genet* 1993 46(3): 263-67.
6. Butler LJ. True Hermaphroditism or Gonadal Intersexuality. Cytogenetic and Gonadal Analysis of 5 new examples related to 67 known cases studied Cytogenetically. *Arch Dis Childh* 1969; 44: 666.
7. Sobel V, Imperato- McGinley J. Gender identity in XY intersexuality. *Child & Adolescent Psychiatric Clin North Am* 2004; 13, 609-22.
8. Diamond M, Sigmunds H K. Management of Intersexuality: Guidelines for dealing with persons with ambiguous genitalia. *Archives Ped & Adolescent Med* 1997; 151, 1046-51.
9. Prat Jaim. Female Reproductive System; Damjanov I and Linder J (ed); Anderson's Pathology; 10th edition; Vol 2; Mosby Publishers; USA; 1996.pp. 2226-75.