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Original Research Paper

Genetics

SIBLING ASSOCIATION IN ANDROGEN INSENSITIVITY SYNDROME- A CASE REPORT

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ABSTRACT

Introduction: Androgen insensitivity syndrome is a condition that affects sexual development of a child. Children with this condition are genetically male, with XY karyotype and female phenotypic presentation. The sex of rearing differs from female to male. The condition is mainly due to genetic mutations in the candidate X and Y chromosomal genes. Due to which the XY chromosomes do not function the way it should be and thereby leading to a condition where the body is unable to respond to androgen.

Source: Genetic referral for Division of Human Genetics, St .John's Medical College.

Aim: A study to bring about sibling association in XY female using pedigree analysis

Material and Methods: Standardized peripheral lymphocyte culture and pedigree analysis

Results: Pedigree analysis showed three daughters born to consanguineous couple. All the three daughters had decreased sexual characters and delayed menarche. Karyotype showed 46,XY female in all the three daughters. MLPA analysis did not show any changes.

Discussion: XY female with decreased sexual characteristics and absent uterus and ovaries with female phenotype are referred to as complete androgen insensitivity syndrome. This condition follows X-linked mode of inheritance. The condition is familial within the family, where maternal aunts and female siblings of the affected individuals are also affected. Hence karyotype is recommended for the other female family members who are also presenting with similar complaints. With cytogenetic evaluation the affected individual and family can be provided with appropriate genetic counseling and management.

KEYWORDS :

INTRODUCTION:

Until recently 46,XY females were referred with terms such as "intersex","pseudohermaphroditism", "sex reversal", "hermaphroditism" and gender-based diagnostic labels. These terms are perceived as potentially pejorative by patients and can be confusing to practitioners (1). Hence, the term "disorders of sexual development" (DSD) is proposed(2) , as defined by congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. Phenotypic sex is characterized by the presence of primary and secondary sexual characteristics of an individual. Genotypic sex refers to the genetic make-up where normal male have 46,XY karyotype and normal female have 46,XX karyotype . It is defined by the presence or absence of a Y chromosome (3).

Classification of 46,XY Female

Clinically, the phenotype of 46,XY females in an adult can be grouped in three major categories based on the presence of uterus and other mullerian derivatives.

I. 46,XY females who develop with functioning testis producing anti-mullerian hormone (AMH) and born without uterus. AMH is produced by Sertoli cells in early gestation can cause the dedifferentiation of the mullerian duct system. Women affected by Androgen Insensitivity Syndrome (AIS), 5 alpha reductase (5α R) deficiency and 17- hydroxylsteroid-dehydrogenase (17-HSD) deficiency fall into this category.

II. 46,XY females with Gonadal dysgenesis – does not produced does not allow the mullerian duct system to differentiate to form a uterus. The mesonephric ducts fails to develop in the absence of testosterone, and the undifferentiated urogenital sinus and external genitalia mature into female structures. Women with 46,XY Gonadal Dysgenesis or Swyer's Syndrome (4) form the majority of this group.

III. 46,XY females with Ovo-testicular DSD who have variable testicular function due to unpredictable secretion of AMH with variable uterine appearance such as hemiuterus with testicular tissue (5).

Table 1: Revised nomenclature of Intersex (6,7).

Previous	Proposed
Intersex	**Disorders of sexual development (DSD)**
Male pseudo-hermaphrodite Under virilization of an XY male Under masculinization of an XY male	46,XY DSD
Female pseudo-hermaphrodite Over virilisation of an XX female Masculinisation of an XX female	46,XX DSD

True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

Complete androgen insensitivity was first described in detail by Morris in the year 1953. He provided the term, testicular feminization (8). The phenotype of this condition is female, despite the normal male karyotype, 46,XY. These individuals have congenital insensitivity to androgens, transmitted by means of a maternal X-linked recessive gene responsible for the androgen intracellular receptor (9). Androgen induction of Wolffian duct development does not occur. Antimullerian hormone activity present prevents the mullerian development. Subsequently the testes descended to the inguinal region because antimullerian hormone mediates the transabdominal descent of the testes (10).

AR gene is mapped to Xq11-12 (11) and is about 90,000bp in length, consisting of eight exons encoding for a single polypeptide of 919 amino acids in length. It belongs to the steroid receptor super family (12).

The main phenotypic characteristics of individuals with AIS were, female external genitalia, a short blind ending vagina, the absence of Wollfian duct derived structures. At puberty, AIS presented with elevated levels of Luteinizing Hormone (10).

Phenotypic variations between individuals in different families were described for several mutations. (9,13).

AIM:

A study to bring about sibling association in XY female using pedigree analysis

MATERIAL & METHODS:

Clinical Data Collection

By personal interview and physical examination which was carried out on patients by clinicians, the information was gathered and noted down in the structured proforma. Consent from all the patients and parents or guardians were taken before drawing blood.

Clinical Presentation:

All the three girls presented with primary amenorrhea, Secondary sexual characters with scanty axillary hair growth and scanty pubic hair and under developed breast. Ultrasound finding showed not visualized uterus and ovaries. Hormonal profile showed elevated levels of FSH and LH and normal levels of testosterone.

METHODS:

Standardized PHA stimulated peripheral lymphocyte culture with GTG banding was used for all the three cultures and chromosome analysis based on ISCN 2016(15). Pedigree analysis states consanguineous marriage in parents, with second degree consanguinity.

DNA extraction and MLPA (multiplex Ligation Probe Amplification) for all the three siblings were carried out through referral lab. The ETDA samples from the three siblings were collected at Division of Human Genetics and outsourced to a referral lab to carry out gene amplification studies for AR gene.

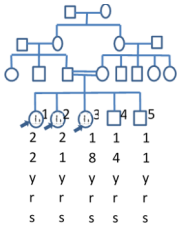

Figure 1: Pedigree of the proband.

RESULTS :

Table 1:Clinical features

	Proband	SIB1	SIB2
Chief Complaint	Primary Amenorrhea	Primary Amenorrhea	Primary Amenorrhea
Age at diagnosis	18years	21years	22years
Breast development	Not developed	Not developed	Not developed
Hirsutism	Absent	Absent	Absent
Voice	Female	Female	Female
Axially/ Pubic hair	Scanty	Scanty	Scanty
Hormonal profile			
FSH	Elevated	Elevated	Elevated
LH	Elevated	Elevated	Elevated
Testosterone	Decreased	Decreased	Decreased
Ultrasound report			
Uterus	Absent	Absent	Absent
Ovaries	Absent	Absent	Absent
Karyotype	46,XY[20]	46,XY[20]	46,XY[20]
MLPA analysis	no pathogenic variants	no pathogenic variants	no pathogenic variants

1. Pedigree and clinical diagnosis result: AIS all in all the three female probands was established by clinical presentation and by pedigree analysis. Sibling association with same features Primary amenorrhea and decreased secondary sexual characteristics with elevated FSH and LH and decreased Testosterone values in all the three female probands.
2. The karyotype Proband 46,XY[20], SIB1: karyotype 46,XY[20] and SIB 2: karyotype 46,XY[20].
3. Molecular analysis using Multiplex ligation Probe Amplification (MLPA) on AR gene showed no pathogenic variants in all the three sibs. Note: MLPA was outsourced to a referral lab.

Image 1: Karyotype images of proband

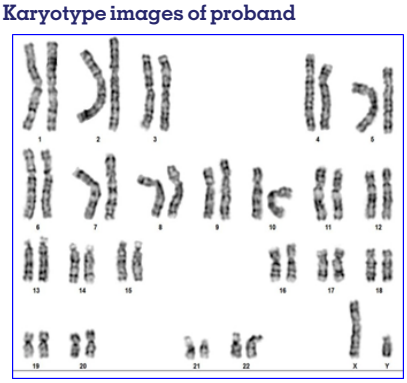

Image 2 : Karyotype images of SIB 1

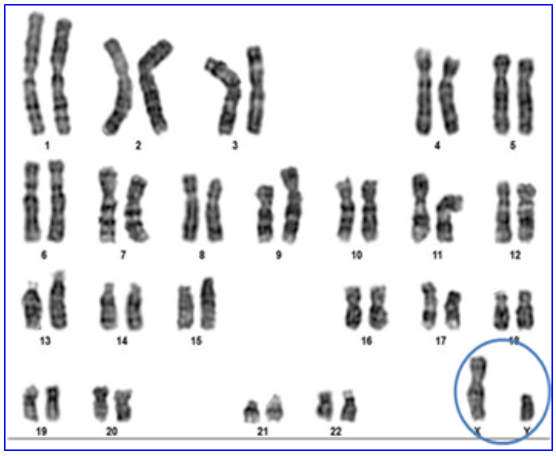

Image 3 : Karyotype images of SIB 2.

DISCUSSION :

46,XY female is a heterogeneous endocrine disorder manifesting itself in a wide variety of clinical symptoms, that affects approximately 4 to 5% of women of reproductive age. Due to its heterogeneous nature, establishing a definition, which encompasses all the clinical and biochemical manifestations, is a difficult task. The most widely accepted definition of 46,XY female is "phenotypic female with male karyotype". Female phenotype with hypoplastic breast, infantile uterus, streak gonads, and failure to menstruate spontaneously were the evidence of 46,XY female. Two siblings and a maternal aunt, from the same family were reported with 46,XY karyotype (16). In another study two siblings with 46,XY were observed by and the clinical features of the two sisters were suggestive of CAIS(17). Two sisters with 46,XY karyotype and female external genitalia due to gonadal dysgenesis were reported (18). 46,XY female condition was reported in a family study of three sisters where the mother, father and younger sister were identified with normal karyotypes (19). Two affected XY siblings had a deletion of *AR* exon lead to the identification of different deletions of different exons of the X-linked *AR* gene in different members of same family (20). It is stated, that sisters of the affected 46,XY females and the female offspring of a normal 46,XX sister have 1 in 6 chance of being XY female (21). It is suggested that karyotyping has to be included as part of the family study for all the family members of the affected individuals, especially mothers and younger sibs who have not attained menarche (22). By doing so, the X-linked mode of inheritance could be evaluated and family members and the affected individual could be appropriately delivered genetic counseling and management.

In the present study, the observation on family history suggested a familial sibling association in 46,XY females indicating that there could be X-linked mode of inheritance where-in mothers are carriers for AIS (46,XY female condition).

CONCLUSION:

Chromosome studies are indicative for women presenting with amenorrhea and to their family members especially maternal aunts who have not attained menarche and for siblings with PA. The transmission of the AIS condition in this family is strongly suggestive of X-linked inheritance.

Genetic counseling: Genetic counseling is being offered to the confirmed 46,XY females and their family members. A team of multidisciplinary consultants were referred to for appropriate management. Apart from counseling for the cytogenetic abnormality, issues related to emotional, social aspects were discussed with the three siblings and their Mother. Periodic follow up was emphasized, with an advice to continue education, career, marriage and linking them to support groups.

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