

Case Study

ANDROGEN INSENSITIVITY SYNDROME AMONG COUSIN SISTERS - A RARE ENTITY

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ABSTRACT

Androgen insensitivity syndrome (AIS), is a X-linked disorder characterized by resistance to androgen caused by mutation of androgen receptor gene in which XY karyotype individuals exhibit female phenotype.

AIS is characterised by evidence of feminization (under masculinization) of the external genitalia at birth, abnormal secondary sexual development at puberty, and infertility in individuals with 46 XY karyotype.

We are presenting here a familial case of complete androgen insensitivity syndrome in south Indian Population. 46 XY karyotype was found in two subjects who were cousin sisters with female phenotype, who presented with primary amenorrhoea. Comet assay was done, which showed results comparable with normal males. In both girls' inguinal gonads was present which was removed and hormonal therapy with estrogen was given to prevent osteoporosis. Androgen insensitivity syndrome can be inherited as an X linked disorder as evidenced by previous studies.

KEY WORDS: testicular feminization syndrome, Androgen Receptor Deficiency, Primary amenorrhoea, Comet assay, CAIS, Familial CAIS.

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INTRODUCTION

Androgen insensitivity syndrome (AIS), is an intersex condition manifested in chromosomally male individuals with partial or complete resistance of the androgenic hormones [1,2] resulting in feministic physical traits. AIS is characterised by evidence of feminization (under masculinization) of the external genitalia at birth, abnormal secondary sexual development at puberty, and infertility in individuals with 46 XY karyotype. AIS has an incidence of 2-5 in 1,00,000 live births [3].

AIS is classified into 3 types (a) Complete (CAIS) – with typical female external genitalia, (b) Partial (PAIS) – with predominantly female/male or ambiguous external genitalia and (c) Mild (MAIS) – with typical male external genitalia [4]. Complete AIS (CAIS) presents with familial inheritance.

Familial inheritance of Complete AIS is not yet reported from the South-Indian population. Here we report two cases of complete androgen insensitivity syndrome in a family from Puducherry (South Indian population).

CASE DESCRIPTION

The present case report is presented from a descriptive study which included 30 cases of primary amenorrhoea. The study was approved by JIPMER Scientific and Ethics committee. Written and informed consent was obtained from the subjects before enrolling them in the study.

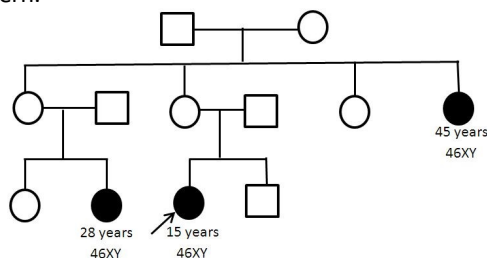
Two cousin sisters from Puducherry came to the cytogenetics division of JIPMER anatomy department with a history of primary amenorrhoea referred from department of Obstetrics and Gynaecology, JIPMER, Puducherry.

History and clinical examination: Case 1 (Index case): Mother of 15-years old female reported that girl was born of consanguineous marriage. She was born at term after an uneventful pregnancy by vaginal delivery in a primary health centre. Her birth weight was 3.2 kg, and birth length was 49 cm.

Inguinal gonads were detected at birth and referred to higher centre for surgery but since mother didn't give consent for surgery it wasn't removed. Further, mother said that the girl had spontaneous thelarche and one of her cousin also has primary amenorrhea. On physical examination her height was 165 cm, weight was 62 kg, she had Tanner stage 4 breast development with well-developed vulva and blind ending 3 cm vagina, palpable gonads in the inguinal region, and absent axillary and pubic hair.

Case 2: A 28-year old female who is the maternal cousin of the index case also had primary amenorrhoea. On physical examination, her height was 168 cm and built was normal. She had Tanner stage 5 breast development, external genitalia resembling that of a female, absence of axillary and pubic hair. Per vaginal examination revealed blind-ending vagina of 2 cm and palpable gonads in the inguinal region.

Fig. 1: Pedigree analysis of subject with Androgen Insensitivity Syndrome, showing X-linked recessive pattern.



Ultrasound examination:

Case 1: Ultrasound examination revealed the absence of left kidney, uterus and ovaries. The right kidney was normal. Inguinal region left side showed gonadal mass. Thereby, congenital uterine aplasia with renal agenesis was diagnosed.

Case 2: Ultrasound examination revealed uterus with 1 cm thin ridge, ovary was not visualized and both the kidneys were normal. Inguinal region gonadal mass was visualized. Thereby, congenital uterine aplasia was diagnosed.

Pedigree analysis: Pedigree analysis of two generation in the family revealed the occurrence of a specific X-linked inheritance pattern. On eliciting history, she had a maternal aunt who also had primary amenorrhoea and died at the age of 45 for reasons unknown.

Hormonal profile: Hormonal profile investigations demonstrated increased testosterone level in both the subjects.

Table 1: Hormonal profile.

Parameters	Case 1	Case 2	Interpretation
FSH (mIU/mL)	2.8	4.2	Normal
LH (mIU/mL)	14.3	15.2	Normal
Testosterone (ng/ dL)	455.6	632.4	Increased for female (Normal for male)
Prolactin (ng/mL)	4.9	6.3	Normal

Chromosomal analysis: Conventional karyotyping of peripheral blood lymphocytes with GTG banding using IKAROS Metasystems was done. 100 metaphase spreads were captured which revealed 46,XY karyotype for both the cases. Barr body examination done from buccal smear was negative in both of them.

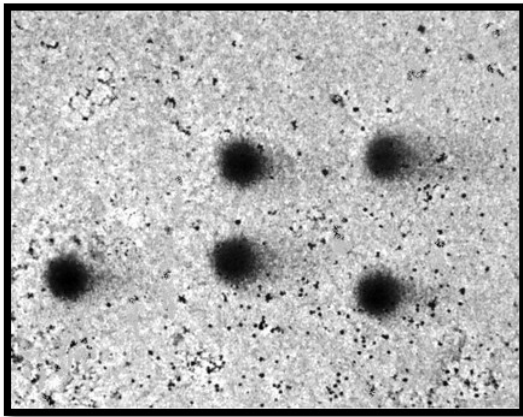
Comet analysis: Comet assay (Single cell gel electrophoresis) of peripheral blood was done. Comet assay variables were analysed using Comet Score Software. Comet variables like comet length, tail length and percentage DNA in head showed values of these cases (1 and 2) were comparable with male.

Table 2: Comet parameters.

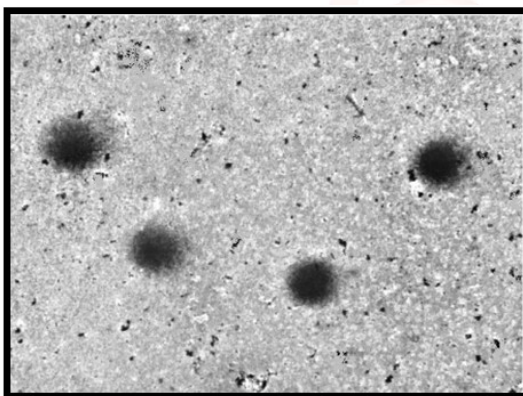
Parameters	Androgen Insensitivity Syndrome	Normal karyotype
Comet Length (μm)	53.68	52.3
Head Diameter (μm)	38.74	24.86
% DNA in Head	87.58	71.45
Tail Length (μm)	14.93	25.46
% DNA in Tail	12.42	3.74

Fig. 2: Comet assay.

2a: Androgen Insensitivity syndrome (46, XY)



2b: Normal Male (46, XY)



DISCUSSION

Androgen insensitivity syndrome is an X-linked disorder, which manifests with male chromosome pattern (46,XY) with apparently normal female external genitalia [4]. AIS is characterized by blind vagina with no uterus or uterine tubes, absent or sparse axillary or pubic hair with testis being located in the abdominal or inguinal region [5-7].

Androgens are important steroid hormones for expression of the male phenotype. They have a distinctive role during male sexual differentiation, development and maintenance of secondary male characteristics and initiation and maintenance of spermatogenesis. The two most essential androgens are testosterone and five alpha-dihydrotestosterone [4]. The actions are mediated by androgen receptor [8]. Both the subjects of this case report presented with increased testosterone level which reinforces the androgen resistance resulting characteristics of these cases. Chromosomal analysis was done capturing 100 metaphase spreads, which revealed 46, XY karyotype in all cell lines for both

the cases. Comet assay variables were resembling normal male as compared with others with primary amenorrhoea [9,10]. Clinical features were similar in both the individuals except for renal agenesis in case 1. This suggests that complete AIS mostly does not present with phenotypic variation within one single family. AIS results due to mutation of the androgenreceptor gene located on the X chromosome at Xq 11-12 in 46,XY individuals. It is accepted that defects in the androgen receptor gene prevent the normal development of internal and external male structures. The end organ resistance to androgens has been designated as AIS [4,7,11,12]. Available evidence has documented the risk of gonadoblastoma is high in undescended testis. 0.8% of individuals with CAIS develop dysgerminoma [3,13]. Histopathological examination of the inguinal mass done in JIPMER revealed features suggestive of testicular tissue in both the cases. Hence, inguinal gonads were removed surgically a month after the karyotyping was reported in JIPMER. Subjects were properly evaluated by a urologist [14], psychologist [15], psychiatrist and Genetic counselling was given [12]. Psychological counselling was given to the subject and the family because it would cause emotional disturbances after knowing karyotype. After removal of the inguinal gonads, subjects were given estrogen replacement to maintain feminization and to avoid osteoporosis and cardiovascular complications [16].

One study had documented the role of genetic predisposition to congenital androgen insensitivity syndrome [17]. In our case, this was proved affecting three individuals within two generations of a single family which could be due to consanguineous marriage or polygenic inheritance.

Females of the family would be carriers for this disorder, and hence they were advised to undergo genetic screening. Androgen receptor gene mutation study by PCR analysis is planned for the subjects and the family members.

CONCLUSION

We report a case of familial inheritance of complete Androgen Insensitivity Syndrome in the South Indian population which could be due to

consanguineous marriage or familial inheritance or environmental influences or the combinations of these.

Conflicts of Interests: None

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