

# Familial Partial Androgen Insensitivity Syndrome in 3 Siblings, Case Report, 2022

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## Abstract

**Background:** Androgen insensitivity syndrome is when a male, genetically XY, because of various abnormalities of the X chromosome, is resistant to the actions of the androgen hormones, which in turn stops the forming of the male genitalia and gives a female phenotype.

**Case Report:** An Eritrean family, currently on their thirties, has three children with all having ambiguous genitalia that are difficult to designate their sex. Almost three of them have similar genital findings with blunt vagina, micro-penis, hypospadias, absent scrotal folds with palpable testes in the inguinal area. CT scan revealed inguinal testes, absent uterus and ovaries. Their karyotyping was 46XY, except the youngest with rudimentary uterus in CT scan and karyotyping 46XX. Their gonadotropin hormone analysis revealed low levels in all pituitary and gonadal hormones. They were referred abroad for further investigation and management.

**Conclusion:** The clinical findings and karyotyping are consistent with androgen insensitivity syndrome. The family occurrence of this syndrome is very rare and its psychosocial impact in the family was very extraordinary. Karyotyping of the family, psychotherapy and intensifying awareness of the health professionals and community to support such cases are highly recommended.

**Key words:** ambiguous genitalia; testicular feminization, androgen insensitivity, eritrea

## Introduction

Androgen insensitivity syndrome in its complete form is a disorder of hormone resistance characterized by a female phenotype in an individual with an XY karyotype and testes producing age-appropriate normal concentrations of androgens. [1] This is resulted from mutations in the X-linked androgen receptor gene, which encodes for the ligand-activated androgen receptor—a transcription factor and member of the nuclear receptor superfamily. [1]

In infancy, complete androgen insensitivity syndrome presents as an inguinal hernia or labial swelling containing a testis in an apparently female infant and the incidence of complete androgen insensitivity syndrome in such patients is 1–2% during infancy. [2] Shortened vagina and the absence of ovaries or fallopian tubes suggest the need for karyotyping and the uterus, cervix, and proximal vagina are absent in complete androgen insensitivity syndrome. [3]

The clinical presentation of partial androgen insensitivity syndrome depends on the degree of responsiveness of the external genitalia to androgens. The typical phenotype is micro-penis; severe hypospadias and a bifid scrotum that might contain gonads. [4] Patients with complete testicular feminization were phenotypically female while those with incomplete testicular feminization had a variable appearance of the external genitalia depending on the degree of androgen insensitivity. [5]

The pattern of gonadotropin and testosterone concentrations is less suggestive of hormone resistance when complete androgen insensitivity syndrome presents in infancy. [6] The levels of gonadotropins were measured and found normal and the pelvic CT scan revealed the lack of uterus and ovaries, hypoplastic vagina, and intra-abdominal prepubertal testes. [7] Since the phenotype of partial androgen insensitivity syndrome generally presents as ambiguous genitalia in neonates, establishment of a diagnosis and

reaching a decision on sex assignment and early management issues that need to be addressed are key. [1]

## Case Report

The family of these children was born and grew up in different villages of one of the subzones of Debub region, Eritrea. When they become on their twenties, they get married and gave birth to three kids at an interval of about 3 years. They didn't have any history of congenital abnormality in their family and they are phenotypically normal. The parents have no any family relationship (consanguinity). Their children were delivered in nearby hospital by spontaneous vaginal delivery and were eventful. They visited Orotta National Referral Maternity Hospital on April 2022.

The oldest child (child A) is now 11 years and was grown up behaved as female. At the age of 6 years, the family noticed male behaviors with gross genital abnormality that made them to bring the child to nearby hospital. They referred the child to higher hospital and were on follow-up and investigations to reach the final diagnosis. On the current physical examination, bilateral testes were palpable on the groin with blunted

genitalia and urethral opening at the base of the ill formed phallus. Scrotum was not formed and it was hard to classify it to labia minora. Ultrasound revealed absent uterus and ovaries with bilateral testes on the groin. Karyotyping revealed 46XY and had low level of gonadotropin hormones.

The second child (child B) is currently 9 years old, who was having similar characteristics on the genitalia and seek medical attention while aged three years. He was confirmed as male with hypospadias and testes in the inguinal area. On subsequent follow-ups, hypospadias repair was attempted three times but failed. The karyotyping showed 46XY with low pituitary and gonadal hormones.

The youngest (child C) is now 5 years old who had also similar genital abnormality and family perceives and raised him as male. This child had also blunt genitalia which can't be categorized to clitoris or phallus. Testes were palpable on the inguinal canal. (Table 1) Ultrasound and CT scan revealed testes in inguinal canal and a rudimentary uterus. Karyotyping was 46XX with similar hormone analysis result to his siblings. (Table 2) Three of them don't show development of secondary sex characteristics and they were sent abroad for further management and constructive surgery.

Child	Age	Karyotype	Testes	Uterus	Penis	Scrotum	Urethra
Child A	11 years	46XY	Inguinal	Absent	Micro-penis	Absent	Hypospadias
Child B	9 years	46XY	Inguinal	Absent	Micro-penis	bifid	Hypospadias
Child C	4 years	46XX	Inguinal	Present	Clitorimegally	Absent	Hypospadias

**Table 1:** Their general physical characteristics

Child	Estradiol (pg/ml)	FSH (mIU/ml)	LH (mIU/ml)	Progesterone (ng/ml)	Prolactin (ng/ml)	Testosterone (ng/dl)
Child A	<5	1.71	0.51	0.07	4.77	<2.50
Child B	<5	1.37	0.55	<0.05	4.45	<2.50
Child C	<5	1.78	0.63	<0.05	7.19	<2.50

**Table 2:** Their hormone analyses results

## Discussion

Three of them were delivered in hospital and their genital abnormality was not immediately identified. As their phenotype was not clear, they were reconceived and grew up as male. This was similar to other study that most infants with partial androgen insensitivity syndrome are raised as male. [1] This is mainly due to that culturally the communities are not regularly practiced to identify the details of the genitalia being male or female if they have unclear external genitalia until the child grew up. Due to their genetic makeup, they may show some male phenotype that makes the family to raise them as male.

Even though the eldest is 11 years old, none of them had done orchidectomy or orchiectomy; and hypospadias repair was attempted only in one child. Studies reported that surgery to repair hypospadias and orchidectomy is done during the second to third year of life. [1] This delayed surgical intervention is mainly due to the decreased awareness of the community on such abnormality and this may predispose them to further risks for malignancy and infertility.

Two of them were karyotypically 46XY and all had testes in the inguinal area with absent uterus. This was similar to other study that all patients had 46XY karyotype. [5] The CT scan findings were also consistent with the available literature that revealed the lack of uterus and ovaries, hypoplastic vagina, and intra-abdominal prepubertal testes. [7] This advocate's health professional's alertness and high index of suspicion on the disease process. Three of them had similar phenotypic genital abnormality with blunt genitalia, hypospadias, micro-penis and testes in the inguinal area. Other studies revealed similar finding. [4] This revealed that, two of them were consistent with partial androgen insensitivity syndrome. But, since the third

had different karyotype, further investigation may be necessary to reach specific diagnosis.

The family had no any reported risk as family history, phenotypic appearance or consanguinity marriage. Literatures reported that other modes of presentation include a known family history of X-linked complete androgen insensitivity syndrome and occasionally, the discovery of a pelvic mass arising from a gonadal tumour. [8] This indicated that genetic screening and karyotyping of the family is crucial for to obtain the association and for their further pregnancies.

The family was very concerned about the recurrence in their kids and further risks for their pregnancies. Any surgical intervention was not yet done for the future fertility and sexual ability of the children. Other studies also showed that management should address functional, sexual, and psychological issues such as disclosure, gonadectomy and subsequent hormone replacement, creation of a functional vagina, and provision of genetic advice. [1]

Three of them had low level of testosterone and other reproductive hormones. This was similar to study that low testosterone concentrations in infants with complete androgen insensitivity syndrome are not fully understood. [9] And, the pattern of gonadotropin is less suggestive of hormone resistance in infancy. [6] But, this is difficult to associate this result to their problem, because this low level of gonadotropin could be normal for their age.

The youngest child was having testes in the inguinal area and rudimentary uterus on CT scan, with karyotype of 46XX. This was difficult to classify to androgen insensitivity syndrome and could be a hermaphrodite. Further genetic screening and karyotyping is necessary to reach diagnosis.

## Conclusion

The clinical presentation, imaging studies and karyotyping were consistent with partial androgen insensitivity syndrome, but the youngest revealed characteristics of hermaphrodite. The familial occurrence is very rare and predicts a carrier state of this syndrome in the mother. The psychosocial impact of the problem in the family was very high and their future management was very difficult. Karyotyping of the family, psychotherapy and intensifying awareness of the community to support such cases are highly recommended.

### Declarations

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### Competing of interest

Authors didn't have any conflict of interest to disclose

### Ethical approval and consent to participate

Informed written consent was attained from the family to participate in the case report

### Author's contribution

All authors have contributed on data interpretation and case report writing

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