Complete Androgen Insensitivity Syndrome in an Adult - A Rare Entity

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ABSTRACT

Introduction: Androgen insensitivity syndrome is a rare disorder affecting androgen receptor gene in individuals with XY karyotype. It is an X linked recessive disorder. It is characterized by resistance of male human cells to respond to androgens resulting in female phenotype due to androgen receptor gene mutation. They have normal female external genitalia, normal breasts but no mullerian duct derivatives with testis in abdominal or inguinal location. They present with bilateral inguinal hernia in females, primary amenorrhea or infertility. Malignant transformation of testis is a risk factor in these individuals. Diagnosis is done by clinical features, imaging, laboratory findings and karyotyping. Management is multidisciplinary approach which includes disclosure of condition to the patient at appropriate age, vaginoplasty for sexual activity, gonadectomy and hormone replacement therapy.

Case Report: We report a case of a female of age 20yrs with complaints of infertility. On investigating there are no mullerian duct derivatives and no ovaries or testis. Final diagnosis was done with karyotyping which showed XY karyotype.

Conclusion: Ultrasound is initial method of investigation for evaluation of mullerian structures. However MRI is gold standard investigation. Medical and surgical care forms part of management.

Keywords: Androgen insensitivity syndrome, XY karyotype, bilateral inguinal hernia.

INTRODUCTION

Disorders of sex development (DSD) refer to a group of congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. Androgen Insensitivity syndrome (AIS), is a DSD affecting the androgen receptor (AR).[1]

From 8 weeks of gestation in male embryo, AR gene is expressed. Testis starts secreting testosterone from 9 weeks. By the action of testosterone, Wolffian duct differentiates into epididymis, vasdeferens and seminal vesicles. 5alpha-reductase type2 acts on testosterone to produce a powerful androgen, dihydrotestosterone. This powerful androgen acts on AR and stimulates differentiation of primordial external genitalia. Androgen receptor is coded by AR gene present on X chromosome and so the inheritance pattern is X linked recessive. Several mutations occur in androgen receptor gene, leading to impairment of receptor function.[2,3]

The phenotype of AIS is variable depending on the functionality of the AR. Three different phenotypic presentations are:
Complete androgen insensitivity syndrome
Partial androgen insensitivity syndrome and
Mild androgen insensitivity syndrome.

Complete androgen insensitivity syndrome

Phenotypic presentation is completely female from birth in CAIS as androgen receptor is completely unresponsive to androgens. They present with primary amenorrhea or infertility. They do not have uterus, cervix, fallopian tubes and ovaries. Breast development is normal with abnormal composition. Pubic and axillary hair is scanty or absent. Undescended testicles may be present or they may be atrophied. Testosterone is in the normal range for males.[1]

Partial androgen insensitivity syndrome

When the patients have some function of the AR, their phenotypic presentation varies from mildly virilized female appearance to undervirilized male appearance. It is suspected when ambiguous genitalia is present at birth. Mullerian structures are absent but some structures of wolffian ducts are present depending on the amount of functionality of AR.[1]

Mild androgen insensitivity syndrome

In MAIS ("undervirilized male syndrome") XY karyotype, Mullerian structures are absent. Spermatogenesis may be impaired. Gynecomastia is seen in puberty.[1]

CASE REPORT

Patient: A Patient aged 20 years with female habitus and voice having normal intellectual function was referred to the radiology department for evaluation of primary amenorrhea and infertility.

Clinical features: Patient came with chief complaints of primary amenorrhea and infertility. Patient's sister was found to have similar complaints. On general physical examination, patient had normal adipose tissue distribution, absent hair over the body and axilla with scanty pubic hair, breast showed tanner stage 3. On gynecological examination, patient had normal female exertnal genitalia, no clitoromegaly and per vaginal examination revealed a long and blind ending vagina.

Imaging: On ultrasound, absent uterus with a normal vagina is seen.
Both the ovaries are not visualized as shown in Tranabdominal image in fig (1).
There is no inguinal hernia and the testis could not be visualized.

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Both the kidneys were normal.
MRI abdomen with pelvis was done, testis could not be visualised. Rest of the findings were consistent with ultrasound i.e., absent uterus and ovaries with intact vagina. Fig (2) is sagittal T2 Weighted Fat sat image showing absent uterus. Fig (3) and (4) are Coronal T1 and T2 – weighted images showing absence of uterus and ovaries respectively.

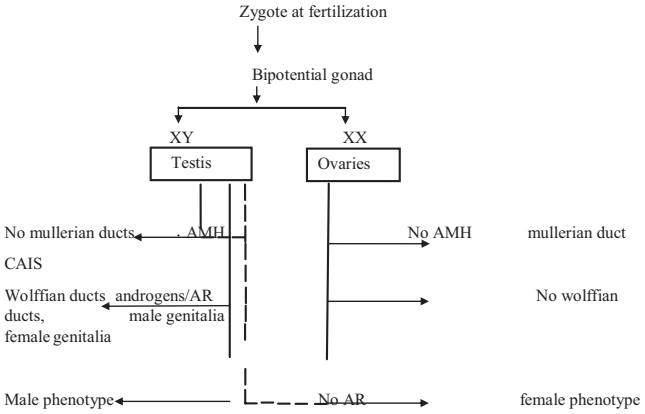
Karyotyping: Blood sample is sent for karyotyping which revealed 46 XY.

DISCUSSION

Complete androgen insensitivity syndrome is an X-linked recessive androgen receptor disorder. It is characterized by a female phenotype with an XY karyotype. The prevalence of this disorder is between 1 and 5 in 100,000 genetic males. They have normal female external genitalia and because these individuals are with XY karyotype, they do not have Müllerian duct derivatives.Testis is present inabdomen,labial or inguinal region.[4]
There are three phenotypes ofAIS which represent a spectrum of defects in androgen action:[5]

- Complete androgen insensitivity syndrome (CAIS), with typical female external genitalia
- Partial androgen insensitivity syndrome (PAIS) with wide range of virilization.
- Mild androgen insensitivity syndrome (MAIS) with typical male external genitalia.

Pathogenesis: X-linked androgen receptor gene, encodes for the ligand-activated androgen receptor--a transcription factor and member of the nuclear receptor superfamily.[6]
AR gene is responsible for normal development of both internal and external genitalia in 46XY individuals. About 400 AR gene mutations are identified which are responsible for AIS.[7] Pathogenesis is shown below[6]:



Clinical manifestations

CAIS have female phenotype with no mullerian duct derivatives and ovaries. They do not even have Wolffian duct derivatives.
These patients may present

1. When there is discrepancy between antenatal and postnatal phenotype or prenatally because of difference in karyotype result and anatomical gender at birth.
2. Monolateral or bilateral inguinal hernia or masses before puberty. On examination these masses are actually testis.

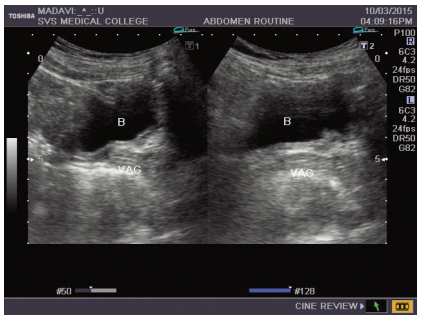


Figure-1: Transabdominal image shows absent uterus with normal vagina. Ovaries are not visualised

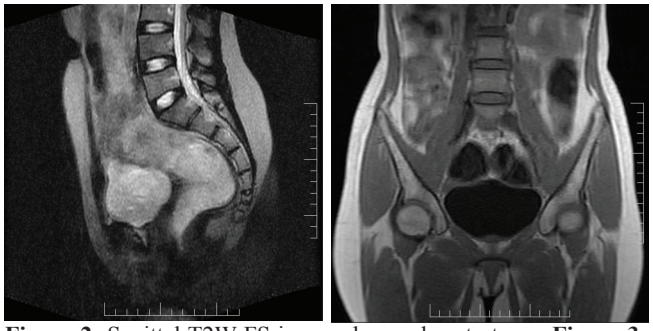


Figure-2: Sagittal T2W FS image shows absent uterus; **Figure-3:** Coronal T1W image showing absence of uterus and ovaries respectively

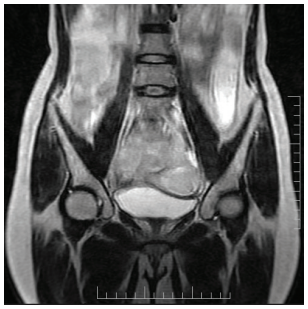


Figure-4: Coronal T2W image showing absence of uterus and ovaries respectively

3. At puberty they present with amenorrhea. They have normal breasts and external genitalia with scanty or absent pubic and axillary hair.On imaging,there is blind ending vagina,no uterus and ovaries.

Testis is generally present in inguinal region,labia majora and can also be intra-abdominal. They are usually fibrosed, atrophied or very small in size. These testis have a risk of malignancy especially germ cell tumors or gonadoblastomas.[2,8]
There are five grades of PAIS depending on the severity of undervirilization

1. Normal female genital phenotype, with androgen-dependent pubic and/or axillary hair development at puberty.
2. Female phenotype with mild clitoromegaly or small degree of posterior labial fusion.
3. There are undifferentiated phallic structures intermediate between clitoris and penis, and the urogenital sinus presents perineal orifice and labioscrotal folds.
4. Predominantly male phenotype with perineal hypospa-

dias, small penis, cryptorchidism or bifid scrotum.
5. Presents with isolated hypospadias and/or micropenis. The clinical features of the last described PAIS forms are very similar to the MAIS.

In MAIS,at puberty,there is alteration in the spermatogenesis and fertility, more commonly they present with impotence and gynecomastia.[3]

Endocrine features: Endocrine features of CAIS and PAIS are the same.

1. During early infancy, serum Luteinizing Hormone (LH) and Testosterone (T) are normal or overproduced.
2. Until the puberty, LH and T levels are in the normal range.
3. At the puberty, because of androgen insensitivity,there is no feedback on hypothalamus and hypophysis and this results in elevated T and LH levels.Normal development of breast in CAIS is due to increased estrogen levels formed by action of aromatase on increased testosterone levels. Anti-Müllerian Hormone (AMH) concentration is normal.
4. The bone mineral density is less in women affected by CAIS and are at risk of osteoporosis.[2,3]

Diagnosis

1. No female internal genitalia and gonads on imaging
2. 46XY karyotype
3. Elevated testosterone and LH hormone levels
4. Clinical findings like female phenotype,normal breast and absent axillary, pubichair.

All these features confirm the diagnosis of CAIS. The specific mutation responsible for androgen receptor defect can also be identified.[2]

Differential diagnosis: The differential diagnosis of CAIS include 17 β-hydroxysteroid dehydrogenase type3 deficiency (17 β HD-3), Swyer syndrome and MRKH syndrome.

In 17 β-hydroxysteroid dehydrogenase type3 deficiency,the external genitalia is of femalephenotype.The presence of wolffian duct derivatives, male voice, pubic and axillary hair growth and sometimes clitoromegaly are important diagnostic clues for differentiating 17 β HD-3 deficiency from CAIS. Because of ineffective level of androgen there is no prostate development in these patients.

In Swyer syndrome, (XY gonadal dysgenesis),there is uterus with normal axillary and pubic hair but lacksbreast development.

In MRKH syndrome,there is no uterus but breast development is normal. It can be differentiated from CAIS by presence of ovaries and 46 XX.[9]

Management: Management of androgen insensitivity syndrome is a multidisciplinary approach.[6]

Full disclosure about the condition to the child should be done before adulthood. Extensive counselling and psychological support is also important. Dilator therapy or vaginoplasty is done before sexual activity is contemplated.[2]

Due to the risk of malignant transformation of testis, gonadectomy should be done. This is done after puberty as risk of developing malignancy is rare before puberty. In patients who develop virilisation, gonadectomy should be done immediately to preserve the female phenotype. Bilateral laparoscopic gonadectomy is the preferred procedure for removal of intra-abdominal testes.[10]

Because gonadectomy is done, hormonal replacement therapy is required to induce puberty and/or maintain secondary sexual characteristics, to maintain bone density. For this purpose, generallyestrogens are used.[11]

CONCLUSION

CAIS is a very rare disorder. Based on Clinical features, imaging, laboratory findings and karyotyping diagnosis is done. Imaging is necessary for planning gonadectomy and-for watchful waiting in those who refuse surgery. Medical care and surgical care forms the mainstay of treatment.Psychosocial support and Hormone replacement therapy are two aspects of medical care. Vaginoplasty and gonadectomy are two aspects under surgical care.

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