

Male Pseudohermaphroditism-XY-Female (Androgen Insensitivity Syndrome)

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We report 2 cases of complete androgen insensitivity syndrome. Both belonged to the same family and presented with primary amenorrhoea in Gynae unit-I Services Hospital. They were investigated, consulted about future gender assignment and managed in collaboration with Urology Department Services Hospital.

Key Words: Pseudohermaphroditism, Primary amenorrhoea, androgen insensitivity syndrome (AIS), intersex, phenotype, androgen receptor (AR). USS (Ultra Sound Scan), SRY gene (Sex determining region of Y chromosome).

Introduction

Androgen insensitivity syndrome (previously known as XY female or testicular feminization syndrome or Morris syndrome¹) is an intersexual condition having genetic sex of male karyotype (46XY) with cryptorchid testes and female phenotype. The end organs are insensitive to androgens due to abnormality of androgen receptor. (AR)² There is loss of function mutation in AR gene located on long arm of X chromosome Xq 11-12³ AIS is said to be complete AIS (CAIS) when there is no response to androgens. The incidence of CAIS is about 1 in 40,000 to 60,000 births⁴. Partial AIS (PAIS) occurs when androgen receptors can partially respond to androgen stimulation.

There are two mechanisms for failure of androgen expression in such patients. The most common cause is AR mutation now referred as Type 1 AIS and is genetically transmitted as an X-linked recessive disorder. Another additional cause referred as Type 2 AIS, is less common and is the result of 5 alpha reductase deficiencies which is necessary for the production of dihydro testosterone, requisite for normal masculinisation of external genitalia in utero. It is autosomal recessive disorder and there is evidence of similar effected members in the family⁵. Both defects can result in complete absence of androgen expression periphally and female phenotype of CAIS. In fetus with CAIS testes form normally due to action of SRY gene. These testes secrete anti Mullerian hormone (AMH) leading to regression of Mullerian ducts, hence CAIS women do not have uterus. Testosterone is produced at appropriate time however due to complete unresponsiveness of AR; the external genitalia do not virilise and instead undergo female development.

Clinical features of CAIS are primary amenorrhoea, female external genitalia, reduced or absent axillary hairs and scant pubic hairs due to absence of androgen effects, intraabdominal or

inguinal testes, inguinal hernia extant or repaired, vaginal hypoplasia (varying from dimple to a blind pouch), hypoplastic labia minora, absent uterus and ovaries and 46 XY karyotype.

Karyotyping is definitive test for confirmation of genetic sex and to rule out mosaicism. It also differentiates undermasculinized male from a masculinized female (CAH), and should be performed in all patients. USS of pelvis confirms absence of uterus and ovaries.

Management includes making correct diagnosis by history, examination and investigations, communicating the diagnosis to both patient and parents along with psychological support, counseling for future gender assignment and surgical treatment in the form of genital and gonadal surgery according to gender selected.

If female gender selected---treatment is gonadectomy followed by long term hormone replacement therapy (HRT) and later on vaginoplasty for vaginal hypoplasia to establish coitally functional vagina, along with psychological support and follow up.

If male gender selected-multistep surgery in the form of:

- (i) Releasing chordee followed by hormonal treatment.
- (ii) Vaginal closure.
- (iii) Construction of urethral tube (Urethroplasty).
- (iv) Penile surgery (Phallo plasty).

Case 1

16 years old unmarried female presented on 4-6-04 with complaints of failure to menstruate and no development of secondary sexual characteristics i.e. no breast development, absent axillary hairs and scant pubic hairs of male pattern, blind short vagina, clitoromegally and well developed labia majora. Right testis in right labium majus and left testis in left

inguinal canal. P/R examination revealed no uterus and USS of the pelvis confirmed absent uterus and ovaries. USS of external genitalia with high frequency probe revealed presence of testis in right labium majus measuring 4 x 2.3 cm while left testis was present in the left labium majus in its upper part measuring 3 x 2.1 cm, Micropenis with chorde and undescended testes. Perineal groove with rudimentary vagina (3-4cm) Chromosomal analyses revealed 46 XY karyotype.

Case 2

18 years old unmarried female elder sister of the first case mentioned above presented a week later with similar complaints and clinical features. On P/R examination revealed no uterus and USS confirmed no uterus and ovaries.

Both patients and their parents were explained regarding diagnosis and future prospects of the condition to select future gender. They opted for male gender and hence, they were referred to urology department for further management. There EUA and cystoscopy was carried out prior to first step of genital surgical treatment that comprised correction of chordee. Following that local massage of testosterone cream was prescribed for 3 months. In the second step vagina was closed. In the third stage urethroplasty will be carried out and following that testicular biopsy to assess the endocrine function of the testes.

Discussion

There are multitude of causes that can lead to XY female, and based on underlying anomaly causes are given in the table below.

1. **End organ insensitivity to androgens:**
 - (i) CAIS.
 - (ii) PAIS.
2. **Enzymatic errors in androgen production:**
 - (i) 5, alpha reductase deficiency.
 - (ii) 17, beta hydroxy steroid dehydrogenase deficiency.
 - (iii) 3, beta hydroxy steroid dehydrogenase deficiency.
 - (iv) 17, alpha hydroxylase deficiency.
3. **Structural abnormalities in the testes:**
 - (i) Complete XY gonadal dysgenesis.
 - (ii) Mixed gonadal dysgenesis (partial 46 XY gonadal dysgenesis).
 - (iii) True hermaphrodite.
 - (iv) Drash-syndrome.
4. **Leydig cell dysfunction:**
 - (i) Leydig cell hypoplasia.
5. **Miscellaneous conditions:**
 - (i) Ambiguous genitalia of unknown

aetiology.

- (ii) Cloacal and bladder extrophy.
- (iii) Micropenis.
- (iv) Penile agenesis.
- (v) Traumatic loss of the penis.

Intersex conditions can present in wide variety of ways. Therefore, thorough review and investigations by experienced multi disciplinary teams is essential for optimal diagnosis and management.

In the past standard management for patients of CAIS whose female gender identity is fully established by rearing, orientation and appearance, was to offer female gender and gonadectomy because of risk of malignancy due to intra abdominal position of gonads. This was followed by ERT to avoid long term complications of osteoporosis and coronary artery disease, and treatment of vaginal hypoplasia for coital function. Vaginal enlargement is achieved by vaginal surgery or progressive manual dilatation with high degree of motivation for success and appropriate psychological input from trained professional having clinical experience with intersex conditions.

Recently, management of intersex conditions has undergone renaissance as society is becoming aware of their existence and willing to discuss these issues. As these patients and their parents mentioned above, after discussion opted to be future male, hence, they were referred to urologist for further management. Gonadectomy was not offered in these patients, as the risk of malignancy is poorly defined (possibly 5 to 10%⁶ in child hood rising to 30% by the age of 50years⁷) and thought to be due to intra abdominal position of testes⁶. In both these patient's testes were not intra abdominal and were accessible for palpation and early detection of any abnormal change. These patients and parents selected the male gender because of better chances of long term adjustment in society as male for example, in getting jobs and adoption of different professions.

Conclusion

Incidence of intersex condition is 1:2000 births and multitude of aetiologies can lead to XY female. These intersex conditions are complex with many management areas remaining highly controversial. Sensitive, pacing information be given to allow young women and their families to make informed decision about treatment and a realistic adaptation to life with AIS.⁸ Some of these conditions have other associated anomalies or particular risk of malignancy. Hence, thorough review and investigations by experience multi disciplinary teams is essential for optimal diagnosis and treatment and the need for referral to experienced center is highly recommended. AIS leads to sexual problems. Treatment for vaginal hypoplasia need to be evaluated with outcome studies of long term sexual function quality of life and satisfaction.

The Clinical services regarding management of intersex condition need to be multi disciplinary and aim to optimize the patient physical and psychological health⁹.

Clinicians involved in providing medical care of intersex patients need to remain open minded to new management options and listen voices of those most

closely involved i.e. those with intersex conditions.

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