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**Review Article**

# Androgen insensitivity syndrome, a case report and literature review

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## ABSTRACT

A case of androgen insensitivity syndrome who presented with left labial mass and inguinal hernia was managed by surgery and counselling. The aim of this report is to present a rare case of androgen insensitivity syndrome, its cause, diagnosis and treatment along with review of literature and its management. Androgen insensitivity syndrome is a X linked disorder of male sexual differentiation caused by mutation affecting the androgen receptor gene Xq 11-12 resulting in decreased peripheral responsiveness to circulating androgens, with variable phenotypic expression. Over 300 mutations have been identical worldwide. A 8 year old girl presented to surgical outpatient department with pain in the left labial mass. She was investigated and operated. She was confirmed of having androgen insensitivity syndrome after testing for abdominal ultrasound, estimation of antimullerian hormone (AMH) levels, karyotyping and histopathological examination of labial mass. A literature search and update was made on the causes, clinical issues and management of androgen insensitivity syndrome (AIS).

**Keywords:** AIS, AMH, AR, CAIS, PAIS

## INTRODUCTION

Sex differentiation is defined as the phenotypic development of structures consequent upon the action of hormones produced following gonadal determination. Sex differentiation is gonadal development only in males because in XY females, phenotypic development is female, whether an ovary develops or not. Sex determination is defined as the commitment of the indifferent gonad to a testis or ovary, a development that is genetically programmed in a critically timed and gene dosage- dependent manner.

Mammalian sex determination is a hormone development process in the male following the development of a testis from the indifferent gonad through a cascade of genetic events. The testis induces male sex differentiation (including testis descent) through a time dependent production of optimal concentration of AIM, insulin like factors(s) and androgens. The post gonadal determination phase of sex determination is almost exclusively hormone dependent and is an active sexually unimorphic process for the male.

AMH and testosterone are the two key hormones produced by the testis in optimal concentration during critical time in early gestation to ensure male development. Also a key component in the process is the developmental expression of the cognate receptor of these hormones in target tissues. The cellular and molecular actions of androgen in development regulation are key to understanding male sex determination. Central

to this process is the androgen receptor (AR), a nuclear transcription factor that controls androgen dependent gene expression. A single AR is ubiquitously expressed and binds all androgens intracellularly in target cells.

In common with other nuclear receptors, the AR comprises three functional domains involved in transcriptional regulation, DNA and ligand binding. The least conserved, large N-terminal domain contains an activation function (AF-1) region which is autonomously involved in gene transactivation. The AR has a unique N-terminal polymorphic glutamine region as a result of a variable number of CAG repeats.

Variation in CAG repeat length affect AR transcriptional efficiency.[1] The central DNA binding domain is the most conserved region; the C- terminal contains a second activation function region (AF-2) and mediates protein interactions, dimerisation, nuclear localisation signalling as well as ligand bindings. The activation function regions interact with an intermediary group of proteins termed co-regulators to form protein. The interactions of these in a ligand - dependent manner either to increase (co-activation) or decrease (co-repressor) gene transcription.[2,3]

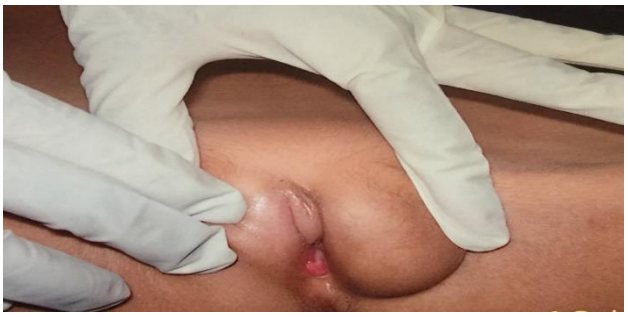

**Figure 1: Phenotypic female genitilia.**

Next to testis determination, the production and action of androgens is the essential requirement for the male sex determination. Gonadotropic control of the foetal testicular steroidogenesis, mediated by human CG and later by LH, operates through the well characterized seven trans membrane G protein-coupled LH/CG receptors.[4] In activating mutations of LH receptors in human results in varying phenotypes in males, including complete sex reversal, ambiguous genitilia or only isolated micropenis.[5] The X linked disorder of the androgen resistance characterized by the AIS has provided useful information on the androgen action and on what may be the phenotypic outcome with a defect in this complex, multistep process.

AIS is caused by the mutation affecting the androgen receptor gene Xq 11-12, resulting in decreased peripheral responsiveness to circulating androgens.[6,7]

In AIS testis function normally producing AMH and testosterone (DHT), which is converted into dihydroxy-testosterone (DHT). However since androgen dependent target tissues are unresponsive to testosterone and DHT, wolfian duct structures do not develop and external genitilia develop along female lines.[8]

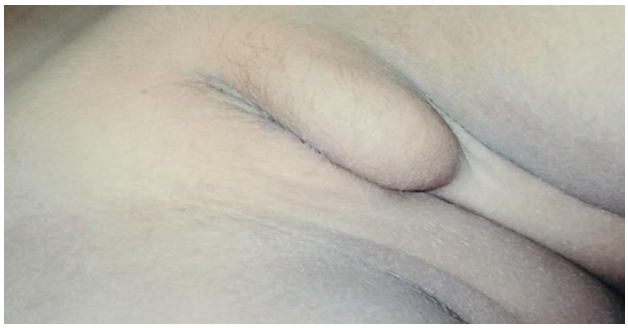

**Figure 2: Labial mass.**

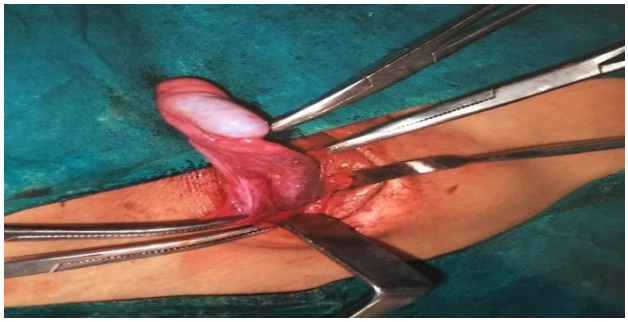

**Figure 3: Testis in the labia majora.**

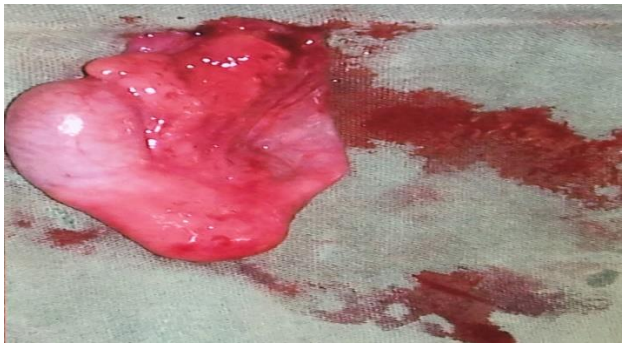

**Figure 4: Postoperative specimen of the testis.**

In the study an 8 year old girl presented with history of swelling in the left labia since birth which was causing pain and increasing in size. The girl had negative past medical and family history. On physical examination, the girl was moderately built and nourished with typical female external genitilia. NO abnormalities were detected in her systemic examination. On examination of the external genitilia, she was detected of having testis in the labia on the left side and in the inguinal canal on the right side, which needed confirmation.

The girl was investigated. Her abdominal ultrasound showed no demonstrable uterus and ovaries, with ectopically located right testis in the medial aspect of

right inguinal canal and left testes in the left labial fold. Karyotyping was done in order to differentiate from other genetic abnormalities. Chromosomal analysis revealed XY karyotype. Antimullerian hormone estimation was done and its level showed 60.13ng/ml. The girl was subjected for surgery. The labial mass was revealed to be testis with well-formed spermatic cord later confirmed by histopathological examination of the tissue. Vagina was examined by nasal speculum which was around 4-5 cm in length. Diagnosis of androgen insensitivity syndrome was made and she was discharged with advice for right gonadectomy after puberty.

## DISCUSSION

The AIS is defined by the complete androgen insensitivity syndrome (CAIS) or partial androgen insensitivity syndrome (PAIS), absence of signs of responsiveness in XY males with normal testis determination and androgen biosynthesis.

AIS are caused by mutation affecting the androgen receptor. Numerous AR gene mutations are reported in AIS and they are detailed on an international database.[9] AIS is the clinical paradigm of hormone resistance that relates to numerous examples of both nuclear receptor and cell membrane receptor related cell signalling system.[10]

The incidence of AIS is approximately 1:20,000 live born XY individuals in CAIS to 1:62,000 in minimal androgen insensitivity syndrome (MAIS). AIS varies from MAIS to CAIS with variable phenotypic expression ranging from phenotypic women of CAIS to men, with minor degree of under-virulisation to infertility of PAIS.[11,12]

Antimullerain hormone is raised in AIS. Estimation of AMH is a powerful tool to assess sertoli cell function in children with intersex states and it helps to distinguish between defects of male sexual differentiation caused by abnormal testicular determination and those resulting from isolated impairment of testosterone secretion and action.[11]

AMH is a glycoprotein produced in feotal sertoli cells and belongs to the TGF-b superfamily which includes inhibin and activin.[12] The primary role for AMH in sex development is to cause a gradient of cranial to caudal regression of mullerian ducts during a short period from 8-19 weeks of gestation in the human.

The role of AMH in male sex differentiation is illustrated by the persistence of mullerian duct derivatives in males with inactivating mutations of either the AMH or AMH type 2 receptors gene, but who otherwise develop normally.[13,14] The ontogeny of expression of AMH was examined by immunohistochemistry in 135 human gonadal tissue specimens of various developmental age ranging from 6 weeks of fetal development to 38 years of postnatal age.[15] The series included specimens form normal pathological conditions affecting gonadal development or with idiopathic infertility manifested as azoo-spermia or severe oligo-spermia.

AMH expression was found only in sertoli and granulosa cells. A 6 week old feotal testis at the indifferent gonadal stage did not express AMH. Later, a majority of testicular specimens, including those from pathological conditions strongly expressed AMH through foetal development and childhood until puberty. In normal testis the switch off of AMH expression was usually associated with the appearance of primary spermatocytes.

In one study AMH was measured from serum in 20 patients with defects of androgen synthesis or action, and in control patients with idiopathic male pseudo-hermophroditism.[16] The serum AMH concentration was elevated in all testosterone insensitive or deficient patients compared with control levels during the first year of life.

From the 1st year of age to the onset of puberty, serum AMH levels in patients with androgen insensitivity reduced to normal levels, but after pubertal development began, AMH levels again rose to extreme high levels in CAIS. The result suggests that AMH is negatively regulated by testosterone not only at puberty, but also during post natal period. Controversy concerning the most appropriate treatment guidelines for intersex children currently exists. This is due to lack of long term information regarding medical, surgical and psychosexual outcome in affected adults. In one study, where 14 women with CAIS were assessed by questionnaire and medical examination of the physical and psychosexual status, all were satisfied with having been raised as females.[17]

Sex assignment at birth of patients with PAIS is classically based upon the virilisation of the external genitilia at birth. Major clinical problems are acceptability and advisability of male ambiguous genitilia. Whether virilisation will increase during puberty or following androgen therapy in neonates with ambiguous genitilia is a crucial question.

The major clinical issues surrounding CAIS includes timing of gonadectomy, hormone replacement, vaginal dilatation and to prevent psychological issues. Several long term follow up studies have shown that in women with CAIS, gonadectomy can be delayed until completion of sexual maturation because puberty will cause the spontaneous conversion of testosterone to estradiol.[18] Various studies have shown that the risk of testicular malignancy is less before puberty, in the rate of 3.6% at 25 years and less to 33% at 50 years of age.

## CONCLUSION

AIS although rare, are extremely distressing to the individual and to the family. It requires expert and

sympathetic handling. Attention is focussed on the main decision of gender of rearing long term management needs to be delineated. However; sensible and candid discussions with parents can only benefit the child. Virtually all CAIS individuals identify themselves as females, because virilisation and fertility are unattainable.

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