DOI: 10.7860/JCDR/2015/11411.5750

Case Report

Genetics Section

Chromosomal Study is Must for Prepubertal Girl with Inguinal Hernia: Opportunity to Diagnose Complete Androgen Insensitivity Syndrome

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ABSTRACT

The sufferers of complete androgen insensitivity syndrome (CAIS) are phenotypic females despite of having functional testes and normal male karyotype. They usually present late with primary amenorrhea but delayed diagnosis increases chance of gonadal malignancy. Alertness for this entity is crucial as with early diagnosis such disorder can be managed more appropriately for a better future. We hereby describe a case of CAIS in an 8-year-old girl presented with bilateral inguinal swellings. Endocrinological analysis, radiological investigations and cytogenetic studies were done. Investigations revealed absence of female internal genitalia. Karyotyping and molecular study confirmed the presence of Y chromosome. Parents were counseled regarding timely gonadectomy, fertility and other long term social issues.

Keywords: Gonadectomy, Karyotyping, Male pseudohermaphroditism

CASE REPORT

An 8-year-old phenotypic female child presented to the pediatrics OPD of Murshidabad Medical College with bilateral inguino-labial swellings for last six months. Upon recording the family history, especially of the maternal side, it was found to be an isolated case.

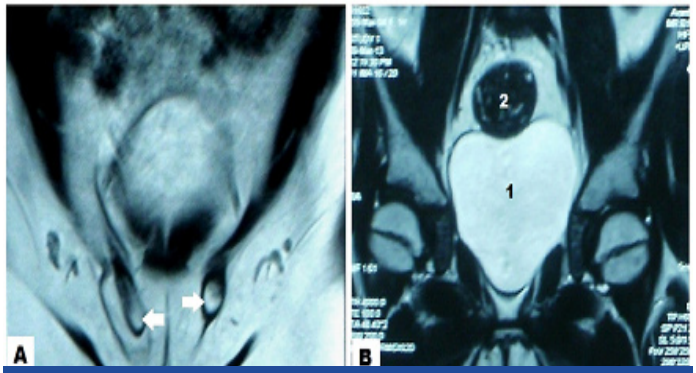
On examination her height was 122 cm and weight 28 kg. Local examination revealed firm non-tender ovoid swellings (5×1 cm) over both the groin above and medial to the pubic tubercle. These were mobile along the inguinal ligaments and could be pushed down into labia majora. The lumps became prominent on coughing or straining and reduced on lying down. The clinical impression was of bilateral indirect inguinal hernia. There were no signs of breast development (Tanner stage 1) and external genitalia were normal. [Table/Fig-1] shows endocrinological analysis.

Ultrasound examination failed to detect uterus or ovaries but revealed bilateral inguinal well-defined homogeneous structures of testis like echotexture. Magnetic Resonance Imaging (MRI) of the pelvic region was performed to obtain the obvious status of the uterus and ovaries [Table/Fig-2-5]. A 6.2 x 1.4 x 1.0 cm swelling was noted in the right inguinal canal extending up to the superficial inguinal pouch and labia. Omental fat was noted within the right inguinal canal just above the swelling. However, there was no herniation of bowel loops or urinary bladder into the canal. A swelling of 6.0 x 1.1 x 0.7 cm was noted in the left inguinal canal without accompanying omentum or bowel loop. Both the inguinal swellings appeared to be testes like structures (hyperintense in T2-weighted MRI). The uterus, cervix and ovaries were not visualised. The vaginal canal was short and blind. Thus the presence of bilateral undescended testes with the absence of ovaries and uterus in a phenotypic female strongly suggested the diagnosis of CAIS, though the final opinion was left for cytogenetic analysis.

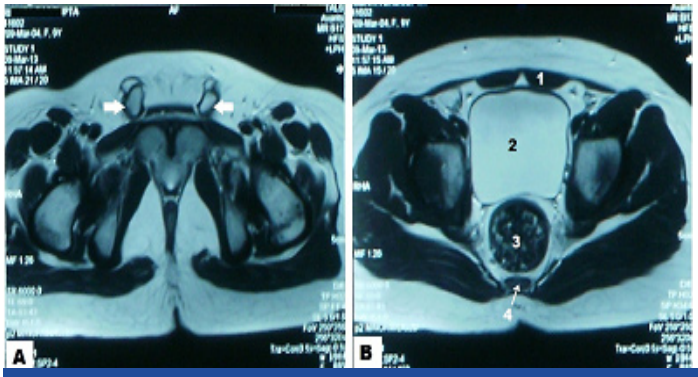
Name of the test	Test value	Reference value *	Method
Serum Follicle Stimulating Hormone (FSH)	7.52 IU/L	≤ 4.1 IU/L	Electrochemiluminescence
Serum Luteinizing Hormone (LH)	3.72 IU/L	0.3-2.8 IU/L	Electrochemiluminescence
Total Serum Testosterone (TTST)	71.74 ng/dL	7-20 ng/dL	Chemiluminescence
Serum Dehydroepiandrosterone Sulfate (DHEA-S)	52.7 mcg/dL	< 120 mcg/dL	Chemiluminescence
Serum Estradiol (E2)	11.80 pg/mL	< 13 pg/mL	Chemiluminescence
Serum Androstenidione (ANST)	30 ng/dL	< 51 ng/dL	Chemiluminescence
Serum 17-hydroxyprogesterone (OHPG)	97 ng/dL	< 110 ng/dL	Radioimmunoassay

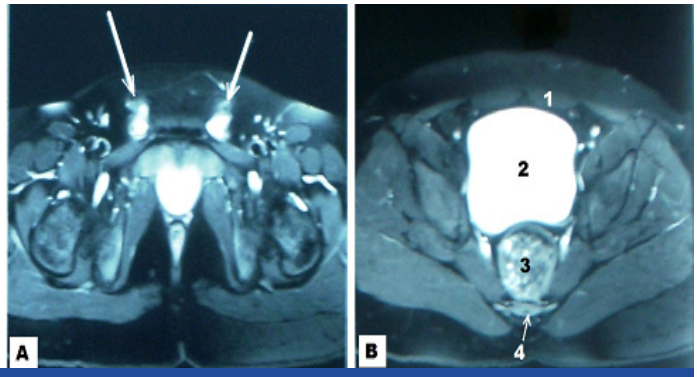
[Table/Fig-1]: Hormonal assay of the subject
* Biological reference values are of prepubertal male

Peripheral blood lymphocyte cultures were set up with phytohemagglutinin stimulation for 72 hours at 37°C. 25 G-banded (trypsin treated) metaphase plates were selected for the preparation of their karyotypes [Table/Fig-6]. Every G-banded metaphase plate contained modal chromosome number 46 with modal karyotype 46, XY [Table/Fig-7]. Presence of Sex determining Region on Y chromosome (SRY) was confirmed by Polymerase Chain Reaction (PCR) [Table/Fig-8].

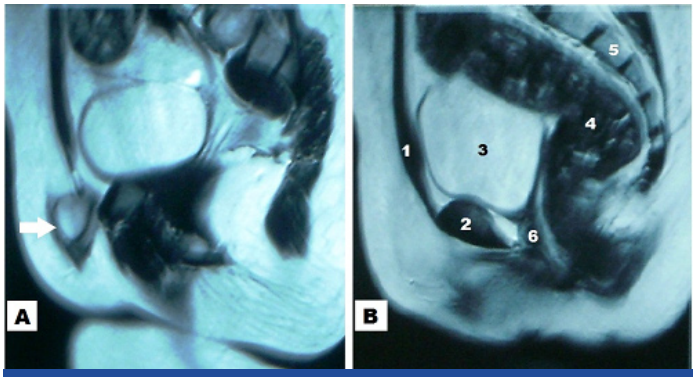


[Table/Fig-2]: Coronal T1-weighted MRI of pelvis showing A. Bilateral inguinal testes (arrow) B. Absence of uterus, uterine tubes, ovaries (1-urinary bladder, 2-rectum)

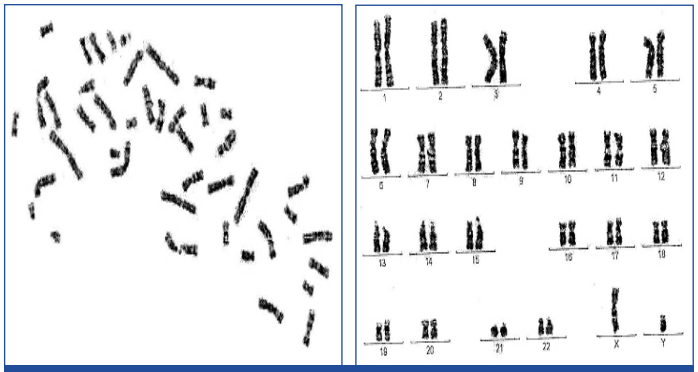




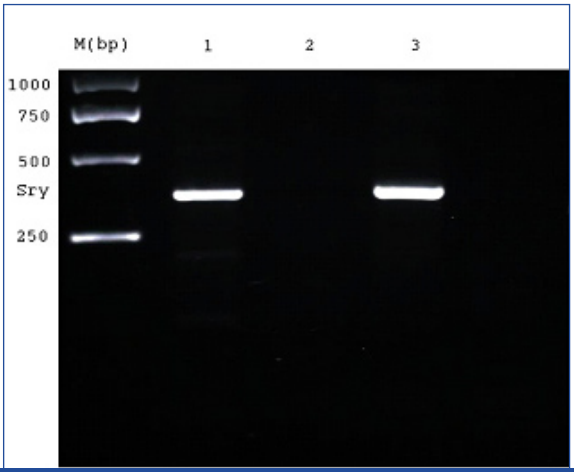
[Table/Fig-3]: Axial T1-weighted MRI of pelvis showing A. Bilateral inguinal testes (arrow) B. Absence of uterus, cervix (1-rectus abdominis muscle, 2- urinary bladder, 3- rectum, 4- sacrum) **[Table/Fig-4]:** Axial T2-weighted MRI of pelvis showing A. Bilateral inguinal testes (arrow) B. Absence of uterus, cervix (1-rectus abdominis muscle, 2- urinary bladder, 3- rectum, 4- sacrum)



[Table/Fig-5]: Sagittal T1-weighted MRI of pelvis showing A. Bilateral inguinal testes (arrow) B. Absence of uterus, cervix (1-rectus abdominis muscle, 2-pubis, 3- urinary bladder, 4- rectum, 5-sacrum, 6- urethra)



[Table/Fig-6]: Metaphase spread of the subject **[Table/Fig-7]:** Karyotype of the subject showing 46, XY genotype



[Table/Fig-8]: Presence of SRY gene by PCR analysis (Lane1- male control, 2- female control, 3- subject)

Proper parental counselling was done and gonadectomy was deferred until puberty is completed.

DISCUSSION

Androgen insensitivity syndrome (AIS) is a type of male pseudohermaphroditism with variable phenotypic expressions ranging from mild (phenotypic male) through partial (ambiguous genitalia) to complete variety (phenotypic female). Commonly AIS results from a point mutation in the androgen intracellular receptor genes located on the X-chromosome (Xq11-q12). Two-thirds of the cases get these mutations from mother (X-linked recessive), while the rest are result of spontaneous mutation in the ovum or zygote [1]. Epidemiological data about AIS are inadequate with estimated incidence varying from 1 in 99,000 to 1 in 13,000 male births [2].

Though individuals with complete androgen insensitivity syndrome (CAIS) are genotypic males (46,XY) and have cryptorchid testes as gonads but they are reared up as girls because of their feminine look, psychological development and subjective gender identity. CAIS sufferers typically present with primary amenorrhea, so they remain undiagnosed until puberty [3-5]. There are also reports where cases have presented after marriage with infertility [6,7] or even with tumours [8,9].

Pathophysiological basis of CAIS is androgen resistance during fetal development and after birth. Due to this genital folds fail to fuse to form scrotum and penis - leading to lack of virilization of external genitalia. Simultaneous testicular secretion of Mullerian Inhibiting Substance regresses the Mullerian structures leading to agenesis of fallopian tubes, uterus, cervix and proximal vagina. Peripheral aromatization of testosterone into estrogen induces female phenotype including breast development [10]. Elevated levels of serum testosterone, FSH and LH result from imperfect feedback mechanism of testosterone at pituitary and hypothalamus due to defective androgen receptor. Normal serum 17α hydroxyprogesterone, DHEA and androstenedione levels rule out testosterone biosynthetic defects [11]. Normal estradiol level signifies sufficient peripheral conversion of testosterone.

Role of testosterone in testicular descent via androgen receptors expressed in the gubernaculum explains undescended testis in CAIS. The undescended testes settle anywhere down the passage of testicular descent - intra-abdominal, inguinal or labial. This makes the sufferers vulnerable to indirect inguinal hernia. The incidence of inguinal hernia in girls is 0.1-0.4% and 1-2% girls with inguinal hernias are diagnosed to have CAIS [12]. So, screening for CAIS should be considered in all prepubertal girls presenting with inguinal swellings. Though a recent UK based study has disclosed 41% of such cases are not investigated for CAIS [13].

The standard management of CAIS is gonadectomy to prevent possible malignant transformation of the testes. Gonadectomy is best delayed until puberty is completed as gonadal tumours in CAIS are rarely encountered before puberty [14]. Additionally late gonadectomy allows pubertal development to proceed smoothly

by endogenous production of estrogen from testosterone. After gonadectomy estrogen replacement therapy is indispensable to maintain femininity [10].

Though CAIS victims are infertile, carrier females have 50% chance of transmitting the mutated gene in each pregnancy. Phenotypic sister of an affected person has 1/3rd chance and female offspring of a normal sister of an affected person has 1/6th chance of XY genotype.

CONCLUSION

Early diagnosis of CAIS is essential for appropriate scheduling of gonadectomy as well as systematic parental counselling regarding several long term issues of hormone replacement therapy and fertility. Moreover pedigree analysis, carrier testing and genetic counselling can be advocated to get a normal child by prenatal diagnosis; hence the transmission of the mutated X chromosome to the coming generations can be prevented.

ACKNOWLEDGEMENT

The authors earnestly do acknowledge the parents of the patient to provide their consent for this study.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 29, 2014**
Date of Peer Review: **Dec 22, 2014**
Date of Acceptance: **Feb 16, 2015**
Date of Publishing: **Apr 01, 2015**