THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (September–October 2016) 66(S1):S358–S362
DOI 10.1007/s13224-015-0736-3

ORIGINAL ARTICLE

Complete Androgen Insensitivity Syndrome in Three Generations of Indian Pedigree

Bibhas Kar[1] · Subbiah Sivamani[1] · Shankar Kundavi[2] · Thankam Rama Varma[2]

Received: 12 June 2015 / Accepted: 30 June 2015 / Published online: 29 July 2015

About the Author

Dr. Bibhas Kar holds a PhD degree in Life Science and has 20 years of research experience in the field of human genetics. He has been honored with many prestigious international and national fellowship and awards which include Stevens Shapiro Memorial Fellowship from UK, International Union of Biochemistry and Molecular Biology Young Scientist Award from the US, and Indian Science Congress Association Young Scientist Award from India for his work in the field of Human Genetics. He has published over 44 original research and review articles in peer-reviewed journals. He has served on the editorial boards of several journals. He is also a life member of various professional bodies. He has earlier worked at Sankara Netralaya as Genetic Scientist, and Apollo Hospitals as Consultant Geneticist & Head.

Abstract

Background Androgen insensitivity syndrome or testicular feminization syndrome is a rare X-linked recessive disorder, which encompasses a wide range of phenotypes that are caused by numerous different mutations in the androgen receptor gene. Complete androgen insensitivity syndrome occurs when the body cannot use androgens at all. People with this form of the condition have the external sex characteristics of females, but do not have a uterus and therefore do not menstruate and are unable to conceive a child (infertile).

Methods In this paper, we report three cases of familial complete androgen insensitivity syndrome who presented with primary amenorrhea.

Results Physical examination, ultrasonography studies, and biochemical, karyotype, and molecular cytogenetic analyses were conducted. Based on the findings, they were diagnosed and confirmed as having complete androgen insensitivity syndrome.

Conclusion A multidisciplinary team is needed from disclosure of the diagnosis, gender assignment, surgical management, hormonal replacement therapy, to counseling and support.

Keywords Androgen insensitivity syndrome · 46,XY karyotype · Mutation · Androgen receptor gene · X-linked recessive disorder

✉ Bibhas Kar
drbibhas_kar@yahoo.co.in

[1] Center for Genetic Studies & Research, The Madras Medical Mission, Chennai, India

[2] Institute of Reproductive Medicine and Woman Health, The Madras Medical Mission, Chennai, India

Introduction

Androgen insensitivity syndrome (OMIM# 300068) is a rare X-linked recessive disorder that occurs in phenotypically normal woman with male karyotype (XY), with an incidence of 1:20,000–64,000 male births [1–3]. Two forms of AIS are described: complete androgen insensitivity syndrome (CAIS) and partial androgen insensitivity syndrome. CAIS, also known as testicular feminization syndrome, is characterized by female external genitalia, adequate breast development, absence or thinning of pubic and axillary hair, and absence of uterus. In childhood, the most common clinical presentation is the presence of bilateral inguinal hernias. Individuals not diagnosed during childhood are detected after puberty because of primary amenorrhea [4]. The hormone profile in these individuals is typical: high Luteinizing hormone (LH) levels, normal to slightly elevated testosterone levels, high estradiol (for men) levels, and normal to elevated Follicle-stimulating hormone (FSH) levels.

This genetic disorder is caused by mutation of the androgen receptor gene (AR gene) (OMIM# 313700) located on the proximal long arm of the X chromosome, specifically locus Xq11–Xq12. This gene has approximately eight exons, which translates into 919 codons, or 2757 nucleotides [5]. Till date, 1110 mutations have been described, including complete and partial gene deletions, point mutations, and small insertions/deletions [http://androgendb.mcgill.ca]. These mutations can cause a variety of functional defects, ranging from a complete loss of receptors on the cell surface because of incomplete protein synthesis to alterations in substrate-binding affinity. Altered substrate-binding affinity causes a signal transmission loss, despite a normal number of cell surface receptors. In this paper, we present three index cases of familial CAIS where the affected individuals are from third generation.

Case Presentation

Case 1

A 27-year-old phenotypic female presented to the outpatient department of the obstetrics and gynecology, Institute of Reproductive Medicine and Women Health and then was referred to Center for Genetic Studies & Research for cytogenetic investigation due to primary amenorrhea. Figure 1 shows the pedigree of the proband (III 10). She was 5′9″ tall and weighed 87 kg. On clinical examination, the proband was found to have normal breast development (Tanner V), normal female external genitalia, with thinning of pubic hair and absence of axillary hair. While collecting history, it was learnt that she had bilateral gonadectomy, i.e., removal of both testicles present in inguinal region which was done at 23 years of age. Histopathological examination suggested severe germ cell hypoplasia with complete spermatocytic arrest and Leydig's cell hyperplasia. There was no evidence of malignancy in the sections studied. Ultrasonography of the proband showed a blind vagina with absence of ovaries. Hormonal profile showed normal serum FSH, slightly elevated serum LH, and testosterone levels in the normal male range (Table 1). Karyotype was 46,XY (Fig. 2a) and metaphase fluorescence in situ hybridization (FISH) analysis confirmed the presence of the SRY gene locus (Fig. 2b).

Case 2

A 24-year-old female (III 14) was referred for karyotyping with a complaint of primary amenorrhea. She was 5′7″ tall and weighed 78 kg. On clinical examination, she was found to have under-developed breast (Tanner II) and clitoromegaly with absence of pubic hair and axillary hair. The patient had bilateral gonadectomy at 3 years of age. Histopathological examination done from the testicular mass suggests bilateral atrophic testis. Ultrasonography of the patient showed a blind vagina with absence of ovaries. Hormonal profile showed normal serum FSH, slightly elevated serum LH, and testosterone levels (Table 1). Cytogenetic analysis showed a 46,XY karyotype.

Case 3

A 21 year-old-female (III 15) was referred for karyotyping with a complaint of primary amenorrhea. She was 5′4″ tall and weighed 79 kg. On clinical examination, she was found to have normal breast development (Tanner V) and normal female external genitalia with thinning of pubic and axillary hair. Ultrasonography of the patient done at the age of 17 years showed no structures morphologically resembling uterus and ovaries in the pelvis indicating blind vagina with bilateral inguinal mobile masses on palpation that resembled testes. Hormonal profile showed elevated serum FSH and LH with normal testosterone levels (Table 1). Cytogenetic analysis showed a 46,XY karyotype

Their family history revealed that three other females, on the maternal side spanning across three generations, presented with similar complaints of primary amenorrhea. The proband's mother (II 5) had a delayed menarche at the age of 19 years and had no axillary hair while one of her cousin sisters (II 8), who had married and had no issues, died at the age of 63 due to cancer (type not known) and had primary amenorrhea. The proband's maternal

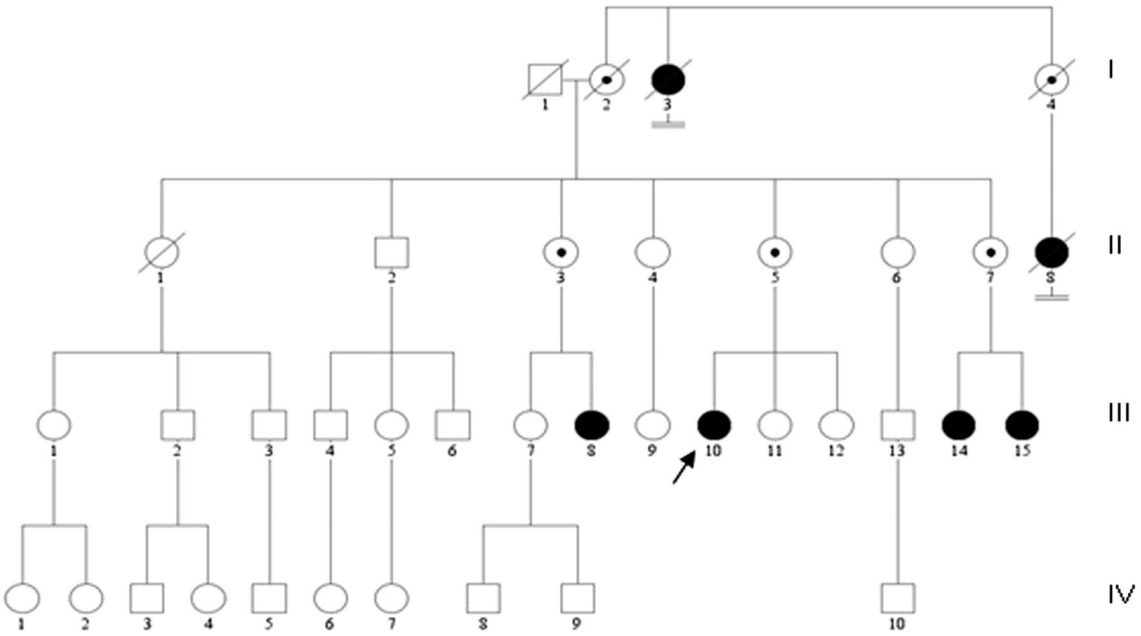

Fig. 1 The pedigree of the family with complete androgen insensitivity syndrome (CAIS). *Black circles* CAIS 46, *XY* individuals, *open circles* normal females, *open squares* normal males, *circle with dot in the center* obligate carrier female, *crossed open squares*, *crossed circle with dot in the center*, *crossed black circles* deceased individuals

Table 1 Hormone levels in the Proband and her two affected cousin sisters

Analyte	Normal range (for men)	Case 1	Case 2	Case 3
Follicle-stimulating hormone (FSH)	1.4–15.4 mIU/ml	8.89	9.13	24.42
Luteinizing hormone (LH)	1.2–7.8 mIU/ml	13.17	12.81	21.08
Testosterone (T)	3.0–10.6 ng/ml	10.90	11.61	4.36

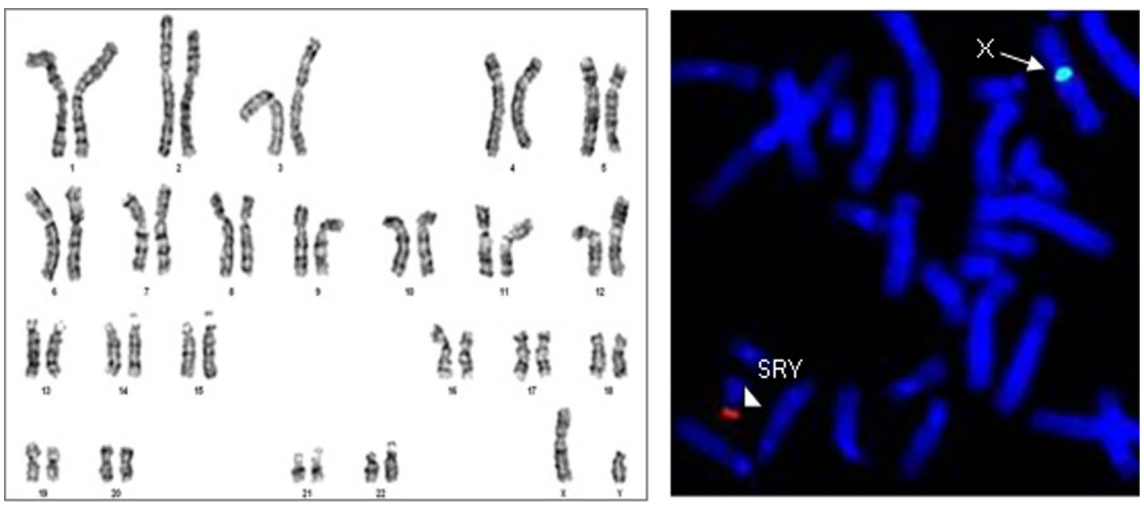

Fig. 2 **a** G-banded karyotype of the proband showing 46,XY. **b** Fluorescence in situ hybridization (FISH) using separate probes for the SRY gene (*red*; *arrowhead*) and the X-centromere (*green*; *arrow*)

grandmother's sister (I 3), who married and had no issues, also died due to cancer (type not known) at the age of 30 and had similar complaints. They had never been investigated and were leading a married life. The proband's cousin sister (III 8) refused to come for investigations who had similar complaints.

Discussion

CAIS can be diagnosed as a result of mismatch between the prenatal sex prediction and the phenotype at birth [6]. 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 tumor [7]. No precise figures are available for the prevalence of CAIS, but estimates range from one in 20,400 to one in 99,100 genetic males on the basis of a proven molecular diagnosis [8].

The typical presentation for complete androgen insensitivity syndrome is either primary amenorrhea in adolescence, or inguinal swellings in an infant. A female adolescent with the disorder has breast development and a pubertal growth spurt at the appropriate age, but no menses. Development of estrogen-dependent secondary sexual characteristics occurs as a result of excess aromatization of androgens. Pubic and axillary hair are usually absent or can be present in sparse amounts [9]. In our index cases, all the criteria were met including the findings of ultrasonography, hormonal assay, karyotyping, and FISH confirming the diagnosis in favor of CAIS. The uterus, cervix, and proximal vagina are absent in CAIS because of the action of antimüllerian hormone produced by Sertoli cells of the testis. The vagina varies from a dimple in the perineum to normal length, but is always blind-ending.

Adult women with CAIS are generally taller than women without the syndrome, but are on average shorter than the male population [10]. Our index cases were also tall, heavy built. The enlarged adult stature in the syndrome is mainly due to the effect of the growth-controlling region on the long arm of the Y chromosome, but genome-wide association studies have identified several loci that affect adult height [11]. Infants with CAIS are on average the same size at birth as male infants, suggesting that factors on the Y chromosome rather than exposure to prenatal androgens explain the sex dimorphism [12].

In our three index cases, hormonal profile showed normal serum FSH, slightly elevated serum LH, and testosterone levels in the normal male range (Table 1).Women with complete androgen insensitivity syndrome who have intact gonads have the endocrine profile of a hormone-resistant state. Serum testosterone concentrations are either within or above the normal range for men and LH concentrations are appropriately increased [13]. The testosterone level of the case 3 is within the normal range. The pattern of gonadotropin and testosterone concentrations is less suggestive of hormone resistance when complete androgen insensitivity syndrome presents in infancy [14, 15]. Serum testosterone concentrations do increase appropriately after stimulation with human chorionic gonadotropin [14].

Ultrasonography report of case 3 shows blind vagina with bilateral inguinal mobile masses on palpation that resembled testes. Gonadectomy with hormone replacement therapy was advised due to the fact that testicular tumors may develop. If gonadectomy is done in childhood, puberty should be induced with estrogen replacement. The principles are similar to induction of puberty in girls with Turner's syndrome [16]. In women who underwent gonadectomy after puberty, several preparations are available, including contraceptive pills such as natural estrogen—estradiol—and synthetic estrogens and hormone replacement therapy.

Long-term psychosexual outcome in complete androgen insensitivity syndrome suggests a trajectory of female-typical development, with the assimilation of a female identity and female-typical behavior, and psychological wellbeing similar to that of other women [17, 18]. In our case series, case 1 had consulted plastic surgeon and clinical psychologist and after confirming that she has normal length of vagina and she could lead a normal sex life after marriage, she recently got married and is leading a happy married life. Less positive outcomes have been reported for sexual functioning and sexual quality of life [19]. Problems with desire, arousal, and dyspareunia were significant in a group of women with XY disorders of sex development, most of which were due to CAIS [20].

XY individuals with CAIS in whom the external genitalia are those of a normal female pose no dilemma of sex assignment. Affected individuals are raised as females, and in such cases the pediatric endocrinologist can handle the problem along with an experienced psychiatrist who will support both the family at diagnosis as well as the patient later in life [21].

The basic etiology of androgen insensitivity syndrome is a loss-of-function mutation in the AR gene. This AR gene is localized to the long arm of the X chromosome, i.e., Xq11–12 [5]. The gene contains eight exons and seven introns, spanning more than 90 kb and codes for a protein with four functional domains (N-terminal regulatory domain, DNA-binding domain, Ligand-binding domain, C-terminal domain). Testosterone and dihydrotestosterone, secreted by the Leydig cells of the testes, bind to this intracellular protein and cause a conformational change that leads to dimerization, nuclear transport, target DNA binding, and eventually transcription. A working androgen receptor is essential to mediate the action of testosterone and dihydrotestosterone, leading to the initiation and maintenance of fetal internal and external masculinization, and pubertal virilization. In CAIS, when the receptor is completely defective, the individual fails to develop both internal and external male genitalia [22].

Most cases (70 %) of AR mutations are inherited and transmitted in an X-linked manner. In this situation, there is a likelihood of 50 % for an XY offspring to be affected and

for an XX offspring to be a healthy carrier of the gene abnormality [23, 24]. In genetic counseling section, we have explained all the risk factors and the younger siblings (III 11, 12) of a proband to evaluate in order to identify as early as possible those who would benefit from institution of treatment and preventive measures. To further delineate the disease process, we have advised necessary evaluation of other family members.

Conclusion

AIS, although very rare, is extremely distressing to the concerned individual. Successful management of androgen insensitivity syndrome 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. Care needs to be individualized, flexible, holistic and multidisciplinary (endocrinology, urology, gynecology, clinical psychology, neonatology and clinical genetics).

Recently, a report was published in Daily Mirror where a woman diagnosed with CAIS gave birth to twin girls through IVF after her womb being encouraged to grow through hormone replacement therapy (HRT) which gives hope to this above group who are otherwise termed as sterile [25].

Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standard of the Institutional research/ethics committee.

References

1. Hensle TW. Genital Anomalies. In: Gillenwater JY, Grayback JT, Howards SS, editors. Adult and pediatric urology. 3rd ed. St. Luis: Mosby Inc; 1996. p. 2529–48.
2. Gurer IE, Demirkiran AE. Sertoli cell tumor in two sibs with testicular feminization syndrome. Turk J Med Sci. 2000;30:385–7.
3. Zorlu F, Cengiz M, Gurkaynak M, et al. Seminoma arising in androgen insensitivity syndrome (testicular feminization syndrome): a case report. Turk J Cancer. 2001;1:168–71.
4. Grumbach MM, Hughes IA, Conte FA. Disorders of sex differentiation. In: Larsen PR, Kronenberg HM, Melmed S, et al., editors. Williams textbook of endocrinology. Philadelphia: WB Saunders Company; 2002. p. 842–1003.
5. Brown CJ, Goss SJ, Lubahn DB, et al. Androgen receptor locus on the human X chromosome: regional localization to Xq11–12 and description of a DNA polymorphism. Am J Hum Genet. 1989;44:264–9.
6. Yalinkaya A, Yayla M, Erdemoglu M. Prenatal diagnosis of a fetus with androgen insensitivity syndrome (AIS). Prenat Diagn. 2007;27:856–7.
7. Stewart CJR, Baker E, Beaton C, et al. Detection of Y-chromosome in gonadal tumours using fluorescence in situ hybridization: diagnostic value in intersex conditions including older patients with clinically unsuspected androgen insensitivity syndrome. Histopathology. 2008;52:175–82.
8. Boehmer AL, Brinkmann O, Brüggenwirth H, et al. Genotype versus phenotype in families with androgen insensitivity syndrome. J Clin Endocrinol Metab. 2001;86:4151–60.
9. Morris J. The syndrome of testicular feminization in male pseudohermaphrodites. Am J Obstet Gynec. 1953;65:1192–211.
10. Danilovic DLS, Correa PHS, Costa EMF, et al. Height and bone mineral density in androgen insensitivity syndrome with mutations in the androgen receptor gene. Osteoporos Int. 2007;18:369–74.
11. Lango AH, Estrada K, Lettre G, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature. 2010;467:832–8.
12. Miles HL, Gidlöf S, Nordenström A, et al. The role of androgens in fetal growth: observational study in two genetic models of disordered androgen signalling. Arch Dis Child Fetal Neonatal Ed. 2010;95:F435–8.
13. Melo KF, Mendonca BB, Billerbeck AE, et al. Clinical, hormonal, behavioral, and genetic characteristics of androgen insensitivity syndrome in a Brazilian cohort: five novel mutations in the androgen receptor gene. J Clin Endocrinol Metab. 2003;88:3241–50.
14. Bouvattier C, Carel JC, Lecointre C, et al. Postnatal changes of T, LH, and FSH in 46, XY infants with mutations in the AR gene. J Clin Endocrinol Metab. 2002;87:29–32.
15. Quigley CA. The postnatal gonadotropin and sex steroid surge-insights from the androgen insensitivity syndrome. J Clin Endocrinol Metab. 2002;87:24–8.
16. Ieuan AH, John DD, Trevor IB, et al. Androgen insensitivity syndrome. Lancet. 2012;380:1419–28.
17. Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. Arch Sex Behav. 2003;32:93–101.
18. Cohen-Kettenis PT. Psychosocial and psychosexual aspects of disorders of sex development. Best Pract Res Clin Endocrinol Metab. 2010;24:325–34.
19. Minto CL, Liao KL, Conway GS, et al. Sexual function in women with complete androgen insensitivity syndrome. Fertil Steril. 2003;80:157–64.
20. Hughes IA. Early management and gender assignment in disorders of sexual differentiation. Endocr Dev. 2007;11:47–57.
21. Dacou-Voutetakis C. A multidisciplinary approach to the management of children with complex genital anomalies. Nat Clin Pract Endocrinol Metab. 2007;3:668–9.
22. Quigley CA, DeBellis A, Marschke KB, et al. Androgen receptor defects: historical, clinical, and molecular perspectives. Endocr Rev. 1995;16(3):271–321.
23. Köhler B, Lumbroso S, Leger J, et al. Androgen insensitivity syndrome: somatic mosaicism of the androgen receptor in seven families and consequences for sex assignment and genetic counseling. J Clin Endocrinol Metab. 2005;90(1):106–11.
24. Boehmer AL, Brinkmann AO, Niermeijer MF, et al. Germ-line and somatic mosaicism in the androgen insensitivity syndrome: implications for genetic counseling. Am J Hum Genet. 1997;60:1003–6.
25. http://www.mirror.co.uk/news/real-life-stories/woman-who-genetically-man-gives-5075269.