

A young infant with complete androgen insensitivity syndrome

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ABSTRACT

Complete androgen insensitivity syndrome (CAIS) is a rare X-linked recessive disorder resulting from maternally inherited or de novo mutations involving the androgen receptor (AR) gene. The AR is a vital steroid hormone receptor that has a critical role in male sexual differentiation and development and preservation of the male phenotype. The diagnosis of CAIS is based on the presence of female external genitalia in an individual with 46, XY karyotype having normally developed but undescended testes and target tissue unresponsiveness to androgen. Our case presented at the age of 2 months with asymmetric labia majora with bilateral labial mass. Ultrasonography revealed absence of female internal genital organs and presence of testes at labial folds. The child was found to have 46, XY karyotype.

Key words: Complete androgen insensitivity syndrome, androgen receptor, karyotype.

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INTRODUCTION

Complete androgen insensitivity syndrome (CAIS) is a classic type of androgen insensitivity syndrome (AIS) with an estimated prevalence of 1 in 20,000 to 64,000 newborn males.¹ Approximately 900 different mutations have been linked with AIS.² AIS is divided into three different disorders depending on the degree of androgen insensitivity: CAIS, partial AIS (PAIS) and mild AIS (MAIS).³ Seventy percent patients with CAIS result from maternally inherited mutations, while the remaining 30% are de novo mutations.⁴ In humans, the vital period for genital virilization is between 8 and 14 weeks of gestation and depends on androgen secretion and functioning androgen receptors.⁵ Any defect in either will compromise the virilization process. Clinical diagnosis of CAIS is established following the typical

presentation of an inguinal hernia or labial swelling in a female infant or primary amenorrhea at puberty in a female with 46, XY karyotype.⁶ It is the third leading cause of primary amenorrhea during puberty.⁷ Considering diagnostic imaging, pelvic ultrasounds or magnetic resonance imaging (MRI) could be helpful in confirming the absence of Mullerian structures, revealing the presence of a blind-ending vagina and identifying testes. Finally, the diagnosis is based on clinical presentation, laboratory tests and imaging in a female with a 46, XY karyotype and confirmed throughout AR gene analysis.⁸

We report a 2-month-old female child who presented with bilateral labial mass. She was diagnosed as a case of CAIS after doing hormone assay, imaging study and karyotyping. To our knowledge, this is the first reported youngest case with CAIS from Bangladesh.

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CASE REPORT

A two-month-old child was referred for evaluation of asymmetry of labia majora with palpable mass. She was first born child of 1st degree consanguineous Bangladeshi healthy parents. She was delivered pre-term by Caesarean section at 34 weeks of gestation with low birth weight (2.2 kg) due to premature labor with foetal distress. For prematurity and early onset sepsis, the baby required neonatal intensive care unit (ICU) care.

At presentation, she was on exclusive breast feeding, weighing 4.42 kg and length 53 cm. She had normal external female genitalia with only one external opening (Figure 1). There was asymmetry in size of labia majora with right side slightly enlarged than that of left having bilateral palpable gonads. Ultrasound revealed absence of uterus and presence of bilateral testes in the labial folds measuring 1.4 cm X 0.91 cm on right side and 1.3 cm X 0.7 cm on the left side (Figure 2). The results of hormonal studies at 2 and 4 months are shown in Table I which were within normal range. The patient's karyotype (Figure 3) was that of a normal male (46, XY). Paediatric surgical onsultation was sought and molecular study of the AR gene (for the patient and mother) was requested for confirmation and genetic counseling.

Table I Serum hormone concentrations at 2 and 4 months age

Hormone (units)	Reference range	2 months age	4 months age
TSH (µIU/ml)	0.4–5.3	4.1	
FT4 (ng/dl)	0.8–1.9	1.3	
17α-OHP (ng/ml)	0.49–4.1	2.52	
LH (mIU/ml)	0.02–7		4.1
FSH (mIU/ml (<4))	0.16–4.1		2.3
S. Testosterone (ng/ml)	0.6–4		2.4
5α-Dihydrotestosterone (pg/ml)	120–850		124



Figure 1 External genitalia showing (a) phenotypically female genitalia with (b) single external opening

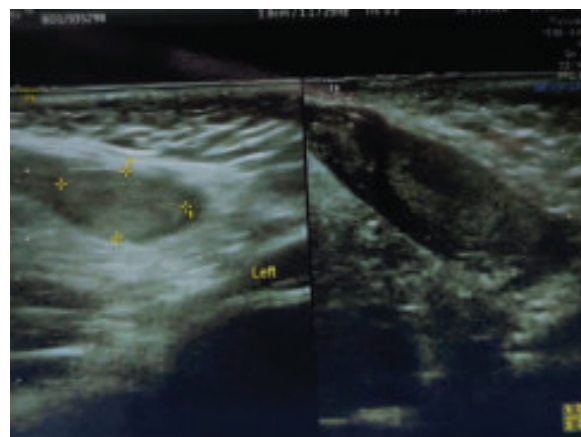
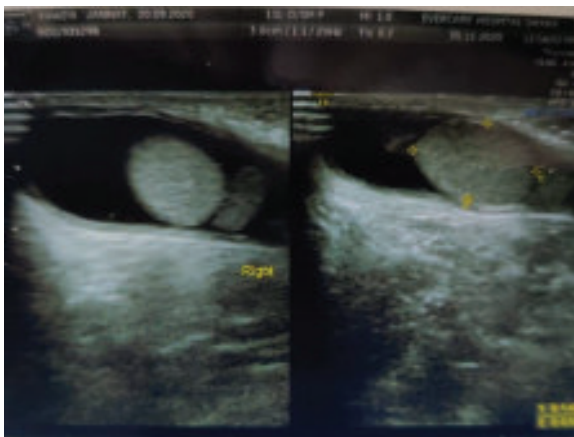


Figure 2 Ultrasound showing (a) right testis (1.4 cm X 0.91 cm) and (b) left testis (1.3 cm X 0.7 cm) in both labial folds

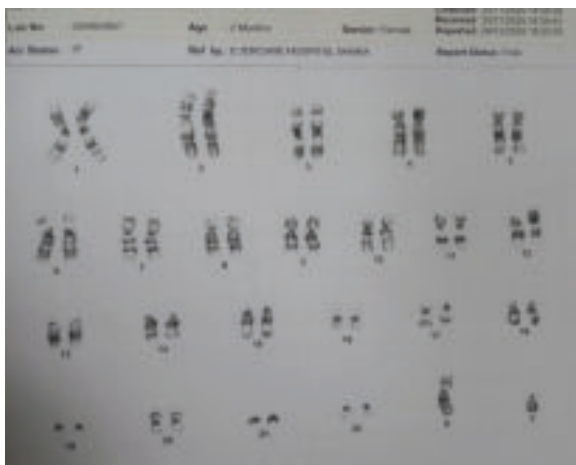


Figure 3 46, XY male karyotype of baby

DISCUSSION

This case presented during early infancy with normal female external genitalia with bilateral palpable gonads at labial folds and only one external opening resembling blind ending vagina. Only 1 to 2% of the CAIS cases present in the neonatal period with the appearance of bilateral inguinal or labial swellings containing a testis in an apparently female infant.⁹

In our case, pelvic and local labial ultrasound revealed absence of uterus and bilateral testes respectively. It is due to the explanation that, in CAIS, Leydig cell secretion of testosterone from testes is normal, which is normally converted into dihydrotestosterone (DHT) through 5-alpha reductase; but the effect of DHT is virtually nil due to the presence of non-functioning AR. Moreover, anti-mullerian hormone (AMH) secretion from Sertoli cells in the gonads is normally maintained, thus preventing the Müllerian system from developing into a uterus and other internal structures.¹⁰ Therefore, a blind-ending vagina is present and the uterus is absent while the gonads migrate independently of androgen.¹¹ The serum concentration of luteinizing hormone, follicle-stimulating hormone, and DHT of our reported case revealed normal for a male infant.

In adolescent women with AIS, breast and female adiposity develop because estrogens are converted from androgens by the normal functioning of aromatase enzyme. However, pubic and axillary hair is absent or sparse.¹² Cases of CAIS are mostly raised as females. In some recent studies, gonadectomy after puberty is recommended due to higher risk of developing germ-

cell tumors in the gonads after adolescence. As tumor risk before adolescence is considered to be as low as 0.8% to 2.0%, spontaneous puberty occurs when gonads are present in patients with CAIS.¹³ After puberty, they require subsequent sustained hormone replacement therapy and after adolescence, may need self-dilatation therapy and vaginoplasty procedures to address hypoplastic vagina.¹⁴ The reported case is raised as female and we explained in detail regarding the necessity of genetic test for genetic counselling, serial follow up and future risk of tumors of gonads; and possible medical and surgical treatment plan.

Conclusion

Appropriate and timely diagnosis of a child with CAIS is crucial. A team approach involving endocrinologists, clinical geneticists, urologists, gynecologists and psychologists is required. It is very important to provide correct information and address the issues of coping social stigmata, timing of patient's puberty, determining the timing of gonadectomy, and maintaining proper sexual function and optimum quality of life.

Authors' contribution: FZ: Conceptualization, literature search and writing manuscript. NF: literature search and review.

Consent of parents: Taken.

Conflicts of interest: Nothing to declare.

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