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An Early Diagnosis of Complete Androgen Insensitivity Syndrome in a 25-Day-Old Neonate: A Case Report

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ABSTRACT
Androgen insensitivity syndrome (AIS) is an X-linked recessive condition with 46XY karyotype which is caused by a mutation in the androgen receptor (AR) gene. It results in failure of normal development of external genitalia in chromosomally male individuals.Complete Androgen Insensitivity Syndrome (CAIS) is generally recognized during puberty, marked by primary amenorrhea and the absence of secondary sexual characteristics. This case highlights an exceptional scenario where CAIS was detected in a neonate displaying external female characteristics. As such, it emphasizes the significance of maintaining a heightened level of suspicion when encountering inguinal swelling in neonates. In this particular scenario, a 25-day-old infant, presenting with a phenotypically female appearance, displayed bilateral irreducible inguinal swelling. Pelvic ultrasound examination unveiled testicular tissue. The blood investigations revealed elevated levels of Serum Androstenedione, Serum Testosterone, and Serum 17-Hydroxy Progesterone. Furthermore karyotyping confirmed a 46XY chromosome pattern, leading to the subsequent diagnosis of CAIS.

Keywords: Complete Androgen Insensitivity Syndrome, Inguinal hernia, Androgen receptor, Karyotype, Genetic mutation

I. INTRODUCTION

Androgen Insensitivity Syndrome is a rare genetic condition, formerly known as testicular feminisation caused by a mutation in the androgen receptor gene located on the Xq11-12 chromosome [1, 2].

Depending upon the amount of residual receptor function, this can either be Complete Androgen Insensitivity Syndrome or Partial Androgen Insensitivity Syndrome (PAIS) [3].

In cases of CAIS, testosterone exerts no impact on sexual development, whereas, in PAIS, it yields partial effects. CAIS occurs in approximately 2-5 per 100,000 genetically male individuals, while PAIS occurs in around 5-7 per 1,000,000 [4]. In this case report, a neonate exhibited bilateral inguinal swelling which was later diagnosed to have CAIS.

II. CASE REPORT

A 25-day-old phenotypically female neonate was brought to the Pediatric Out-patient Department(OPD) with complaints of swelling in the bilateral inguinal region. This infant is the first twin conceived through IVF with a birth weight of 2.66 kg. Following the birth, the baby was identified as a female. It cried soon after birth but developed respiratory distress for which it was admitted to the NICU. The baby needed bCPAP for 3 hours following which it became better. Supportive IV fluid, IV antibiotics and supplemental feeding were given. Therest of the hospital stay was uneventful and the baby was discharged on 4th day from NICU.

Subsequent reviews in the OPD show no abnormalities.On the 25th day, the baby again presented with bilateral inguinal swelling. Examination revealed hard, irreducible swelling on both sides which increases with crying. An emergency ultrasound of abdomen and pelvis was performed to exclude obstructed hernia, revealing testes within both hernial sacs while failing to visualize the presence of uterus or ovaries. Examination of external genitalia showed normal labia majora, normal urethral meatus and vaginal opening with no clitoromegaly. In accordance with Prader scale, there was no features of virilisation observed.

Abdominal and pelvic ultrasound (Fig 1 (a)) revealed right inguinal hernia (11mm defect) with a 13x6mm heterogenous area resembling testis and left inguinal hernia (8mm defect) with a 16x8mm heterogenous area resembling testis, both containing bowel loops and omentum.

Complete blood count was normal [TLC 16,300 cells/cu.mm] with normal platelet count

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[3.8 lakhs/cu.mm] and inflammatory parameters (CRP-0.7 mg/L, ESR-6 mm/h). Serum Sodium and Serum Potassium were at 133 and 5.70, respectively. Serum Cortisol was low [2.02 microgram/dl (normal range: 3-21)], while serum Androstenedione [4.34 ng/dl (normal range: 0.05-0.35)], serum Testosterone [358.1 ng/dl (normal range: 20-64)], and serum 17-Hydroxy Progesterone [16.27 ng/ml (normal range: 0.25-1.10)] were elevated. Karyotyping confirmed a 46XY karyotype (Fig 1 (b))

(a) (b)

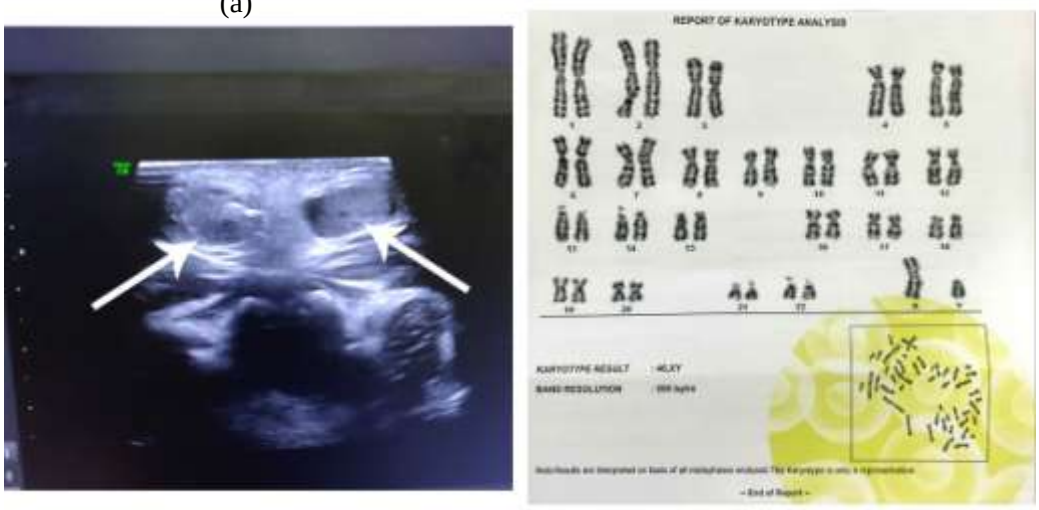

Fig 1. (a) USG showing bilateral testes in the hernial sac (b) Karyotype showing 46XY.

Potential differential diagnosis considered included Disorders of Sexual Differentiation such as AIS, 5-alpha reductase deficiency syndrome, or Congenital Adrenal Hyperplasia (CAH). The normal testosterone and dihydrotestosterone ratio ruled out 5-alpha reductase deficiency. Moreover, the absence of significant elevation in 17-OH Progesterone levels, coupled with the lack of hyponatremia or hyperkalemia, inclined the diagnosis towards AIS. Additionally, the absence of salt-wasting symptoms and the baby's weight gain made CAH less likely [5]. Given the male karyotype and the phenotypical female features, the diagnosis aligns more closely with AIS. However, to achieve a definitive diagnosis, a clinical exome analysis is deemed necessary for which a geneticist evaluation has been scheduled.

III. MANAGEMENT

A multidisciplinary approach was taken which consist of Pediatrician, Paediatric surgeon, Endocrinologist, Geneticist and Psychiatrist. Baby's parents were educated regarding the nature of AIS. They were recommended to undergo regular follow-up appointments to assess the baby's growth and development of secondary sexual characteristics. Despite the fact that performing an orchidectomy before puberty can diminish the risk of malignancy, testes were retained for achieving puberty, maintenance of sexual function, psychosocial well-being and bone health.

Nonetheless, it is essential to monitor the inguinal swelling for potential occurrences of obstruction, ischemia or any malignant changes to the testes, which might warrant the consideration of orchidectomy.

IV. DISCUSSION

Male sexual development is mainly regulated by two androgens: testosterone and dihydrotestosterone [2]. AIS develop due to the AR encoding gene mutation situated on the X chromosome and currently over 900 mutations have been identified [6]. Even though AIS develops as X linked inheritance, it can also occur due to spontaneous mutation without any family history [1]. This can result in complete loss of cell surface receptors or alteration in substrate binding affinity which can lead to loss of signal transmission. Hence there will not be any hormonal effects on tissues. This results in undervirilization of the external genitalia and the absence of secondary sexual characteristics [7].These patients will have normal amounts of testosterone and dihydrotestosterone as they have functioning testes. They do not have a uterus, fallopian tubes or

proximal vagina because of the presence of Mullerian Inhibiting Factor [1]. However, they have fully developed breasts, sparse pubic and axillary hair, short blind-ending vagina and the presence of undescended testes in the pelvic cavity or inguinal canal [8].

During prenatal assessment, CAIS may be incidentally detected when ultrasound scans reveal female external genitalia, while Non-Invasive Prenatal Testing (NIPT) indicates male sex chromosomes [2]. Investigations typically reveal elevated LH levels and normal to slightly elevated FSH levels. Testosterone and estradiol levels tend to be within the upper limits of the normal range or slightly elevated for males [9].

V. CONCLUSION

CAIS is challenging to diagnose during the newborn period due to the absence of any discernible abnormalities prior to gonadal development. A more comprehensive evaluation is required when the physical examination of the baby reveals ambiguous genitalia, inguinal or labia majora nodules, and the presence of scrotal emptiness or hypospadias. The baby's presentation of bilateral inguinal swelling facilitated an early diagnosis in the neonatal stage, followed by subsequent investigations that prompted the initiation of early management. In the evaluation of AIS, it is important to consider 17-Hydroxylase Deficiency Syndrome, 5-Alpha Reductase Deficiency, CAH and other intersex or Disorders of Sexual Development (DSD) as potential differential diagnoses [2].

Gender assignment is multifaceted, influenced by factors like genital appearance, fertility prospects, treatment options, family perspectives, and cultural biases. In India, genital reconstructive surgery is generally reserved for life-threatening situations due to ambiguous genitalia. DSDs are sensitive issues, presenting complex dilemmas. Allowing individuals the autonomy to choose their gender as they mature is crucial and addressing these matters requires a compassionate and empathetic approach towards patients and their families [10].

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