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Case Report on Primary Amenorrhea in a Female: Uncovering the Diagnosis of Complete Androgen Insensitivity Syndrome, a Rare Entity

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Abstract
We present the case of a 20-year-old female with primary amenorrhea who was evaluated for absent menstruation. On examination, breast development was normal (Tanner stage 5), but the patient had no vaginal orifice. Investigations, including hormonal assays, revealed elevated levels of testosterone, FSH, and LH. Imaging studies (ultrasound and MRI) showed the absence of the uterus and ovaries. Karyotyping confirmed a 46, XY chromosomal pattern, leading to the diagnosis of Complete Androgen Insensitivity Syndrome (CAIS). This case highlights the importance of considering AIS in the differential diagnosis of primary amenorrhea, especially in the presence of normal female secondary sexual characteristics and absence of menstruation. The appropriate workup, including hormonal testing, imaging, and karyotyping, is essential for the timely diagnosis and management of AIS.

Key words– *Primary amenorrhea, Androgen Insensitivity Syndrome, Disorder of Sexual Development.*

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I. Introduction

Androgen Insensitivity Syndrome (AIS) is a rare X-linked recessive androgen receptor (AR) disorder[2]. The individuals with Androgen Insensitivity Syndrome have 46XY karyotype. AIS could be classified as complete, partial, or mild AIS according to the gradation of androgen insensitivity. Complete AIS (CAIS) is characterized by complete resistance to the actions of androgens. It is presented as female appearance and normal breast development, absence of uterus and ovaries, bilateral undescended testis, and elevated testosterone levels. Complete Androgen Insensitivity syndrome is a rare disorder affecting 2–5 per 100,000 genetically male individual while partial AIS affects 5–7 per 1,000,000 genetically male individuals [1].

II. Case Report

A 20year old female came to OPD with complaint of primary amenorrhea. Patient was evaluated with the consent of the patient and her parents. On examination, her height is 166cm, weight 55kg, breast examination showed Tanner V, axillary and pubic hair not developed Tanner I, on per abdomen examination no palpable masses were noted. On local examination no vaginal opening was seen. Her blood investigation showed raised testosterone levels, increased LH and FSH levels. An ultrasound examination was done which showed absence of uterus, ovaries, fallopian tubes which arose the suspicion of Disorder of Sexual Development (DSD). MRI pelvis was done, which also revealed absence of ovaries, fallopian tube, uterus and cervix. Testis were not visualised, but a mass in inguinal region with the lymph nodes was suspicious of atrophic testis. Patient and the family were counselled and karyotyping was done which revealed XY. Therefore, the diagnosis was concluded as Androgen Insensitivity Syndrome. Patient and the family were counselled regarding the condition, the problems related and the further treatment modalities.

Figure1 Breast development tanner stage V, Axillary hair Tanner I

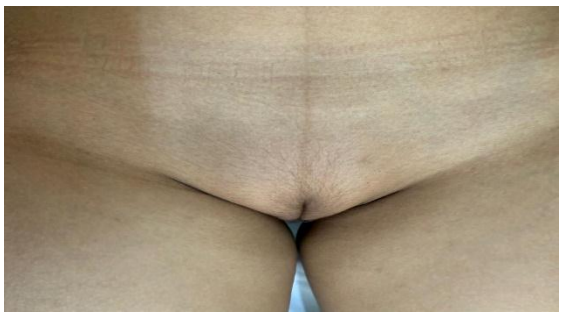

Figure 2 Pubic hair Tanner I

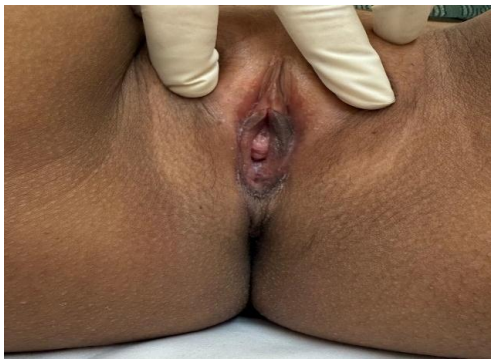

Figure 3 Blind Vaginal orifice.

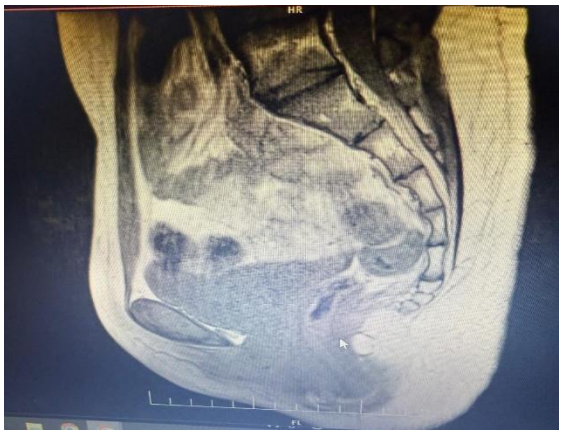

Figure 4: MRI Pelvis – No uterus, cervix, bilateral ovaries, fallopian tube.

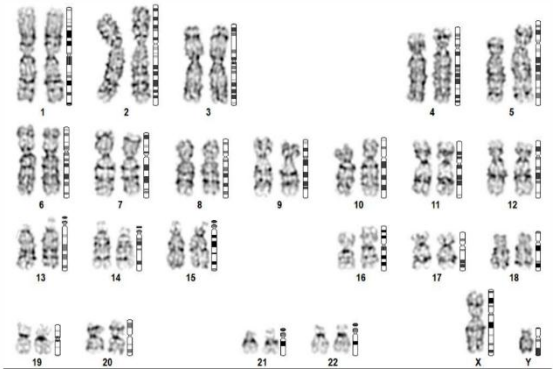

Figure 5 -Karyotyping revealed - 46, XY.

III. DISCUSSION

Androgen insensitivity syndrome is a X-linked recessive genetic disorder caused by mutation in the Androgen Receptor (AR) gene. Due to this mutation in AR gene, during foetal development, the cells fail to respond to androgen hormones thus preventing masculinization of male genitalia. It also prevents development of male secondary sexual characteristics during puberty [3]. Genetic alterations in the coding sequence of androgen receptors linked to the chromosome Xq11 - 12, which is the gene encoding the androgen receptor, of a genetically male individual (46 XY) [4],[5] causes the AIS. Androgen Insensitivity Syndrome (AIS) is classified into complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS) and mild Androgen Insensitivity Syndrome (MAIS) based on phenotype [2]. Other names given to various presentations of AIS are Reifenstein syndrome, Rosewater syndrome, Morris' syndrome, Gilbert-Dreyfus syndrome, Goldberg-Maxwell syndrome, Lubs syndrome, Aiman's syndrome [6].

Clinical features in complete androgen insensitivity syndrome are absent or rudimentary mullerian structures i.e., uterus, fallopian tube, cervix and a blind ended short vagina; two non-dysplastic, undescended testes; absence or scanty pubic hair and axillary hair; normal to underdeveloped breast. Family history would reveal a X-linked pattern inheritance with affected male individuals, although no significant family history does not preclude the diagnosis of CAIS [6,7]. Androgen Insensitivity Syndrome is most commonly diagnosed at puberty when the patient presents with primary amenorrhea. It can also be diagnosed prenatally with dissimilarity between the karyotype mapped from amniotic fluid and genetic sex verified on ultrasound. In rare cases the diagnosis is made in later period of life when the patient presents with infertility. Although no formal diagnostic criteria for identifying AIS have been established yet, karyotype mapping, elevated level of serum testosterone, normal or elevated level of serum FSH, LH and oestradiol, radiological imaging of pelvis and molecular genetic testing showing mutation in AR gene helps in the diagnosis of AIS. Karyotype mapping holds maximal importance as it also helps to differentiate AIS from other genetic abnormalities like Klinefelter syndrome (47, XXY), Turners syndrome (45, XO), Mixed gonadal dysgenesis (45, XO; 46 XY), Tetragametic chimerism (46, XX; 46, XY) [8].

The hormonal profiles of patients with CAIS and PAIS are identical. Serum testosterone (T) and luteinizing hormone (LH) are at or above the upper normal limit during the first 3 months of life, while prepubertal patients generally have Testosterone and LH concentrations in the normal range for their age [9,10]. In CAIS, testosterone levels are elevated at the time of puberty. Elevated luteinizing hormone (LH) levels are found, indicating androgen resistance at the hypothalamic-pituitary level. The high levels of testosterone, a substrate for aromatase activity, result in substantial amounts of oestrogens, which are responsible for very good breast development at puberty in CAIS individuals. Adults with in situ testes usually have increased levels of LH, normal (sometimes elevated) concentration of Testosterone and Follicle-Stimulating Hormone (FSH) as compared to normal males, and oestradiol at the upper normal limits. [11,12]

Androgen insensitivity syndrome and individuals with cryptorchid testes have an increased risk of tumorigenesis. Cryptorchidism in partial androgen insensitivity syndrome (PAIS) should be corrected surgically soon after diagnosis to maintain testicular function and minimize the risk of malignancy. These tumors may be germ cell tumors and gonadoblastomas. They tend to occur in approximately 1.5 to 2 percent of undescended testes and may become malignant.[15]

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 individualised, flexible, and holistic. Management is dependent wholly on a multidisciplinary team. Membership of the team varies, but should include key members from endocrinology (paediatric or adult), urology, gynaecology, and clinical psychology.[16,17,18]

IV. CONCLUSION

To conclude, Androgen Insensitivity Syndrome although rare, is very distressing to the individual and family members. It requires expert and sympathetic handling. Close collaboration between a surgeon, gynaecologist and psychiatrist essential for proper management of complete androgen insensitivity syndrome. Due to the risk of degeneration of the gonad and malignancy of undescended testes, orchidectomy should be performed. The patient is also benefitted by hormonal replacement therapy as well as proper psychiatric counselling [7,13,14].

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