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Two Sisters with Testicular Feminization or Complete Androgen Insensitivity Syndrome

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Abstract: Androgen Insensitivity Syndrome (AIS) is a disorder of sexual development (DSD). It is caused by a mutation in the androgen receptor (AR) gene resulting in deficient action of androgens and therefore incomplete masculinization. Two forms of AIS are described: Complete Androgen Insensitivity Syndrome (CAIS) and Partial Androgen Insensitivity Syndrome (PAIS). CAIS is also known as testicular feminization (TF). Patients with CAIS are all phenotypically female while having 46, XY karyotype and testis, and sometimes first come to medical attention with complaints of amenorrhea or infertility. We report the case of two sisters, aged respectively 38 and 40 years, who have a CAIS. The diagnosis was made in front primary amenorrhea with high testosterone levels, the presence of testicular formations in the labia majora and 46, XY karyotype. The younger of the two sisters had bilateral orchiectomy and was put on hormone replacement therapy. The search for the gene mutation of AR is in progress. Through these two observations we recalled the physiopathological basis of this syndrome and its clinical aspects and the therapeutic implications.
Keywords: Complete Androgen Insensitivity Syndrome, CAIS, Disorder of Sexual Development, DSD, Testicular feminization, 46, XY Karyotype.

INTRODUCTION

Androgen Insensitivity Syndrome (AIS) or Testicular feminization is a disorder of sexual development (DSD) referred to as XY DSD. AIS is caused by a mutation in the androgen receptor (AR) gene resulting in deficient action of androgens and therefore incomplete masculinization. Two forms of AIS are described: Complete Androgen Insensitivity Syndrome (CAIS) and Partial Androgen Insensitivity Syndrome (PAIS). Patients with CAIS are all phenotypically female while having 46, XY karyotype and testis, and sometimes first come to medical attention with complaints of amenorrhea or infertility [1].

We report the case of two sisters who have a CAIS through which we will recall the physiopathological basis of this syndrome and its clinical aspects and the therapeutic implications.

CASE REPORT

Case 1

A 38-year-old woman, unmarried, muslim, from a very conservative family, was referred to endocrinology for etiological research of primary amenorrhea. In his personal history, there was nothing special. In his family history, we noted the case of a nephew who has a DSD for which he underwent surgery at the age of 6 years and a sister who also has primary amenorrhea. Physical examination revealed secondary sexual characteristics of female phenotype, Tanner stage S5P5. There were no signs of virilisation. Examination of external genitalia objectified a short vagina and two inguinal swellings. The remainder of the physical examination was unremarkable. Sexual hormones in the blood were determined. Testosterone was elevated to 14,61 ng/ml (NV: <0,1- 0,62 ng/l); LH at 21,7 UI/l and FSH at 20,7 UI/l; the Dihydrotestosterone (DHT) was also elevated to 3,41 nmol/l (0,17-0,96 nmol/) and the Anti-Müllerian Hormone (AMH) was normal at 18 pmol/l (NV: 14- 48 pmol/l). Trans abdominal ultrasonography revealed masses in the labia majora consistent with testes. Theses gonads were 25x20 mm and 22x15 mm in size at right and left respectively. Uterus and ovaries were not detected. Cytogenetic analysis showed a 46,XY karyotype. Bone densitometry objectified osteopenia. The most probable diagnosis was considered to be CAIS. The patient was consulted with a psychologist about her DSD and was then referred to urologist for bilateral gonadectomy. Orchiectomy was accomplished on both sides and the patient was discharged without

complication (Fig.1). Histopathology revealed testicular parenchyma with seminiferous tubules wall thickened by hyaline fibrosis. Cells spermatogenesis line was absent. It persisted a seat of Sertoli cells. The interstitial tissue was the seat of a Leydig cell hyperplasia and some congestive vessels. No signs of testicular cancer were identified. Long-term hormonal (estradiol) replacement therapy was prescribed. The search for the gene mutation of AR is in progress. Currently the patient has asked the treatment options for her to have a normal sex life. Specialist advice of a gynecologist is now intended.

Case 2

A 40-year-old woman, older sister of the first case, divorced because of infertility. In his personal history, she had a vaginoplasty during her first marriage. She was also invited to our hospital via her sister. Physical examination revealed secondary sexual characteristics of female phenotype, Tanner stage S5P5. There were no signs of virilisation. Examination of external genitalia objectified two inguinal swellings. The remainder of the physical examination was unremarkable. Sexual hormones in the blood were determined. Testosterone was elevated to 9,65 ng/ml (NV: 0,09-0,56ng/ml); LH at 19,5 mUI/ml and FSH at 38,70 mUI/ml. Trans abdominal ultrasonography revealed masses in the labia majora consistent with testes. Theses gonads were 24x11,5 mm and 19x9,5 mm in size at right and left respectively. Uterus and ovaries were not detected. Cytogenetic analysis showed a 46,XY Karyotype. Bone densitometry objectified osteopenia. Like her sister, the most probable diagnosis was considered to be CAIS. The patient was consulted with a psychologist about her DSD. Gonadectomy was recommended but the patient chose to marry for a second time before undergoing this procedure.

Fig. 1: Left orchiectomy

DISCUSSION

DSD's are congenital anomalies due to atypical development of chromosomes, gonads and anatomy. Since 2006, new nomenclature of DSD was proposed [1]. The incidence of DSD is estimated as one in 5500 live births [2]. CAIS is a rare form of AIS and the prevalence is estimated at between one in 20000 and one in 60000 live births. CAIS is rarely recognized at infancy because of the female phenotype [3]. This syndrome has been described for the first time by John Morris [4], and it's in 1989 that we were able to determine the location of the human AR gene whose mutation was responsible for this syndrome [6].

The differentiation of testicular, from the genital ridges, begins during the 6th week of the male fetal development under the influence of SRY gene located on the Y chromosome. At the end of the 8th week, Leydig cells appear and begin to produce testosterone. Then, the rest of the male sexual characteristics are slowly taking place under the influence of androgens. But, in the absence of testosterone female sexual characteristics develop [7].

Testosterone acts on cells through androgen specific nuclear receptors, proteins encoded by a gene specifically located at the Xq11-Xq12 locus on the proximal long arm of chromosome X. Until 2010, more than 400 mutations in this gene have been discovered. Mutations can be transmitted on a recessive X-linked or occur de novo [7]. However, not all mutations result in a defective AR. This protein is composed of several functional parts. The transactivation domain is more than half of the receptor. Achieving this area causes an inability of all cells to recognize and use testosterone, leading to AIS [8]. In a normal cell, testosterone enters, and under the influence of 5-alpha-reductase, it is converted to dihydrotestosterone. However, both hormones exert their effects after binding to the field of steroid binding of the AR. Following binding, the receptor undergoes a cascade of changes leading to the transcription of target genes [9]. Mutations can affect any of these stages and the effect is one of the various forms of AIS [8].

Primary amenorrhea in adolescence or inguinal swelling in an infant is the typical form of a presentation in CAIS. In this syndrome, breast development and pubertal growth spurt are age appropriate, but without menses. Otherwise, the excess androgen aromatization is responsible for development of estrogen-dependent secondary sex characteristics. The pubic and axillary hair is usually absent or may be present in rare quantities [10]. In infancy, CAIS can manifest as inguinal hernia or labial swelling containing testis in an apparently female infant. Bilateral inguinal herniae are rare in female infant. The incidence of CAIS in such patients is 1-2% [11,12]. The measurement of the vaginal length can be an alternative for screening of this syndrome in prepubertal girls undergoing inguinal hernia repair. A short vagina and the absence of ovaries or fallopian tubes suggest the need for a karyotype [12]. The Anti-Mullerian hormone produced by the Sertoli

cells of testis is responsible for the absence of the uterus, cervix and of the proximal portion of vagina [13]. The vagina can be in the form of a dimple in the perineum or with a normal length, but is still blind ending.

Diagnosis of CAIS can happen by chance. Currently, the sex of a fetus is becoming increasingly known before birth [14]. So, CAIS can therefore sometimes be diagnosed due to the mismatch between the prenatal prediction of sex and phenotype at birth [15]. There are others forms of presentation including a family history of known X-linked CAIS as is the case in our second patient, and sometimes the discovery of a pelvic mass arising from a gonadal tumor [16].

In case of CAIS, serum testosterone concentrations are either within or above the normal range for men and boys and luteinising hormone (LH) concentrations are inappropriately increased [17]. Generally concentrations of follicle stimulating hormone (FSH) and inhibin are normal. Serum concentrations of estradiol, in case of CAIS, are higher than those noted in men and boys, but remain below those reported in women without CAIS. This is due to peripheral aromatization of testosterone produced in excess and the direct action of LH on the secretion of testicular estrogen [18]. Concentrations of sex hormone- binding globulin (SHBG) are sexually dimorphic; androgens decrease and oestrogens increase hepatic production, respectively. Concentrations of this protein in patients with CAIS are similar to those in women without the syndrome and do not decrease after androgen administration [19].

The main differential diagnosis for CAIS are dominated by complete gonadal dysgenesis, Mayer-Rokitansky-Kuster-Hauser syndrome, and other mullerian duct anomalies [20,21].

Management of CAIS must be individualised, flexible, holistic and involving a multidisciplinary team: endocrinologist, urologist, gynecologist, neonatologist, clinical geneticist and social services [22, 23].

When CAIS present in infancy, early gonadectomy with induction of puberty later can be done, or gonadectomy may be delayed until adulthood. Although the prevalence of malignancy is very low in childhood and the parents' decision could be affected by this obsession [24, 25].

Puberty should be induced by estrogen replacement if gonadectomy is performed in childhood. The principles are similar to the induction of puberty in girls with Turner's syndrome starting with 2 µg / day of Ethinyl Estradiol until the age of 11 years. Then the dose is increased by level of 2-4 µg during two years to reach a daily dose of 30 µg. Finally in women who have a gonadectomy after puberty, estrogen replacement may be orally or transdermally either as synthetic or natural estrogens. These are recommended by some authors [26].

In CAIS, bone mineral density is reduced, but fracture risk seems low [27]. At diagnosis and then every two years an evaluation of bone density is necessary in younger women with CAIS to assess the effectiveness of hormone replacement [28].

If gonadectomy was not done in infancy, it is generally recommended in early adulthood to avoid the risk of gonadal tumours. The procedure is done laparoscopically if the gonads are intra-abdominal. According to studies, there is an increased risk of tumors of more than 30% in late adulthood if gonadectomy is not done. A review of the risk of adult women with CAIS having a gonadal tumour could not be more specific than 0-22% [29, 30]. According to the literature, the risk of germ cell tumor is as low as 0.8-2%, especially before puberty [24, 25]. Benign tumors of non-germ cell origin are dominated by the Sertoli cell tumors and hamartomas. In the absence of preventive gonadectomy, monitoring is based solely on imaging. Vaginal Surgery is rarely used for the creation of a functional vagina. Vaginal dilators are offered in the first because it is an effective treatment while some women can achieve a similar effect with sexual intercourse [31]. Surgery is indicated only after the consent of the woman and her ability to manage dilator therapy herself postoperatively [32]. Infertility is the major problem of women with CAIS. Individuals can adopt or could choose to use donor oocytes and surrogate mother with the sperm of their partner to achieve pregnancy. In our context this choice is not currently possible.

Finally, psychosocial support is primordial in the multidisciplinary approach to the management of CAIS. [33] The partial or full disclosure procedure is currently recommended [34, 35]. The disclosure must be made with care, especially for children with CAIS as they approach the age of puberty. This information should be shared with the parents first, with the release of the appropriate age as the child grows [36]. Mothers of girls with CAIS should also benefit from psychosocial support because of guilt. In terms of sexual functioning and sexual quality of life, the results are less positive [37]. Vaginal penetration difficulties

due to hypoplasia can be corrected by vaginal dilators or regular sex.

CONCLUSION

CAIS is a rare disease that must be diagnosed and treated through close work between gynecologists, endocrinologists, geneticians, urologists, anatomic pathologists and psychiatrists. It is an inherited recessive disease linked to chromosome X. The diagnosis is often made after puberty, during a primary amenorrhea. Bilateral laparoscopic orchiectomy is a minimally invasive effective procedure of removing the intra-abdominal testes, in order to avoid their malignant transformation. Gonadectomy should be followed by a combined hormonal replacement therapy to prevent involution of secondary sexual characteristics. Finally, a genetic investigation in the family is essential to detect unknown event.

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