Introduction

CAIS is defined as a sexual developmental disorder caused by complete resistance to the biological action of androgens. It constitutes one of the most common causes of disorders of sex development and was first described by Morris in 1943. It is caused by missense mutations in the Androgen Receptor (AR) gene [1]. Patients with CAIS have a 46, XY karyotype and undescended testes. The defect lies in the X chromosome affecting the gene responsible for the androgen intracellular response to testosterone or dihydrotestosterone.

We report 2 cases of CAIS in 21-year-old and 19-year-old phenotypic girls who presented with primary amenorrhea. From these observations, we present the clinical and pathological aspects and therapeutic strategy.
Case 2

A 19-year-old patient was referred to our gynecology department due to primary amenorrhea. During her interrogation, she had no significant pathological history and no cases of primary amenorrhea have been reported in the family. She revealed that her puberty proceeded normally at the age of 13, with normal breast development and a harmonious female morphotype. Clinical examination found a female phenotype: the fat distribution was gynoide; breasts were well developed contrasting with the absence of pubic and axillary hair. This patient weighted 57 kg and measured 1.63 m. Regarding external genitalia, a normal-looking vulva, a non-hypertrophied clitoris and a permeable vagina were observed. The vagina was short (4 cm), ending in the fornix without cervix and uterus. Complementary examinations were performed with pelvic ultrasound and pelvic MRI, which confirmed the absence of internal female genitalia (uterus and ovaries) and the presence of the testicles in the intra-abdominal position (Figure 4). The hormone tests revealed a high plasma level of testosterone and delta 4 androstenedione at 9 ng/ml and 2.8 ng/ml respectively. In addition, the blood level revealed: FSH at 7 ml/ml, LH at 17.6 ml/ml and estradiol at 39 μg/ml. The karyotype showed a 46, XY. Surgical castration was performed and histological examination concluded the existence of a testicle. Estrogen / progesterone hormone replacement therapy (climaston 2/10) was initiated.

Discussion

The CAIS is an inherited X-linked recessive disorder. It is due to a dysfunction of testosterone receptors. The consequence of this androgen insensitivity is sexual differentiation in the feminine sense [1,2]. The frequency of this syndrome is variously appreciated according to the authors. The Prevalence of AIS was found to be 4.1 per 100000 live-born females [3]. The prevalence of CAIS proven via molecular diagnosis estimated to range from 1 in 20400 to 1 in 99100 genetic males [4].

Complete Androgen Insensitivity Syndrome, with its female phenotype, is overlooked at birth, nevertheless, it could be found even prenatally if the karyotype is determined from the amniotic fluid, and the genetic sex would be verified through ultrasound.

The diagnosis is rarely made before puberty. At puberty, it is diagnosed when the patient reports primary amenorrhea such as in ours cases. Attention must be drawn to the absence or rarity of ambosexual hair (inconstant sign) [1,5]. After puberty, the diagnosis is made during a primary amenorrhea or in a context of infertility. The physical examination often finds a female and harmonious morphological development, fat and gynoide distribution, well developed breasts and normal implanted hair. In contrast, the ambo sexual hair is insufficiently developed, even replaced by a fine down.

On gynecological examination, the external genitalia are of the female type: the clitoris is small, the majora and minora labia are well developed, the vagina is small and permeable ending in the fornix, but the internal genitals (cervix, uterus) are absent. The gonads are usually in the intraperitoneal position and are rarely found in the inguinal canals [6].

Hormonal investigations typically reveal testosterone levels in the normal male area and elevated serum LH levels due to hypohalamic-pituitary insensitivity to testosterone. The HCG stimulation test is useful for diagnosis; the testosterone response must be important. At the same time, plasma levels of delta 4 androstenedione and testosterone binding globulin are increased [1,6].

Pelvic ultrasound, MRI and possibly laparoscopy confirm the absence of uterus and ovaries. The karyotype is male 46, XY.

Currently, the diagnosis of the complete androgen insensitivity is based on the search for the mutation; however, it can be very strongly evoked on the clinical and karyotype, recently an antenatal diagnosis became possible by the search for the causal mutation or using the polymorphisms of the gene of the androgen receptor on analysis of the amniotic fluid or by trophoblastic biopsy [7-10].

Both patients had a complete clinical picture including well developed breasts, rare pubic and axillary hair growth, and very high plasma testosterone levels. Pelvic ultrasound and MRI confirmed the absence of uterus, ovaries and the presence of male gonads in the intra-abdominal position. For reasons of accessibility, none of our patients has benefited from gene mutation research.
The physiopathological mechanism of CAIS is better understood through the study of androgens in the fibroblasts of the genital skin. Indeed, it is currently demonstrated that the main abnormality of the syndrome of feminizing testis is at the level of the cytosolic receptors of dihydrotestosterone.

The feminizing testicle, like any ectopic testicle, exposes to the risk of malignant transformation [11,12]. This risk is variously appreciated by the authors [13-15]; it is estimated at 5% to 10% according to some authors and at 22% according to others. In addition, it is established that this risk of malignant degeneration increases with age, justifying castration as soon as the diagnosis is confirmed.

The management of CAIS requires a close collaboration between gynecologist, endocrinologist and psychologist. Castration is to be carried out because of the risk of degeneration of the gonad [8,14]. Estrogen/progestin replacement therapy should be instituted, aimed at preventing regression of secondary sexual characteristics, preserving normal sexual activity and preventing the consequences of estrogen deficiency. It can act as a minidosed pill or a sequential treatment combining estradiol and a progestogen devoid of metabolic effects according to the scheme proposed for the replacement treatment of menopause.

The CAIS is a rare inherited X-linked recessive disorder. The diagnosis is often made after puberty, during a primary amenorrhea. Attention is drawn to the rarity of ambosexual hair contrasting with good breast development and a feminine and harmonious morphotype. Castration is to be carried out followed by the institution of estrogen/progestin treatment to prevent the involution of secondary sexual characteristics.

References
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