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Case Report

Morris Syndrome

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Abstract

Morris syndrome or Complete Androgen Insensitivity Syndrome (CAIS) is a rare genetic disorder characterized by androgen resistance. It associated the coexistence in the same subject of a male karyotype (46, XY), with male gonads, and a normal female morphology. Patients with CAIS are phenotypically females, with male gonads, but their genetic composition is that of make karyotype 46, XY. CAIS, formerly called feminizing testicle, is considered as the most complete and most frequent form of male pseudo hermaphrodism. It is caused by complete or partial resistance to the biological action of androgens. Here, we report 2 cases of CAIS in 21-year-old and 19-year-old phenotypic girls who presented with primary amenorrhea. The clinical and pathological aspects and therapeutic strategy for CAIS are also reviewed and discussed.

Keywords: Complete androgen insensitivity syndrome; Disorders of sex development; Androgen receptors; Feminized testicle

Introduction

CAIS is defined as a sexual developmental disorders 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 CAIS patients have a female phenotype, normal female external genitalia with 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 Presentation

Case 1

A 21-year-old patient was referred to our gynecology department due to primary amenorrhea. She has no family medical history. History of the patient revealed that her puberty manifested itself as early as age 15 with normal breast development contrasting with poorly developed axillary and pubic hair. A physical examination performed and showed that her height and body weight were 1.71 m and 52 kg, respectively. On physical examination, the patient was 1.71 m tall and weighs 52 kg. At inspection, a female morphology with normally implanted hair was noted and the breasts were well developed. On the other hand, ambosexual hair was insufficiently developed (Figure 1). The gynecological examination showed external genitals of the female type with a small clitoris and a normal minora and majora labia. Vagina was permeable and examination with the speculum found a terminal vagina without cervix. The pelvic exam showed a cupuliform vagina without cervix or uterus. Somatic examination is normal. The hormonal assessment showed: FSH at 6.8 ml/ml, LH at 21.3 ml/ml, estradiol at 44 µg/ml and a high testosterone level at 8.85 ng/ml, as well as delta 4 androstenedione at 1.9 ng/ml. Pelvic ultrasound confirmed the absence of uterus and ovaries and localized the testicles within the external iliac vessels (Figure 2A and B). The patient's karyotype was that of a normal male, 46, XY. This patient underwent laparotomy removal of both gonads followed by estrogen/progestin replacement therapy and psychological management. The histological examination of the testes found dysplastic testicular tissues with immature seminiferous tubules (Figure 3).

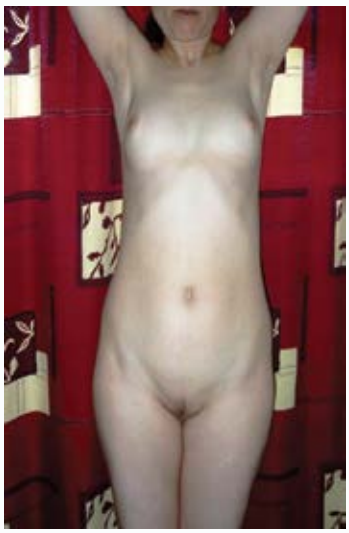

Figure 1: Patient photo: Normal feminal morphotype, but absence of axilair and pubar pilosity.

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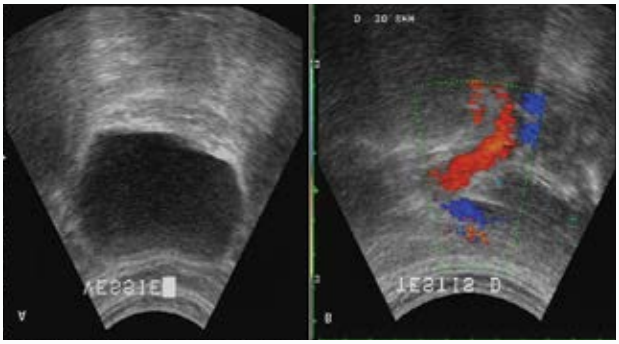

Figure 2: Pelvic ultra sonography: A) Absence of internal genital organes. B) Presence of male gonads in the internal zone of iliac vessels.

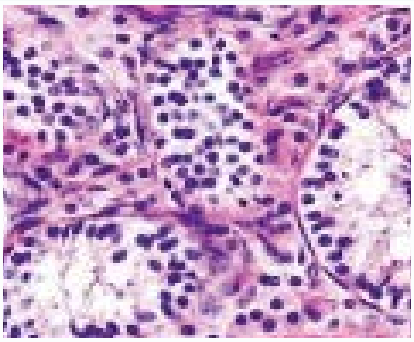

Figure 3: Histologic exam of the feminized testicle: immature seminar conducts (HE X 250).

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

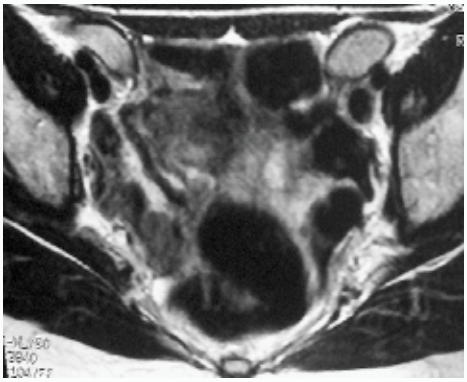

Figure 4: Pelvic IRM: axial sequence in T1, two bilateral ovular forms with intermediar signs forward the femoral vessels.

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 hypothalamic-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.

At the same time, psychological support in collaboration between the psychologist and the family is necessary; it aims to inform the patient about the nature of her illness and to reduce the psychological impact of the announcement of infertility to these patients wishing to maternity while hiding the genetic identity.

In ours cases, both patients underwent surgical castration followed by estrogen/progestin replacement therapy.

Conclusion

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.

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