Primary amenorrhea: when a frequent consultation results in an unusual diagnosis.

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Introduction

Complete androgen insensitivity syndrome (CAIS) is an X-linked recessive genetic variation involving mutations in androgen receptors that lead to hormone resistance [1, 2]. It is the most common cause of differences of sexual development (DSD) in 46,XY individuals [2, 3]. They present with a biological female phenotype with normal external genitalia. Physicians should suspect the diagnosis in adolescents with primary amenorrhea and pubertal development, prepubertal girls with inguinal hernia, or newborns with a female phenotype and a prenatal karyotype of 46, XY [2, 4]. Due to the psycho-emotional impact of this diagnosis on patients and their families, a multidisciplinary approach for care is mandatory [3, 4]. The following case describes a 16-year-old female adolescent who consults for primary amenorrhea.

Case description

A 16-year-old cisgender female adolescent, was referred to the Adolescent Gynecology department for primary amenorrhea. As medical history, her mother reported she was a term newborn without obstetric complications. Additionally, she presented with mild asthma and no surgical history. She lived with her parents and siblings and attended high school.

From a gynecological perspective, thelarche was reported at 12 years old, without the onset of pubarche. She had no episodes of abdominal pain. Obtaining a sexual history, she mentioned being attracted to men, had no sexual partners and denied engaging in sexual intercourse.

Clinical examination revealed a female phenotype, height upon admission was 1,65 cm (75th percentile), with complete breast development at (Tanner stage 5), absent axillary

and pubic hair and normal external biological female genitalia with blind-ending vagina. Bilateral inguinal hernia were palpable, which was firm and elastic with a 3 cm bulge.

Additional tests were requested. Sexual hormones in blood were measured: LH 11.75MUI/ml, FSH 4.71MUI/ml, estradiol 34.7pg/ml, negative beta-hCG, SDHEA 174ng/ml, delta 4 androstenedione 2.25ng/ml, 17-hydroxyprogesterone 1.47ng/ml, testosterone 7.67 ng/ml, anti-Müllerian hormone (AMH) 369.80pmol/l (upper limit for women: testosterone - 0.5ng/ml, AMH - 84pmol/l respectively). The ultrasound did not reveal Müllerian structures or pelvic gonads.

A pelvic magnetic resonance imaging (MRI) was performed and the absence of the uterus or ovaries was confirmed. However, bilateral inguinal hernias with solid tissue compatible with gonads were detected (Fig. 1). Based on the findings of the physical examination and complementary studies, a presumptive diagnosis of CAIS was made. Chromosomal analysis confirmed a 46, XY karyotype. Furthermore, genetic testing was performed in peripheral blood for sequencing of introns and exons of the androgen receptor (AR) gene. The presence of the hemizygous variant (having only one allele at a specific gene locus) described in CAIS was detected, (Fig. 2). The mother's genetic study did not identify this mutation.

Diagnostic feedback was provided by a multidisciplinary team together with members of Endocrinology, Mental Health, and Gynecology. It was determined that that risk of gonadoblastoma was low at this time and the risks of gonadectomy, including the development of menopausal symptoms, were significant. Expectant management was decided. Options for follow-up were explained: clinical monitoring and imaging with possible gonadal biopsy in suspicious cases, topics related to sexual health were addressed. Treatments for sexual and reproductive health were discussed, such as vaginal elongation (dilators versus surgery) and future fertility options.

Discussion

Primary amenorrhea is a frequent reason for consultation in adolescent girls. Gynecologists should identify whether it is a structural anomaly of the genital tract, alterations of the hypothalamic-pituitary-gonadal axis or other endocrine disorders. A detailed medical history, physical examination and complementary examinations will allow to identify the cause in most cases. In adolescents with primary amenorrhea and development of secondary sexual characteristics, uterine agenesis should be suspected.

Additional tests should include testosterone, FSH and karyotype. In countries where genetic testing is not available, testosterone levels in the male range directs towards CAIS, whereas in the female range, the differential diagnosis is Rokitansky. [5].

Sexual determination and differentiation during embryogenesis is determined by three components: chromosomal sex, gonadal sex, and phenotypic sex. Karyotype will determine the development of typical male or female gonads. The SRY gene, located on the short arm of the Y chromosome, is responsible for gonadal differentiation into testes, and in its absence, into ovaries. Consequently, Leydig cells start producing testosterone, the main hormone involved in the differentiation of biological male internal and external genitalia. Anti-Müllerian hormone secreted by Sertoli cells prevents the development of the Müllerian ducts. The lack of androgen stimulation leads to impaired virilization [2, 4].

Androgen insensitivity syndrome (AIS) is an inherited condition and one of the most common causes of disorders of sex development (DSD) [1, 3, 6]. These are congenital conditions in which chromosomal, gonadal or anatomical sex development is atypical. The approximate incidence of CAIS is 1:20,000 [1]. Breast development occurs spontaneously, due to aromatization of testosterone to estrogen in adipose tissue. Also, the absence of testosterone receptors prevents the testosterone from suppressing breast development as occurs in biologic males. Sparse/null hair is due to lack of androgen action [1, 8]. As in the case of this patient, testosterone levels are increased in the biological male range without clinical signs of hyperandrogenism [2, 4]. Elevated AMH is responsible for uterine agenesis, cervix and upper and middle third of the vagina. They present with normal external genitalia with short vagina or blind vaginal pouch [1, 8].

In the past, prophylactic gonadectomy was recommended in all cases. According to current scientific evidence, gonadectomy is disputed due to the secondary effects of hormone deprivation [4, 7, 9]. Furthermore, the risk of malignancy of intra-abdominal gonads is low, less than 2% unlike the high risk of gonadoblastoma/dysgerminoma in gonadal dysgenesis [1, 9]. Since the risk increases with age, biopsy and eventual gonadectomy can wait until they reach the age of 30. Subsequently, hormone replacement therapy should be indicated [1, 4]. Currently, no written guidelines or evidence-based screening exists. Counseling and imaging follow up is recommended

annually [2, 7]. Shared decision-making is crucial, assessing the risks and benefits of expectant management versus surgery [3, 9].

The desire of neovagina depends on the adolescent's needs or preferences. Vaginal dilators are the first line treatment [1]. Reconstructive surgery can be considered in case of unsuccessful conservative treatment or upon the patient's request. Several vaginoplasty procedures are available and depend on the surgeon's choice and expertise, for instance the laparoscopic sigmoid vaginoplasty [5].

An adolescent with primary amenorrhea, who presents with tall stature, absence of pubic and axillary hair, and palpable inguinal hernia strongly suggests CAIS. A 46XY karyotype and testosterone in the typical biological male range differentiate it from Mayer-Rokitansky-Küster-Hauser syndrome [1, 4]. The definitive diagnosis is made by molecular studies of the AR gene, which also provides information on genetic counseling for the rest of the family [2, 5].

Summary

The management of CAIS should address functional, sexual and psychological aspects [1, 2]. These include monitoring puberty, counseling on the adolescent's reproductive future, explaining the available treatment options for creation of a functional vagina and discussing the need and timing for gonadectomy and subsequent hormonal replacement therapy [2, 3, 9]. An interdisciplinary and comprehensive approach is essential since this pathology affects sexual, menstrual, and reproductive function [1, 3].

Figure 1. Image of Pelvic MRI

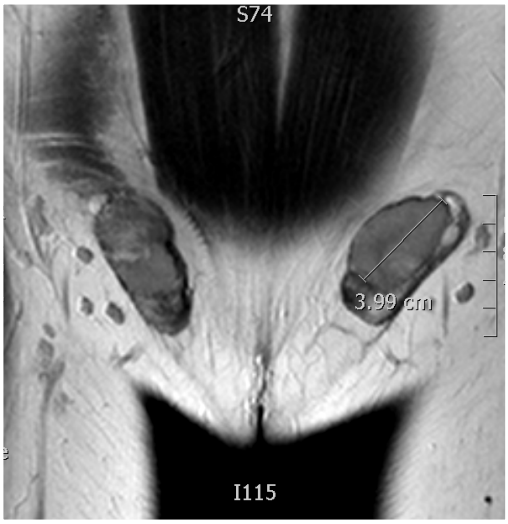
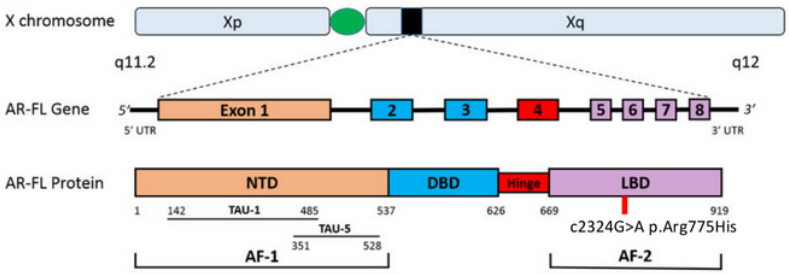


Figure 2. Genetic sequencing of *AR* gene



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