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Case Report Open Access

Two Clinical Cases and Some General Aspects of Complete Androgen Insensitivity Syndrome

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Introduction

The complete androgen insensitivity syndrome, formerly called testicular feminization syndrome [1], is a rare genetic disease in which an individual with a male XY karyotype expresses a female phenotype. They present apparently normal female external genitalia, although they have a blind vagina or short vagina with variable length, and they do not have uterus and fallopian tubes. There are testes in the abdomen or inguinal canal. Their function is normal, with testosterone secretion in normal amounts that is metabolized to estrogens and they are responsible for breast development.

Although the testes secrete androgens normally, there is no response to them in the organs due to an absence of androgen receptors in the cytoplasm of the target cells [2]. The mutation ranges from a deletion of the androgen receptor gene of the X chromosome to point mutations in the androgen binding domain or the DNA binding domain of the androgen receptor protein.

Leydig cells from the fetal testicles produce androgens that stimulate the mesonephric (or Wolf's) ducts to form the male genital ducts. Sertoli cells produce a hormone, the Müllerian Inhibitory Substance, which inhibits the formation of the paramesonephric or Müller ducts, which give rise to the fallopian tubes, uterus and upper third of the vagina. The lower two-thirds of the vagina and hymen originate in the urogenital sinus, The insensitivity to androgens together with the presence of the Müllerian Inhibitory Substance in these patients justifies its phenotype [3]. Makiyan proposes a new theory of uterovaginal embryogenesis [4]. In this new hypothesis the mesonephral ducts in female embryos form Fallopian tubes and vagina. The uterus derives in cross-section between mesonephral ducts with gonadal ridges. The paramesonephral ducts are absent.

Clinical Cases

We present the case of an 18-year-old patient (case A), who comes to our office for primary amenorrhea. As a family history of interest, she has two maternal aunts and a 16-year-old sister with primary amenorrhea. To the exploration, it is a woman of normal stature with mammary development and of external normal genitalia, although with little pubic hair (Tanner Stage 2), and a 2 cm blind vagina. In the ultrasound there is absence of uterus and ovarian tissue, with a bilateral nodule formation of 3 cm compatible with gonads.

She is referred in consultation to her 16-year-old sister (patient B), who has similar examination, except for a 5 cm vagina. A hormonal analysis and a karyotype of the sisters are requested, with the results shown in Table 1.

The karyotype was the same, 46XY, with R54OX mutation in hemizygous located at exon 5 of the gene of the androgen receptor of the X chromosome.

Table 1: Hormonal analysis and a karyotype of the sisters.

	Case A	Case B
FSH	5.21 mUI/ml	8.51 mUI/ml
LH	18.10 mUI/ml	28.09 mUI/ml
Testosterone	12.17 ng/ml	4.22 ng/ml
Estradiol	36 ng/ml	38 ng/ml
Karyotype	46XY	R54OX hemyzigous
Mutation	46XY	R54OX hemyzigous

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After these findings, the sisters were diagnosed with Androgenic Insensitivity Syndrome. Both were informed in detail and were offered surgical treatment, with gonadectomy, creation of a neovagina to patient A (using the laparoscopic technique of Vecchietti with REEMEX) and vaginal dilation to patient B. Both had good postoperative evolution.

The histopathological examination findings of the gonads were "testicles with dissociation of maturation (interstitial maturation with abundant Leydig cells and fetal-looking seminiferous tubes). Multiple Hamartomas of Sertoli-Leydig cells. A mytomatous hyperplasia of lower pole muscle of testicle". These histological findings are usually observed in androgen insensitivity syndromes in post-pubertal age.

Discussion

The complete androgen insensitivity syndrome is a disorder of sexual development. Disorders of sexual development are rare diseases due to chromosomal and gonadal alterations, with an incidence of 1 in 5500 live births [2,5,6]. Congenital Adrenal Hyperplasia is the most frequent of all [5]. Androgen Insensitivity Syndrome is a type of sexual developmental disorder that was described by Morris in 1953 as "testicular feminization syndrome" in a series of 82 cases of women with testicles [1]. Its prevalence is estimated at 1 of every 20000-60000 live births [2].

The Androgen Insensitivity Syndrome is inherited in a X-linked recessive pattern. It is caused by a mutation in the androgen receptor gene, located on the long arm of the X chromosome (Xq11.2-q12) [6]. It results in deficient action of androgens and therefore insufficient masculinization [5]. There are several forms of insensitivity to androgens [7]: Complete insensitivity (patients with normal female genitalia), partial insensitivity (patients with ambiguous external genitalia), and minimal insensitivity to androgens (men with normal male genitalia who are infertile habitually). More than 500 mutations of the androgen receptor gene have been described (from a complete deletion of the androgen receptor gene of the X chromosome to point mutations in the androgen binding domain or the DNA binding domain of the androgen receptor protein [2], indicating the great genetic heterogeneity of this syndrome [8]. Most of the mutations are situated in the conserved splice sites close to the exon-intron junctions [6]. An intronic mutation was identified in one study [9] and it severely disrupts the normal splicing through pseudo-exon activation, a mechanism that is increasingly being recognized as a cause of human disorders, but, in our knowledge, has not been earlier demonstrated in AIS. Currently, there are approximately 750 known AR mutations resulting in various diseases including complete androgen insensitivity syndrome, partial androgen insensitivity syndrome, minimal androgen insensitivity syndrome, and spinal and bulbar muscular atrophy (Kennedy's disease) [6].

Although testes secrete testosterone in a normal way, there is no response to them in the organs due to an absence of androgen receptors in the cytoplasm of the target cells. The receptor protein, encoded by an X chromosome gene, has the mission of forming a complex with testosterone and dihydrotestosterone. If this complex is not formed, the hormone cannot enter the nucleus and cannot stimulate the transcription of genes necessary for differentiation to target the male pathway [2].

Complete Insensitivity to Androgens is a severe dysfunction of the androgen receptor [10]. Its incidence is estimated at 1 in 2000 to 6,000 live births [11]. The diagnosis is usually made at puberty, although it can also be diagnosed in childhood, in the presence of bilateral inguinal hernia [12,13] or in adulthood due to infertility [5].

The most frequent reason for consultation of these patients is primary amenorrhea. Facing primary amenorrhea in a phenol typically normal adolescent, the fol-

Table 2: SEGO protocol. Primary and secondary amenorrhea. Infrequent bleeding.

	Mayer-rokitansky-küster-hauser syndrome	**Complete androgen insensitivity syndrome**	**Complete gonadal dysgenesis**
Phenotype	Female	Female	Female
Genotype	XX	XY	XY
Breast development	++	++	-
Pubis/axillary hair	++	-	+/-
Vagina	No/hypoplastic	Yes	Yes
Uterus	No/rudimentary	No	Hypoplastic
Gonads	Ovary	Testicle	Dysgenesis
Testosterone	Low	Male level	Low
LH	Normal	Normal	High
FSH	Normal	Normal	High
Estradiol	Normal	Low	Low
Inheritance pattern	Occasional	X-Linked recess	Genetic heterogeneity
Other anomalies	30% renal, 12% skeletal		

lowing diagnostic possibilities should be considered: Mayer-Rokitansky-Küster-Hauser syndrome, Complete Androgen Insensitivity Syndrome or Complete Gonadal Dysgenesis (Table 2). The high testosterone level in these patients with Androgen Insensitivity Syndrome serves as a substrate for the synthesis of estrogens and this is why they present a normal female phenotype [5]. However, male dysgenetic gonads tend to become malignant with age, so extirpation after puberty is recommended, once the secondary sexual characteristics have been developed, and to preserve the female sexual identity. The risk of malignancies before puberty is less than 0.8% [5]. After removal, patients should receive hormone replacement therapy until the age of menopause. Another aspect of the treatment is the creation of a neovagina in the case of a blind vagina or a short-length bottom of sac, in order to enable them to have sexual intercourse. The technique of Vecchietti by laparoscopy is a little aggressive technique. Continuous progressive pressure was exerted by an acrylic olive applied to the vaginal dimple, using the principles of Frank's dilator method. Two threads are attached to the olive, pass through the vesicorectal space, course subperitoneally and connect transabdominally to a traction device mounted on the abdominal wall. Constant traction is exercised on the olive from the traction device to produce 1-1.5 cm of invagination per day, creating a neovagina in 7-9 days [14].

We must not forget the psychological treatment. There is complete agreement between the female phenotype and the sexual identity of these patients [15-17]. It is not usually a problem to educate these girls because they live as women, and the diagnosis is usually not made until infancy (in the context of a bilateral inguinal hernia), adolescence (by amenorrhea), or in the Adulthood (as part of a sterility study). The allocation of sex is not a problem and the psychosexual development and sexual function of these patients are those of a normal woman (except for fertility) [3]. They are women from the medical, legal and social point of view [3]. However, making the diagnosis of complete insensitivity syndrome to androgens can have an important psychological impact on these girls because of the importance of sex in our identity [15]. The Money group [18] recommends communicating the diagnosis to the patient when he completes his studies in high school, although there are still cognitive limitations. However, other clinicians prefer to hide the diagnosis from the patient, and sometimes even the parents as well. The argument is to avoid psychological damage to a fragile patient [5]. Other authors argue that damage can be minimized if the diagnosis is communicated by a team of specialized psychologists [19]. The appropriate time to communicate the diagnosis seems to be that in which the girl has already acquired the capacity to tolerate ambiguity and uncertainty, and if possible when she is over 18-years-old [15]. Long-term studies show that a medical and psychological approach allows these patients an adequate psychosexual development [6].

Conclusions

The complete androgen insensitivity syndrome is a rare disease that is caused by a mutation in the androgen receptor gene of the X chromosome. There are more than 400 mutations described in this gene, which results in the expression of variable phenotypes. Appropriate treatment consists of post-pubertal gonadectomy due to the low risk of malignization that exists before puberty and to allow the correct development of secondary sexual characteristics. The need for neovagina will depend on the anatomical characteristics of each case. The Vecchietti technique by laparoscopy is the least aggressive from our point of view, and can be performed at the same time as the gonadectomy. After the same, the patient should receive hormone replacement therapy. It is very important to adequately inform these patients and if necessary through the help of a psychologist so that they can understand their illness without affecting their sexual identity.

References

1. Morris JM (1953) The syndrome of testicular feminization in male pseudohermaphrodites. Am J Obstet Gynecol 65: 1192-1211.
2. Nussbaum RL, McInnes RR, Willard HF (2008) Thompson and Thompson. Genética en Medicina. (7th edn), Elsevier, España.
3. Keith L Moore (2016) Embriología Clínica. (10th edn), Elsevier, España.
4. Makiyan Z (2016) New theory of uterovaginal embryogenesis. Organogenesis 12: 33-41.
5. Verim L (2014) Complete androgen insensitivity syndrome in three sisters. Int J Fertil Steril 7: 353-356.
6. Oakes MB, Eyvazzadeh AD, Quint E, et al. (2008) Complete androgen insensitivity syndrome--a review. J Pediatr Adolesc Gynecol 21: 305-310.
7. Sharma V, Singh R, Thangaraj K, et al. (2011) A novel Arg615Ser mutation of androgen receptor DNA-binding domain in three 46XY sisters with complete androgen insensitivity syndrome and bilateral inguinal hernia. Fertil Steril 95: 804.e19-804.e21.
8. Gottlieb B, Beitel LK, Nadarajah A, et al. (2012) The androgen receptor gene mutations database: 2012 update. Hum Mutat 33: 887-894.
9. Känsäkoski J, Jääskeläinen J, Jääskeläinen T, et al. (2016) Complete androgen insensitivity syndrome caused by a deep intronic pseudoexon-activating mutation in the androgen receptor gene. Sci Rep 6: 32819.
10. Wiener JS, Teague JL, Roth DR, et al. (1997) Molecular biology and function of the androgen receptor in genital development. J Urol 157: 1377-1386.

11. Quigley CA, De Bellis A, Marschke KB, et al. (1995) Androgen receptor defects: historical, clinical, and molecular perspectives. Endocr Rev 16: 271-321.

12. Ahmed SF, Cheng A, Dovey L, et al. (2000) Phenotypic features, androgen receptor binding, and mutational analysis in 278 clinical cases reported as androgen insensitivity syndrome. J Clin Endocrinol Metab 85: 658-665.

13. Burge DM, Sugarman IS (2002) Exclusion of androgen insensitivity syndrome in girls with inguinal hernias: current surgical practice. Pediatr Surg Int 18: 701-703.

14. Baptista E, Carvalho G, Nobre C, et al. (2016) Creation of a Neovagina by Laparoscopic Modified Vecchietti Technique: Anatomic and Functional Results. Rev Bras Ginecol Obstet 38: 456-464.

15. Berg JS, French SL, McCullough LB, et al. (2007) Ethical and legal implications of genetic testing in androgen insensitivity syndrome. J Pediatr 150: 434-438.

16. Deeb A, Mason C, Lee YS, et al. (2005) Correlation between genotype, phenotype and sex of rearing in 111 patients with partial androgen insensitivity syndrome. Clin Endocrinol (Oxf) 63: 56-62.

17. Hooper HT, Figueiredo BC, Pavan-Senn CC, et al. (2004) Concordance of phenotypic expression and gender identity in a large kindred with a mutation in the androgen receptor. Clin Genet 65: 183-190.

18. Money J (1994) Sex errors of the body and related síndromes: A guide to counseling children, adolescents, and their families. (2nd edn), PH Brookes Publishing Company, Baltimore.

19. Slijper FM, Drop SL, Molenaar JC, et al. (1998) Long-term psychological evaluation of intersex children. Arch Sex Behav 27: 125-144.