Management Quandary

Androgen Insensitivity Syndrome: An Update on the Management of Adolescents and Young People

Nicolas Mendoza MD, PhD *, Cristina Rodriguez-Alcalá MD, Miguel Angel Motos MD, PhD, Alberto Salamanca MD, PhD

Departamento de Ginecología, Obstetricia y Genética Facultad de Medicina, University of Granada, Granada, Spain

Key Words: Androgen insensitivity syndrome, Disorders sexual development, Androgen receptor, Gonadectomy, Sexual identity

Introduction

Androgen insensitivity syndrome (AIS; Online Mendelian Inheritance in Man 300068; ORPHA99429; International Classification of Diseases 10th Revision: E34.5) is an X-linked recessive genetic disease that is a result of mutations in the androgen receptor (*AR*) gene (Xq11-q12). AIS is characterized by the resistance of target tissues to androgens, is present in individuals with the 46,XY karyotype, and has a highly variable phenotype. AIS individuals usually develop as women from birth or childhood. At present, AIS is preferred to other terms used in the past (testicular feminization syndrome, Morris syndrome)[1] because the patients and their relatives are more comfortable with it and because it more accurately describes the disease's pathophysiology.[2]

The *AR* gene, located on the long arm of the X (Xq11-12) chromosome, encodes a protein with 3 major functional domains: an N-terminal domain, with a modulatory function, encoded by exon 1; a DNA-binding domain encoded by exons 2 and 3; and an androgen-binding domain encoded by 5 exons (4-8). The AR protein is included in class I steroid receptors. For a thorough review of the *AR* gene and receptor, consult Online Mendelian Inheritance in Man database.[3]

This update is provided because of the advances in the diagnosis, the new acceptance of indeterminate sex, and the controversy regarding the oncological risks of this syndrome, which influence the many decisions that are now made by adolescents and young adults.

Clinical Description and Prevalence

Depending on the severity of the disorder, AIS is divided into 3 groups: complete AIS (CAIS) (formerly Morris syndrome, testicular feminization syndrome), partial AIS (PAIS) (formerly Reifenstein syndrome), and mild AIS (MAIS). Although AIS is the most common form of disorders of sexual development (DSDs), it is a rare disease, and its prevalence is estimated to be 1 in 90,000-100,000 individuals. Data on the prevalence of CAIS indicate that 1 in 20,000-64,000 newborn male babies are affected, and the prevalence of MAIS or PAIS is unknown.[4] Orphanet's report from November 2011 estimated that the prevalence of AIS is 13 in 100,000 individuals, and the report from May 2014 did not present any information about the prevalence or the number of registered cases.[5]

CAIS individuals are raised as female because they have female external genitalia and the inability of their cells to respond to androgens. However, CAIS-affected individuals have testes that can be located in variable locations but are often found in the inguinal canals (Fig. 1). AIS is frequently diagnosed because of primary amenorrhea at adolescence and sometimes, but less frequently, in adult life because of infertility. A study suggests that the onset of puberty occurs at the same age as in normal women.[6]

CAIS individuals are raised as female and are frequently diagnosed because of primary amenorrhea or infertility. Amenorrhea has been described in women with normal or increased breast development, high stature, and female hair without baldness. Breast development occurs spontaneously at puberty and is maintained afterward by the aromatization of circulating androgens. Nevertheless, there is a lack of pubic and axillary hair, and these individuals have no facial acne because of their lack of androgen sensitivity. Imaging tests might show a short vagina, an absence of the uterus, or the presence of Müllerian or Wolffian duct remnants. The gonads are always testicles and can be found anywhere from the abdomen to the labium/scrotum but are most frequently found in the inguinal canals. Less commonly, signs of genital masculinization or the development of Wolffian or Müllerian ducts might be present.[3]

PAIS is less frequent than CAIS and has a highly variable clinical presentation from almost complete feminization to almost normal masculinization to individuals with overt sexual ambiguity. This variability reflects the different *AR* gene mutations. The trend in recent decades has been to grant a male designation at birth.[6] In individuals who are characterized as male, it is common to observe a micropenis, hypospadias, and cryptorchidism. During puberty,

The authors indicate no conflicts of interest.

* *Address correspondence to*: Nicolas Mendoza, MD, PhD, University of Granada, Obstetric and Gynecologic, Maestro Montero, 21 Granada, 18004, Spain; Phone +34653673769.

E-mail address: nicomendoza@telefonica.net (N. Mendoza).

1083-3188/$ - see front matter
http://dx.doi.org/10.1016/j.jpag.2016.08.013

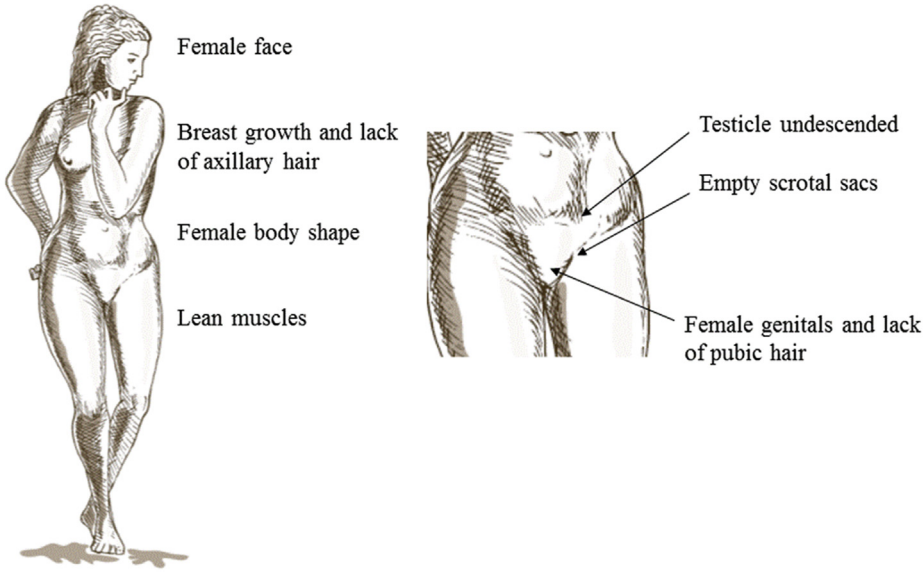

Fig. 1. Complete androgen insensitivity syndrome phenotype.

individuals with PAIS are eunuch-like and have gynecomastia. On the contrary, individuals with PAIS who are characterized as women have been observed to have clitoromegaly and fused labia during puberty.[6]

MAIS is manifested in men by normal or decreased virilization, some gynecomastia, and some spermatogenesis. Individuals with MAIS often develop normally throughout childhood and puberty. Furthermore, some plan to have a family, and others have children.[7]

Other Manifestations Associated With Alterations in the AR Gene

Extragenital manifestations, primarily of the neurological or endocrine type, are caused by polymorphisms or mutations of the *AR* gene. A rare X-linked neurodegenerative disease characterized by the loss of motor neurons, muscle weakness, atrophy, and twitching can appear within the third to fifth decades of life. Affected men can show other signs of partial insensitivity to androgens (gynecomastia, reduced fertility, and testicular atrophy).[8,9]

Associated Neoplasias

The most common tumors that affect type II germ cells include seminomas, dysgerminomas, and several types of nonseminomas and nondysgerminomas. Three studies have analyzed the relationship between the number of cytosine adenine guanine repetitions and testicular cancer.[10–12] Together, the results indicate that, when 17-25 repetitions are present, a greater frequency of nonseminomatous testicular tumors and a greater risk of metastasis exist. In another Italian study, <21 or >24 repetitions increased the risk of testicular cancer and metastasis.[13]

Although some studies have associated various mutations of the *AR* gene with prostatic and breast cancer risk or its severity, it is not proven that patients with CAIS, PAIS, and MAIS have an increased risk for prostate and breast cancer.[14–18]

Diagnosis

In adolescents and young people, the hormonal profile is similar for individuals with CAIS and PAIS: in PAIS, normal or slightly elevated testosterone and luteinizing hormone levels are detected, whereas in CAIS, elevated luteinizing hormone and androgen levels are found as a consequence of hypothalamic-pituitary insensitivity to androgens. Similarly, estrogen activity is increased, and aromatase activity is preserved, which is responsible for breast development. Anti-mullerian hormone level remains normal because the secretion and function of Sertoli cells is not affected. However, Müllerian remnants and an inadequate function of anti-mullerian hormone synthesis have been described for some cases of CAIS.[4]

Moreover, the karyotype is an essential diagnostic test to be performed in all cases of suspected AIS, although the diagnosis is confirmed with the determination of the molecular defect in the *AR* gene. However, recent findings of individuals with AIS without *AR* gene mutations have limited the universal validity of this claim. In a large study population of 59 patients with mutations in the *AR* gene that was performed in Spain, 46/59 (78%) of the affected individuals had a complete form of AIS and 13/59 (22%) had a partial form.[19]

The differential diagnosis with other DSDs is shown in Table 1.

Genotype-Phenotype Correlation

A relationship exists between genetic variables, gene functionality, and the development of external genitalia. However, it is currently not possible to establish a uniform genotype-phenotype correlation because of the existence of different types of mutations and mosaics, the role of coregulatory proteins, the coexistence of multiple mutations in the same individual, the presence of mutations in phenotypically normal individuals (or phenotypic abnormalities in