Androgen Insensitivity Syndrome

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Androgen insensitivity syndrome (AIS), also sometimes referred to as androgen resistance and formerly known as testicular feminization syndrome, is the biomedical name for a group of associated symptoms resulting from a cell's inability to respond to androgenic ("masculinizing") hormones. AIS, an X-linked genetic mutation, can occur regardless of a person's karyotype (chromosomal make-up), but it is only clinically significant in individuals with Y chromosomes due to its effects on the body's masculinization processes. Thus, a person with a 46,XX karyotype will likely not experience problems from AIS because it will not impair typical feminization processes. The vast majority of people diagnosed with AIS have a 46,XY karyotype. The incidence of AIS varies depending on the population as well as on its severity, but is thought to affect between 2 and 5 per 100,000 people with 46,XY karyotype (NCBI 2014).

HISTORY

Anecdotal evidence of AIS dates back over 200 years (Hughes and Deeb 2006) and includes speculation that women including Queen Elizabeth I of England and Joan of Arc were affected by the condition. John McClean Morris (1953) provided the first clinical descriptions of AIS in the mid-twentieth century after reviewing 82 cases of patients, and Lawson Wilkins (1950) demonstrated AIS's pathophysiology by giving a 46,XY female patient daily doses of testosterone to which her body failed to show any signs of virilization.

Morris (1953) first named the condition "testicular feminization syndrome" based on the observation that the testes were producing estrogen-like hormones that led to genital feminization. The condition was later renamed AIS because of the recognition of the body's resistance to androgens (Oakes et al. 2008).

TYPES

There are three categories of AIS, each determined by the level of genital masculinization. Complete Androgen Insensitivity Syndrome (CAIS) refers to the total inability of cells to respond to androgens. This non-responsiveness prevents masculinization of the body (i.e., development of a penis and scrotum in utero and secondary sex characteristics at puberty), leading to the development of a phenotypically female body, with external genitalia appearing typically female, as the androgens are aromatized into estrogen. Symptoms usually do not appear until puberty, and may include atrophied or herniated internal testes, infertility, and vaginal hypoplasia.

Partial Androgen Insensitivity Syndrome (PAIS) refers to a limited ability for cells to respond to androgens. The body's partial responsiveness to androgenic hormones impairs full masculinization of the body such that external genitalia are often ambiguous from partial masculinization. PAIS is often diagnosed at birth due to the appearance of ambiguous genitalia. Because of the body's ability to partially process androgens, phenotypes can range from slightly under-masculinized male to

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slightly over-masculinized female. Symptoms may include gynecomastia, underdeveloped prostate, micropenis, infertility, and feminized secondary sex characteristics in male phenotypes, and internal testes, labial fusion, and enlarged clitoris in female phenotypes.

Mild Androgen Insensitivity Syndrome (MAIS) refers to the least limited ability for cells to respond to androgens. People with MAIS have a typical male phenotype, as cells are able to process enough androgenic hormones such that genital development is unaffected. MAIS typically presents as mild impairment to spermatogenesis (the production of mature sperm cells). People with MAIS can also develop mild gynecomastia and slightly feminized secondary sex characteristics.

CLINICAL DIAGNOSIS AND MANAGEMENT

Diagnosis of AIS depends on which type of AIS is present, but generally diagnosis begins with an observation of atypical or impaired development, including ambiguous genitalia at birth, descending testes and the development of abdominal hernias in early childhood, or impaired spermatogenesis post-puberty. Diagnosis of AIS is sometimes confirmed through androgen receptor (AR) gene sequencing, though a mutation in this gene is not always present (Hughes and Deeb 2006).

Clinical management of patients with AIS also depends on which type of AIS is present. Typically it includes management of symptoms, but has also included sex/gender assignment, gonadectomy, and hormone therapy, among others. A joint consensus statement issued in 2006 by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology (Hughes et al. 2006) recommended the following guidelines for clinical management of intersex children, including children with AIS:

- sex/gender assignment in newborns be avoided before evaluation by an expert;
- evaluation and management occur at an institution with an interdisciplinary team experienced with intersex conditions;
- all children receive a sex/gender assignment;
- communication with patients and families be open and honest, and patients and families be included in decision-making;
- address patient and family concerns with respect and in strict confidence.

SEE ALSO: Biochemistry and Physiology; Intersex Movement; Intersexuality; Sex Versus Gender Categorization

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