Androgen Insensitivity Syndrome: Symptoms and Treatment

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Androgen insensitivity syndrome (AIS) is a condition in which there is partial (PAIS) or complete (CAIS) resistance to testosterone. As a result, individuals with this disorder are a genotypical male with XY karyotype, but without masculinization of external genitalia or virilization. This condition is believed to develop due to mutations in the androgen receptor gene.

Definition

One in 20,400 XY individuals is born with one of 300 mutations of the androgen receptor. The gene for the androgen receptor is located on the X chromosome and therefore follows an X-linked pattern of inheritance. Forty percent of patients with complete androgen insensitivity syndrome (AIS) have a de novo mutation. The majority of mutations result in single amino acid substitutions.

AIS is also known as androgen receptor deficiency, androgen resistance syndrome, and dihydrotestosterone receptor deficiency. The androgen receptor is activated by androgenic hormones including dehydroepiandrosterone (DHEA), testosterone, and dihydrotestosterone (DHT). These steroid sex hormones have anabolic effects on muscles and bones and stimulate sexual differentiation and spermatogenesis in males (see
Pathophysiology

AIS is an X-linked recessive condition that occurs due to a mutation in the androgen receptor (AR) gene. It is a loss of function mutation; although androgen synthesis is normal, typical post-receptor events mediating the hormonal effects on the tissues are absent (see image).

Based on the degree of androgen insensitivity, the sexual characteristics of affected individuals can vary from typically female to mostly male. At birth, feminized external genitalia are present. During puberty, the absence of secondary sexual characteristics becomes apparent, and infertility occurs in genotypical males.

**AIS can be classified into three types:**

1. Complete AIS (CAIS): Typical female external genitalia
2. Partial AIS (PAIS): Either female or male, or ambiguous, genitalia
3. Mild AIS (MAIS): Typical male external genitalia
Complete vs. Partial AIS

**CAIS** occurs in unambiguous XY females, who typically present with amenorrhea and infertility. CAIS is generally associated with a complete absence of androgen binding and androgen receptor activation.

**Partial AIS (PAIS)** is a male phenotype that presents with gynecomastia, hypospadias, and infertility.

Epidemiology

The incidence of CAIS incidence is approximately 2-5 per 100,000 genetic males. PAIS is less common, and MAIS is rare.

Clinical Presentation

In infancy, individuals with CAIS present with inguinal or labial swellings. In adolescence, individuals may present with primary amenorrhea, with age-appropriate breast development and a pubertal growth spurt.

Affected individuals have sparse or an absence of pubic and axillary hair. An absence of ovaries and fallopian tubes with a short vagina is an indication for karyotyping. The vagina always ends in a blind sac, as there is no uterus or fallopian tubes. Adult women with CAIS are taller than average.
Clinical presentation of the syndrome in individuals with PAIS depends on the response of external genitalia to androgens. **Features include hypospadias, micropenis, and bifid scrotum** that may or may not contain testes. Some individuals may have clitoromegaly.

MAIS is a rare condition. Clinically, it **presents as infertility in men with normal-appearing genitalia**. High-dose androgens are needed to restore fertility. Another possible manifestation in MAIS is spinal and bulbar muscular atrophy, also known as Kennedy’s disease.

These individuals may have **wasting of facial, bulbar, and limb muscles with elevated testosterone concentrations** and gynecomastia and diminished fertility.

**Diagnosis**

Antenatal ultrasonography can diagnose AIS incidentally. **Subsequent karyotype analysis, chorionic villi sampling, or amniotic fluid sampling can confirm the diagnosis**. Currently, no diagnostic criterion has been defined for the diagnosis of AIS. Extensive biochemical, molecular, and morphological variations are seen in individuals with this syndrome.

The diagnosis is based on:

- History
- Physical examination
- Laboratory testing
- Genetic analysis

Occasionally, the **sex of an individual may be determined based on the predominant phenotypical characteristics**.

**Laboratory testing includes:**

1. **Karyotype analysis**: Required to differentiate a masculinized female from an under-masculinized male.
2. **Fluorescent in situ hybridization**: Can confirm the presence of a Y chromosome.
3. **Testosterone levels**: If low, levels of dehydroepiandrosterone, androstenedione, and their precursors, 17-hydroxyprogrenolone and 17-hydroxyprogesterone, can be determined. Estimating the levels of these different hormones helps to determine other errors in the steroidogenesis pathway. An elevated testosterone-to-DHT ratio may indicate a 5-alpha-reductase deficiency, while low testosterone levels in the absence of defective steroidogenesis are suggestive of testicular dysgenesis or Leydig cell hypoplasia.
4. **Pelvic ultrasound**: If the uterus or fallopian tubes are identified, then the diagnosis of CAIS and PAIS should be reconsidered.
5. **Histopathology of testes**: Reveals the normal architecture of testes with markedly reduced spermatogonia and/or sperm in post-pubertal patients.

**Management**

Management depends on the severity of insensitivity, the patient’s phenotype, and gender identity. In general, gonadectomy is performed to eliminate the risk of tumors developing in the cryptorchid testis. Then, hormone replacement therapy is initiated and
plastic surgery is performed according to the gender with which the patient identifies. Psychological counseling and support are always required.

**CAIS:** Orchiectomy may be required either before or post-puberty to prevent testicular malignancies, although the risk of malignancy is low. Vaginal dilatation may be required to prevent dyspareunia.

**PAIS:** In individuals with predominant female genitalia, pre-pubertal orchiectomy may be required to avoid pubertal clitoromegaly. In individuals with ambiguous or predominantly male genitalia, sex may be assigned after expert evaluation. Individuals raised as males may require orchiopexy and hypospadias repair, while those raised as females may require post-pubertal orchiectomy with estrogen-androgen replacement therapy.

**MAIS:** Mammoplasty may be indicated for gynecomastia.

All individuals, whether they have CAIS, PAIS, or MAIS, should have calcium and vitamin D supplementation along with weight-bearing exercises for optimal bone health. Treatment with bisphosphonates may be necessary for those patients with diminished bone density or multiple fractures.

**Genetic Counselling**

*AIS is an X-linked disorder, and affected individuals are infertile.* A heterozygote female who is a carrier for an AR variant may have a 25% risk of delivering an affected XY baby, an XY normal baby, an XX carrier, or an XX normal baby (see image).
References


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