Androgen Insensitivity Syndrome (AIS) —
Symptoms and Treatment

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 and Synonyms

1:20,400 live-born XY individuals will have 1 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. 40% of patients with complete 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
- AR deficiency
- Dihydrotestosterone receptor deficiency
Androgen Insensitivity Syndrome: Complete vs. Partial

**Complete AIS (CAIS)** is unambiguous XY females who typically present with amenorrhea and infertility.

**Note:** CAIS is generally associated with complete absence of androgen binding and androgen receptor activation.

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

**Epidemiology of Androgen Insensitivity Syndrome**

CAIS (Complete Androgen Insensitivity Syndrome) incidence is approximately 2—5 people in a population of 100,000 of genetical males, while PAIS (Partial Androgen Insensitivity Syndrome) is less common and MAIS (Mild Androgen Insensitivity Syndrome) is rare.

**Pathophysiology of Androgen Insensitivity Syndrome**

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

Based on the degree of androgen insensitivity, the **sexual characteristics of affected individuals can vary from typically feminine to mainly male.** At birth, there is a feminization of external genitalia, the absence of secondary sexual characteristics at puberty, with infertility in a genotypical male. AIS can be classified into three types:

2. Partial androgen insensitivity syndrome (PAIS): either female or male or ambiguous genitalia.
Normal function of the androgen receptor. Testosterone (T) enters the cell and, if 5-alpha-reductase is present, is converted into dihydrotestosterone (DHT). Upon steroid binding, the androgen receptor (AR) undergoes a conformational change and releases heat shock proteins (hsps). Phosphorylation (P) occurs before and/or after steroid binding. The AR translocates to the nucleus where dimerization, DNA binding, and the recruitment of coactivators occur. Target genes are transcribed (mRNA) and translated into proteins.

Clinical Presentation of Androgen Insensitivity Syndrome

**CAIS:** In infancy, the presentation is inguinal or labial swellings. In adolescence, the patient may present with primary amenorrhea with age-appropriate breast development and 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 the absence of the uterus and fallopian tubes. Adult women with CAIS are taller than normal women without CAIS.

**PAIS:** Clinical presentation in these individuals depends on the response of external genitalia to androgens. **Features include hypospadias, micropenis, bifid scrotum** which may or may not contain testes. Some individuals may have clitoromegaly.

**MAIS:** This 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** with gynecomastia and diminished fertility.
Diagnosis of Androgen Insensitivity Syndrome

Due to antenatal ultrasonography, the condition may be diagnosed 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 AIS.

The diagnosis is based on:

- History
- Physical examination
- Laboratory testing
- Genetic analysis

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

**Laboratory testing includes:**

1. **Karyotype analysis:** Is required to differentiate a masculinized female from an under-masculinized male.
2. **Fluorescent in situ hybridization (FISH):** Can confirm the presence of a Y chromosome.
3. **Testosterone levels:** If low, levels of dehydroepiandrosterone (DHEA), androstenedione and their precursors, 17-hydroxypregnenolone and 17-hydroxyprogesterone can be determined. Estimation of levels of these different hormones helps to determine other errors in the steroidogenesis pathway. An elevated testosterone to DHT ratio may indicate 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:** Will reveal the normal architecture of testes with markedly reduced spermatogonia and/or sperm in post-pubertal patients.

Management of Androgen Insensitivity Syndrome

**Treatment**

**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 irrespective of 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 who have diminished bone density or multiple fractures.

<table>
<thead>
<tr>
<th>Gonadectomy</th>
<th>Undervirilized male phenotype</th>
<th>Plastic surgery</th>
<th>Psychological counseling and support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performed to eliminate the risk of tumors developing in the cryptorchid tests → then HRT is initiated depending on what gender the patient prefers.</td>
<td>For example, Reifenstein syndrome (PAIS) could benefit from high doses of DHT or testosterone.</td>
<td>It can correct gynecomastia, and if the patient wishes to identify as a female vaginal dilation with dilators or surgical is possible,</td>
<td></td>
</tr>
</tbody>
</table>

Genetic Counselling

AIS is an X-linked disorder with affected individuals being infertile. A heterozygote female who is a carrier for an AR variant may have a 25% risk of delivering an affected XY baby or an XY normal baby or an XX carrier or an XX normal baby.

References

