Disorders of Sexual Differentiation and Sex Development

The determination of a baby's sex begins at the chromosomal level with the insemination of the ovum. Further sexual differentiation follows during the subsequent embryogenesis. However, chromosomal anomalies, gene mutations, and other exogenous or endogenous factors can cause disorders of sexual differentiation. These disorders manifest during childhood or at the latest in puberty, making patients consult their doctor. Here, we offer you an overview of the most common syndromes resulting from disorders of sexual differentiation.

Turner Syndrome

A important disorder of genital development is the Turner Syndrome, which involves a chromosomal aberration. It is based on a monosomy of the sex chromosomes, i.e., the presence of only one chromosome X of the two sexual chromosome. This manifests as a 45 XO karyotype with female phenotype.

It is the only monosomy that is compatible with a relatively normal life. With an
incidence of 1:2500 – 7500 (of females born alive), it is the most common **gonadal chromosome anomaly** of females. The syndrome is associated with a **high rate of spontaneous abortion**.

The anomaly is based on the loss of one **sex chromosome** during **embryogenesis**, which can happen at different stages of development (**spermatogenesis** or **oogenesis, insemination**) and is due to a **nondisjunction** of the **chromosomes** or **chromatids**. In 70% of the cases, it is the **X chromosome** of the father.

A structurally altered **X chromosome** can also be the cause. Furthermore, there might be **chromosomal mosaicsm**s with inconspicuous or conspicuous cells (e.g., 46, XX / 45, X0), but these have a less pronounced clinical manifestation.

While the occurrence of Turner Syndrome does not correlate with the age of the mother, an older age of the father possibly plays a role for the development of the disease.

### Symptoms and Clinical Presentation of Turner Syndrome

Individuals with **Turner Syndrome** have both a female **phenotype** as well as a female **psychosexual identity**. Cardinal symptoms are **primary amenorrhea** and **short stature** (143 – 147 cm). Patients are **infertile** and have **sexual infantilism** (**hypoplastic female genitalia** due to the lack of hormonal stimulation). While the **gonads** initially develop normally, they start to **degenerate** and **fibrose** in the third month of pregnancy; from which moment on, the **ovaries** only exist as fibrous tissue, called **streak gonads**.

Other **facultative** symptoms are:

- Short neck
- Pterygium colli (webbed neck)
- Low hairline
- Lymphedema on the back of hand and feet (in first weeks of life)
- Cubitus valgus (X-shaped arms)
- Shield chest with widely spaced nipples and funnel chest
- Multiple (benign) pigment naevi
- Nail and ear dysplasia
- Malformations of the kidneys and urinary tracts
- Malformation of the skeleton (e.g., deformities of the spine) and anomalies of the ligaments
- Primary hypogonadism
- Short stature
- Osteoporosis
- Metabolic disorders (insulin resistance, diabetes mellitus, dyslipidemia)
- Cardiovascular anomalies (e.g., aortic coarctation, hypertension, vasculopathies, aortic stenosis, aortic isthmus stenosis, pulmonary vein anomalies)

These symptoms are not necessarily present all at once and may be more or less pronounced in different individuals. The intelligence of affected individuals is normal or can be seen generally reduced partially compromising skills such as mathematics and spatial visualization.

As mentioned above, patients with mosaicism show less pronounced physical abnormalities. Depending on the degree of ovary functionality, the development at puberty and even the possibility of a spontaneous pregnancy, which, however, occurs with an increase in the rates of abortion and congenital malformations of the child.

### Diagnosis and Differential Diagnosis of Turner Syndrome

**Amenorrhea** and the absence of puberty are usually the reasons why patients consult their doctor, in approximately 60 to 70% of cases, when the diagnosis is not made in prenatal or early postnatal life.

Because of the insufficiency of the ovaries, not enough estrogen is being produced, which makes the superior centers increase their hormone production. In an endocrinological examination, this results in increased levels of FSH and LH, and a diminished concentration of estrogen. Since this disorder occurs at the level of the gonads, it is also referred to as hypergonadotropic or primary hypogonadism.

The most suited method for making the diagnosis is a chromosome analysis which is performed on peripheral lymphocytes. With a karyogram, the karyotype of the examinee can be determined.
With regard to **differential diagnoses**, a tumorous condition (e.g., **gonadoblastoma**, **dysgerminoma**) has to be excluded.

**Treatment of Turner Syndrome**

**Turner Syndrome** cannot be cured since the defect is of molecular nature (missing chromosome). Therefore, treatment will always be **symptomatic**, trying to enhance the physical and psychological female traits.

With the onset of puberty (around age 12 – 13), **hormone replacement therapy** should be commenced. **Estrogen** stimulates the growth of **primary** and **secondary sexual characteristics** (vagina, uterus, breasts, pubic hair) and serves the **prevention** of **osteoporosis** and **arteriosclerosis**. **Estradiol valerate** (1 – 2 mg) is often prescribed in this context. **Gestagens** should be taken on at least 10 days of a month in order to ensure a proper **menstruation**. This transforms the **endometrium** instead of continuously stimulating it and thus prevents the development of **endometrial carcinoma**.

An early beginning of **growth hormone therapy (hGH)** can yield **final height increments** of up to 10 cm. For such a result, treatment has to start in early childhood (age 3 – 4).

The infertility of affected women with Turner’s syndrome is not reversible. However, they can be candidates for egg donation for those couples who wish to have children. The **legal status** of egg donation varies by country. While it is completely illegal in some countries (e.g., Germany), it is legal and egg donors can even be compensated in the U.S.

The **surgical** removal of bothering stigmata (e.g., webbed neck) is an option. Furthermore, **psychological** counseling can be very important to the affected patients.
Complications of Turner Syndrome

Women who suffer from Turner Syndrome have a higher tendency than the normal population to develop cardiovascular diseases, diabetes mellitus, thyroid disorders, and inflammatory diseases of the intestine.

The life expectancy of the affected individuals can be reduced by 13 years on average.

Adrenogenital Syndrome (AGS)

Definition, Epidemiology, and Etiology of Adrenogenital Syndrome

The adrenogenital syndrome (AGS) is the most common cause of feminine pseudohermaphroditism (chromosomal and gonadal female, male habitus). It comprises a group of diseases which stem from a genetic defect of enzymes of the cortisol synthesis in the adrenal cortex. The result of these enzymatic defects is an increased production of male sexual hormones (androgens) with virilization of the outer female genitals.

The autosomal recessive disease has an incidence of 1 : 5,000 to 1 : 15,000.

Classification of Adrenogenital Syndrome

Generally, every enzyme involved in cortisol synthesis can be affected by a defect. The clinical presentation varies depending on the affected enzyme. The following enzymes are most frequently affected:

- 21-hydroxylase
- 3-beta-hydroxysteroid-dehydrogenase
- 11-beta-hydroxylase

The damage of the enzyme may be complete or incomplete, which accordingly results in differently pronounced clinical manifestations (see below).

Since the 21-hydroxylase deficiency is with 95 % the most frequent cause, it will be the focus of the following discussion.

Pathophysiology of Adrenogenital Syndrome

Because of the 21-hydroxylase deficiency, cortisol is not produced at all or only in a very small amount. Since there is no negative feedback in the superior hormone control centers, this results in an increased release of ACTH from the hypophysis. This hormone stimulates the adrenal cortex to the point where it becomes hyperplastic (congenital adrenal hyperplasia, CAH).

This results in an increased production of androgens and an accumulation of intermediate products, which can again be utilized in further androgen synthesis.
Picture: “Post-mortem examination of a baby showing adrenal hyperplasia” by Patou Tantbirojn, Mana Taweevisit, Suchila Sritippayawan, Boonchai Uerpairojkit. License: CC BY 2.0

Picture: “Abdominal computed tomography scan before surgery showing the very enlarged and heterogeneous left adrenal gland (arrow) with soft tissue, fat and calcium attenuation” by Openi. License: CC BY 2.0

Picture: “Congenital adrenal hyperplasia” by StarBuG. License: CC BY-SA 3.0
Symptoms and Clinical Presentation of Adrenogenital Syndrome

In the following, the effects of the disease on the female patient will be described.

Patients have **karyotype 46, XX** and normally developed female inner genitals. However, there is **masculinization (virilization)** of the outer genitals, which can be manifested to varying degrees depending on time and severity of the excess **androgen production**. The manifestations reach from sole **hypertrophy** of the **clitoris** to fusion of the **labioscrotal folds** and the development of a male **urethra**.
The **time of manifestation** is also variable and can fall into the **fetal period**, **childhood**, or in or after **puberty**.

The classic childhood-onset **simple virilizing 21-hydroxylase deficiency** already manifests in the **prenatal** period as **virilization** of the female **fetuses**; at birth, the **outer genitalia** can be masculinized to varying degrees.

If the condition is left untreated, **pubic and axillary hair** will begin to grow already in
the second year of life. The affected children are also taller than other children of the same age. This, however, is reversed in adolescence and adulthood as the epiphyseal plates close prematurely and patients will be shorter than other adults. In addition to the male body hair (hirsutism), patients can experience a change of voice with more severe tones and because the patients do not present a classic female puberty, is therefore, suffer from amenorrhea and infertility.

The non-classic 21-hydroxylase deficiency (late-onset CAH) manifests later in life; at birth, the affected female babies appear inconspicuous. The onset of the disease during puberty is characterized by a mild form of virilization (possibly acne, hirsutism, and seborrhea). In addition, patients may experience menstrual disorders with prolonged menstrual cycles or amenorrhea.

In some cases, the synthesis of aldosterone may also be impaired, which can result in a salt-wasting crisis including dehydration, hyponatremia, hypokalemia, and acidosis. The affected infants are apathetic, develop severe vomiting, and need immediate treatment—if not, the condition can rapidly cause death.

Diagnosis and Differential Diagnosis of Adrenogenital Syndrome

A 21-hydroxylase deficiency can be confirmed by performing an ACTH stimulation test: First, the patient must fast for at least 6 hours, and the basal serum levels of 17-hydroxyprogesterone (17-OHP) and cortisol are measured. Then, ACTH is injected intravenously (250 mg). One hour after the ACTH injection, 17-OHP and cortisol are measured again. In healthy individuals, the difference between the first and the second measuring of 17-OHP should not exceed 2.5 ng/ml. Any increase higher than that is
diagnostic of **congenital adrenal hyperplasia (CAH)**.

## Treatment of Adrenogenital Syndrome

Treatment of **CAH** should start as early as possible in order to prevent any further **virilization** of the patient and to maintain a normalized **ovarian function**. Affected individuals will have to undergo life-long **glucocorticoid replacement** (e.g., with hydrocortisone or dexamethasone). This reduces the ACTH production and thus, the formation of androgens. The treatment has to be adjusted to each patient individually in order to avoid the occurrence of **Cushing's syndrome** or **growth failure**. With **sufficient** treatment, a normal female development can be achieved and even the **infertility** can be reversed so that a **pregnancy** becomes viable. Healthy offspring will however be carriers of **CAH**.

**NOTE**: Excess exposure to glucocorticoids can lead to Cushing’s Syndrome!

Patients with a salt-wasting form of CAH have to be administered mineralocorticoids (e.g., **fludrocortisone**), and the associated electrolyte imbalances have to be remedied.

## Prevention of Adrenogenital Syndrome

The disease is of **autosomal recessive** inheritance. This means that if a mother has had one child with **AGS**, there is a probability of **25 %** for the next child to also have **AGS**. Administration of **dexamethasone** (1 - 1.5 mg/d) during pregnancy can prevent the **virilization** of a diseased infant. If male genitalia are detected or **AGS** can be ruled out through **prenatal diagnostics** at a later point of the pregnancy, the administration of **dexamethasone** can be stopped.

## Androgen Insensitivity Syndrome (AIS)

The androgen insensitivity syndrome (AIS) is a form of **masculine “pseudohermaphroditism”** (genetic and gonadal male, female habitus). Due to a **receptor defect**, the affected individuals are **unresponsive to androgen** which results in the development of **female external genitalia**.
AIS stems from a **mutation** of the **androgen receptor gene**. This gene is located on the **X chromosome**, which gives the disease an **X-linked recessive** mode of inheritance.

The incidence of this condition is 1 : 20,000.

### Classification of Androgen Insensitivity Syndrome

Based on the phenotype, **AIS** is classed as either **complete androgen insensitivity syndrome (CAIS)** or as **partial androgen insensitivity syndrome (PAIS)**. The latter is indicated when the **androgen resistance** is only incomplete and the development of the external genitalia is highly **variable** (ambiguous, male, or female).
The following sections deals with complete androgen insensitivity syndrome.

**Symptoms and Clinical Presentation of Androgen Insensitivity Syndrome**

Affected individuals have karyotype 46, XY and male gonads (testes). The testes are located either within the abdomen, in the inguinal rings, or in the labia majora.

Due to a genetic defect of the testosterone receptors in the target tissues, the testosterone produced by the testes cannot be effective. This results in female external genitalia, which is why the affected individuals are raised as girls. In puberty, the condition becomes noticeable since there are no internal female sex organs (ovaries, fallopian tubes, uterus), which consequently leads to amenorrhea and infertility. The outer appearance of patients is characterized by a tall, slender stature. Breast development is not impaired. A further sign is absent secondary terminal hair (axillary and pubic hair). The vagina is often short and blind-ended.

**Diagnosis of Androgen Insensitivity Syndrome**

Patients will usually present because of absent menstruation. The suitable diagnostic method is a chromosome analysis, which can reveal the male genotype standing in contrast to the female habitus. Furthermore, testosterone levels will be in the normal male range, but estrogen levels will be too low for a woman.

**Treatment of Androgen Insensitivity Syndrome**

Patients usually identify as female. The diagnosis used to be hidden from the affected children, but current practice is the age-appropriate disclosure by the parents and psychological counseling. Patients are capable of cohabitation but remain infertile.

Standard of care is the post-pubertal surgical removal of the testes (orchidectomy) in order to prevent a malign degeneration, followed by hormone replacement therapy with estrogen and gestagen. Some patients with a short vagina or vaginal aplasia may also require surgical corrective treatment.

**Popular Exam Questions on Disorders of Sexual Differentiation and Sex Development**

Solutions can be found below the references.

1. Which symptom is not typical of Turner syndrome?
   A. Webbed neck
   B. Short stature
C. Streak gonads
D. Virilization of the genitals
E. Amenorrhea

2. Which statement about the adrenogenital syndrome is correct?
   A. 11-beta-hydroxylase is the most frequently affected enzyme.
   B. Hirsutism is one of the possible symptoms.
   C. Affected individuals are generally not able to become pregnant.
   D. Patients have karyotype 46, XY.
   E. AGS is the most frequent cause of masculine pseudohermaphroditism.

3. The androgen insensitivity syndrome...
   A. ... has an autosomal-recessive mode of inheritance.
   B. ... is associated with infertility.
   C. ... makes the affected individual incapable of cohabitation.
   D. ... is due to an estrogen resistance.
   E. ... results in male external genitalia.

References

**Correct answers:** 1D, 2B, 3B

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