Disorders of sexual differentiation and sexual maturation

Sexual development is a cascade of actions, which include gonadal determination, gonadal differentiation, development of the internal and external genitals, development of the male or female phenotype and secondary sexual characteristics in puberty. The superstructure is **psychosexual development**, which includes gender identity, gender role and sexual orientation.[1]

Disorders of sex development, (*DSD*) is a congenital condition with atypical chromosomes or with atypical somatic sexual development. [1] Individuals with sexual development disorders are more likely to have other congenital malformations.[2]

Sexual development

1. **Prenatal** sexual development: from an indifferent basis have developed a fetus and a newborn with specified sex;
   - controlled exclusively androgens – without androgens the female sex is developed, under the influence of androgens is developed the male sex → for boys are necessary the formation of testes, the ability to synthesize testicular androgens and the susceptibility of peripheral tissues to androgens;
2. **Postnatal** sexual maturation: takes place mainly during puberty;
   - girls are controlled by estrogens, boys by androgens. .[2]

🔎 *For more information see Puberty.*

Physiology of sexual development

- firstly *pronephros* (the common basis for gonad and kidney) and two nephritic outlets are developed - Wolff's and Müller's;
- the base for the kidney(*metanephros*) and the undifferentiated genital ridge (*mesonephros*) are gradually separated;
- gonadal determination is influenced by gene expression and transcription factors - some also affect the early development of other systems;
- **male sexual development**:
  - begins with the development of the gonad into testis - under the influence of transcription factors (SRY, SOX-9, SF-1, WT-1);
  - Leydig cells in embryonic / fetal testicular tissue synthesise testosterone;
  - testosterone stimulates the development of Wolff's ducts (male internal genitals) and affects the descent of the testes into the scrotum;
  - testosterone is metabolized in peripheral tissues to dihydrotestosterone (DHT) = the main active androgen required for the development of the male external genitals (first trimester of pregnancy);
  - sexual bump → penis; merging protrusions → scrotum; sex canal → urethra;
  - Sertoli cells in the testes produce antimüllerian hormone (AMH) during intrauterine development → inhibits Müllerian leads;
  - if **Sertoli cells are missing** → ↓AMH → the uterus, fallopian tubes and upper vagina are formed;
  - if **Leydig cells are missing** → ↓testosterone → external genitals are virilized insufficiently or not at all; the urethral orifice is hypospadic or the urethral orifice in the urogenital sinus;
  - if **the sensitivity of the tissues to androgens is completely impaired** (androgen receptor disorder) → the female external genitals develop (clitoris, labia, short blind-sheathed vagina);
  - if **the sensitivity of the tissues to androgens is only partially impaired** → the double genitals develop (mildest form: hypospadias).
- **female sexual development**:
  - does not require the presence of female gonads → it can also occur in genetically male individuals (in case of impaired testosterone production or case of complete insensitivity to testosterone, DHT and case of impaired AMH production). [2]

🔎 *For more information see Development of the urogenital system.*

Classification of sexual development disorders (DSD)

- 46, XY DSD: individuals with sexual development disorders, with male sex chromosomes and male gonads;
- 46, XX DSD: individuals with sexual development disorders, with female sex chromosomes and female gonads;
- ovotesticular DSD: individuals with sexual development disorders, with female and male sex chromosomes, and the presence of ovarian and testicular tissue;
- sex reversal: 46, XX testicular DSD or 46, XY complete gonadal dysgenesis.[1][2]

Chromosomal DSD

- 45,X0 (Turner´s syndrome and its variants)
- 47,XXY (Klinefelter´s syndrome and its variants)
- 45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)
- 46,XX/46,XY (chimeric, ovotesticular DSD)

46,XY DSD

1. Disorders of gonadal (testicular) development:
   - complete gonadal dysgenesis (Swyer's syndrome)
   - partial gonadal dysgenesis
   - gonadal regression
   - ovotesticular DSD
2. Disorders of androgen production or function::
   - androgen synthesis disorders (LH receptor mutations - hypoplasia / Leydig cell aplasia, Smith-Lemli-Opitz syndrome, StAR mutations, 17-hydroxysteroid dehydrogenase mutations, 5α-reductase deficiency,...))
   - androgen resistance - complete or (CAIS, PAIS)
   - disorders of anti-Mülleric hormone and its receptor (persistent Müller's duct syndrome)
   - isolated hypospadias, cryptorchidism,...

46,XX DSD

1. Disorders of gonadal (ovarian) development
   - ovotesticular DSD
   - testicular DSD (SRY+, duplicate SOX9)
   - gonadal dysgenesis
2. Androgens excess
   - fetal (lack of 21-hydroxylase, 11β-hydroxylase,...))
   - fetoplacental(aromatase deficiency, P450 reductase deficiency)
   - maternal (luteoma, exogenously)
3. other (cloacal anomalies, vaginal atresia, MURCS - Mülleric, renal, cervicothoracic abnormalities,...)..

Examination

- anamnesis (especially prenatal and perinatal period, family anamnesis);
- somatic examination - the appearance of the external genitals and the degree of sexual development;
- karyotype, or molecular genetic testing;
- USG of the abdomen and small pelvis, or MR;
- hormonal tests: testosterone, dihydrotestosterone, 17-OH progesterone, other adrenal steroids, estradiol, FSH, LH, prolactin, SHBG;
- hormonal stress tests: test with the administration of gonadotropin-releasing hormone GnRH, test with the administration of human chorionic gonadotropin hCG, event. ACTH stimulation or suppression test with dexamethasone;
- gonadal biopsy - gonadal dysgenesis, true hermaphroditism. [2]

Therapy

- replacement of sex hormones → induction of puberty, maintenance of feminization / virilization;
- enzyme defect with impaired adrenal steroidogenesis → targeted treatment with costacosteroids;
- tumors → oncological treatment;
- genital surgery: feminizing genitoplasty for girls with genital virilization; virilization is difficult;
- gender reassignment optimally up to 2 years of age, an adjustment in the register. [2]

46,XX DSD (female pseudohermaphroditism)

- The individual has karyotype **46XX**, normal ovaries, normal ovaries, developed Müllerian lead structures, and virilized external genitals;
- virilization can range from a simple enlargement of the clitoris through the fusion of the labia to the complete development of the external genitals, the phenotype depends on the time when androgens are increased in the circulation (excessive endogenous or maternal production, exogenous source).

According to Prader, the degree of virilization of the genitals is expressed from 1 (normal female genitals) to 5 (normal male genitals).

Virilization by fetal androgens

- Most often due to **congenital adrenal hyperplasia** with decreased production of *21-hydroxylase*, *11β-hydroxylase* or *3β-hydroxysteroid dehydrogenase* (recessively transmitted defects in cortisol synthesis);
- The level of cortisol is reduced, due to the feedback the level of ACTH increases also with androgens.

The most common is a 21-hydroxylase deficiency (insufficient cortisol production)

1. **Classical form**

    - cave: there is also a decrease in mineralocorticoids (mineral breakdown);
    - develops 5-15. day after birth;
    - clinical image: vomiting, failure to thrive, dehydration, metabolic breakdown
    - for girls with virilization, CAH usually does not escape from attention immediately after birth, for boys dg may be more difficult (risk of death due to metabolic disruption);
    - laboratory there is increased ACTH, *17α-hydroxyprogesterone* and other androgens, cortisol is low (+ hypoglycemia), in case of mineralocorticoid deficiency there is decreased aldosterone, increased renin, hyponatremia and hyperkalemia;
    - cave: diagnostics must be urgent if CAH is suspected.
2. **Non-classical form**
    - A milder variant of the enzymatic defect;
    - the neonatal genitals are not virilized;
    - manifestations of androgen excess: pubertas praecox, acne, hirsutism.

11β-hydroxylase deficiency

- It is manifested by masculinization of the newborn genitals of girls;
- mineral breakdown may also occur;
- some patients have hypertension.

3β-hydroxysteroid dehydrogenase deficiency

- Partial virilization of the genitals of a genetically female individual;
- may be a mineral breakdown;
- an increase of 17α-hydroxypregnenolone is typical;
- the partial form manifests as mild hyperandrogenism in adolescence.

The increase of fetal androgens may be due to fetal adrenal adenoma, nodular adrenal hyperplasia, or persistent fetal adrenal zone in premature infants.

Virilization by maternal androgens and iatrogenic causes

- May be caused by androgens produced by the mother's ovarian or adrenal tumors;
- iatrogenic impairment - exogenous cause;
- does not progress when removing the cause of virilization;
- a disorder of the conversion of androgens to estrogens (placental aromatase) causes manifestations of hyperandrogenism (acne, hirsutism) in the mother, virilization occurs in the female fetus.

46,XY DSD (male pseudohermaphroditism)

- Result of a disorder of normal sexual development of genetically male individuals with the **46XY** karyotype and male gonads;
- a wide range of anomalies from the complete female genitals to the male genitals with micropenis or perineal hypospadias;
- the disorder may be inhibitory (persistence of Müllerian leads to a disorder of factor formation inhibiting Müllerian lead development) or stimulatory (impaired testosterone or dihydrotestosterone synthesis), and may be a disorder of androgen sensitivity.

Disorders of testicular development

- Gonadal dysgenesis is associated with impaired genital development and impaired onset and course of puberty.

XY complete gonadal dysgenesis (Swyer's syndrome)

- Both gonads are striped without germinal structures;
- female phenotype, karyotype 46XY, spontaneous development does not occur;
- the disorder is diagnosed only in puberty.

Mixed gonadal dysgenesis

- On the one hand, intra-abdominal testis;
- on the other hand, a striped gonad with the presence of Müllerian outlet structures;
- varying degrees of masculinisation;
- karyotypes **45X0**, **46XY** and other variants of mosaicism with Y chromosome abnormalities.

Dysgenetic male pseudohermaphroditism

- A heterogeneous group with bilateral gonadal dysgenesis, persistent Müller duct, cryptorchidism and insufficient virilization;
- due to the risk of malignancy, we perform gonadectomy.

Disorders of androgen biosynthesis and metabolism

Leydig cell hypoplasia

- Disorder of testosterone production;
- female phenotype, Müllerian leads are not developed;
- Inhibitory mutations of the sixth transmembrane domain of LH receptor.

Congenital disorder of testosterone biosynthesis

- infraction of Wolf duct differentiation, incomplete virilization of the external genitals, Müller's leads are not formed;
- in the most severe disability, the individual has a female phenotype;
- enzyme defects often associated with adrenal steroid dysfunction (congenital lipoid adrenal hyperplasia);
- disorder of the production of all adrenal steroids;
- varying degrees of feminisation can be female phenotype and severe mineral breakdown:
  - I.*17α-hydroxylase* deficiency;
  - II. *3β-hydroxysteroid dehydrogenase* deficiency;
  - III. *17β-hydroxysteroid dehydrogenase* deficiency;
  - IV. *5α-reductase* deficiency.

Androgen insensitivity

1. **Complete androgen resistance** (testicular feminization) − female genitals with a short blind-ended vagina, pubic hair is rare or absent.
2. **Partial androgen resistance** − different degrees of virilization.

Ovotesticular DSD (hermaphroditism verus)

- Presence of **ovarian and testicular tissue** in an individual with zwitterionic genitals (various combinations of ovaries, testes, ovotestis);

Sex reversal

- **XX men** − a special group, no ambidextrous genitalia, gynecomastia, in puberty, partial deficiency in testosterone production and spermiogenesis.[3]

References

Related articles

- Testicular feminization
- Development of the genitourinary system • Endocrine diseases of the gonads • Psychophysiology of human sexuality • Gender identity disorders • Transsexuality
- Puberty • Pubertas praecox • Pubertas tarda

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