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Review Article

False Hermaphroditism

Bon L.I *., Maksimovich N.Ye., Varabyou H.Y., Kharyk A.A

Candidate of biological science, Assistant professor of pathophysiology department named D. A. Maslakov, Grodno State Medical University; Grodno State Medical University, 80 Gorky St,230009, Grodno, Belarus.

***Corresponding Author:** Bon L.I, Candidate of biological science, Assistant professor of pathophysiology department named D. A. Maslakov, Grodno State Medical University; Grodno State Medical University, 80 Gorky St,230009, Grodno, Belarus.

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Abstractss

This article examines the challenges associated with the condition known as false hermaphroditism, detailing its pathogenetic mechanisms and diagnostic complexities. It also addresses potential complications affecting various organ systems and the social difficulties faced by patients with these conditions.

Kew Words: false hermaphroditism; disorders of sex development; intersex conditions; androgen insensitivity syndrome; clinical manifestation, pathogenesis

Introduction

False hermaphroditism is a clinical term describing a condition where an individual exhibits a discrepancy between their internal gonads (testes or ovaries) and the development of external genitalia (phenotype) [1]. A key manifestation is genital ambiguity, where the structure of the genitalia is intermediate between typical male and female forms.

Two conditional forms of this condition are distinguished:

1. Male pseudohermaphroditism: Characterized by the presence of testes and a 46, XY karyotype; however, the external genitalia or secondary sexual characteristics display female-like traits [2]. 2. Female pseudohermaphroditism: In this form, ovaries and a 46, XX karyotype are present, but virilization (masculinization) of the external genitalia is observed [1, 2]. It is important to differentiate pseudohermaphroditism from true hermaphroditism—an extremely rare condition where an individual simultaneously possesses both ovarian and testicular gonadal tissue [1]. Both types of pseudohermaphroditism belong to the spectrum of intersex variations. This group encompasses various congenital conditions characterized by atypical, mixed combinations of male and female anatomical features [1]. Terms such as intersex, pseudohermaphroditism, hermaphroditism, sex reversal, and gender diagnostic designations are particularly controversial. Patients may perceive them as potentially derogatory, and for physicians and parents, they can be confusing. The term "Disorders of Sex Development" (DSD) is proposed for use, defined as congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical [3].

46, XX DSD

Female pseudohermaphroditism (46,XX DSD) develops due to: abnormalities in ovarian development (ovotesticular DSD, gonadal dysgenesis, testicular DSD); excessive androgens in the prenatal period, fetal (21-hydroxylase deficiency, 11-hydroxylase deficiency), fetoplacental (aromatase deficiency, cytochrome P450 oxidoreductase deficiency — POR), or maternal (luteoma, maternal androgen drug use) origin; as well as other developmental anomalies, such as cloacal exstrophy, vaginal atresia, or MURCS syndrome [4].

46, XX DSD Clinical Evaluation

Clinical signs that may suggest a disorder of sex development in a newborn include: isolated clitoral hypertrophy, isolated posterior hypospadias, bilateral cryptorchidism or testicular ectopia, as well as unilateral cryptorchidism or ectopia combined with hypospadias or micropenis [5, 6]. In adolescence, virilization of external genitalia, delayed puberty, or primary amenorrhea may be indicative. Clinical assessment involves a precise description of the genital tubercle size, the presence or absence of labial fusion, the number and location of orifices, and palpation of the gonads in the labial-scrotal region. Based on this data, the Prader scale [6,7] is used to objectively assess the degree of genital masculinization, encompassing five stages: I — clitoromegaly without labial fusion; II — clitoromegaly with partial fusion of the posterior labia without the formation of a urogenital sinus; III — marked clitoromegaly with near-complete fusion of the folds and a single urogenital orifice on the perineum; IV — formation of a penis, complete fusion of the folds, a urogenital sinus with an orifice at the base of the penis; V — a fully formed penis and scrotum-like folds without palpable gonads, with the urethra terminating distally [8].

Additionally, a quantitative index of external masculinization can be calculated by assigning points to the following parameters: penis/clitoris size (from 0 — micropenis to 3 — normal), degree of labial fusion (from 0 — absent to 3 — complete fusion), location of gonads (for each: 0 — abdominal or non-palpable, 1 — inguinal, 1.5 — labial-scrotal), and urethral meatus

location (0 — perineal, 1 — mid-shaft, 2 — distal, 3 — apical) [9]. Measuring blood pressure is an obligatory component of the examination, which is particularly significant for diagnosing certain forms of congenital adrenal hyperplasia. Following the clinical examination of the external genitalia, an essential step is instrumental visualization to assess internal structures: the urogenital sinus, Müllerian derivatives, gonads, adrenal glands, and in some cases, the urinary tract, due to their shared embryological origin [9,10].

The primary imaging method is ultrasound. However, its capabilities are limited in identifying dysgenetic or fibrous gonads, intra-abdominal testes, and the uterus in prepubertal patients – for the latter, re-evaluation with estrogenization may be required [9]. When ultrasound has low diagnostic value, particularly for assessing Müllerian derivatives, ectopic or dysgenetic gonads (though testes located outside the abdominal cavity are usually visualized satisfactorily), as well as associated congenital anomalies of the urinary system, magnetic resonance imaging (MRI) is recommended [10, 11].

The examination focuses on the pelvic region and perineum, extending to the abdominal cavity if assessment of the adrenal glands or tumor formations is necessary. Although genitography can be used to characterize internal reproductive pathways, it is often replaced by genitoscopy – an endoscopic method that provides direct visualization and precise determination of the anatomical relationships between the urogenital sinus, Müllerian structures, and the urethra [9]. Laparoscopy is indicated in cases requiring direct intraoperative revision of gonads for their visualization, biopsy, or removal of intra-abdominal masses [12].

46, XX DSD Metabolism

21-hydroxylase deficiency (caused by CYP21A2 mutation) leads to a metabolic block in aldosterone and cortisol synthesis, making it impossible to convert progesterone to deoxycorticosterone and 17-hydroxyprogesterone to 11-deoxycorticosterone, while the substrates are utilized for androgen synthesis [13, 14]. Cortisol synthesis deficiency results in ACTH stimulation. The enzyme *11β-hydroxylase* (encoded by CYP11B1, expressed in the fasciculata zone) is involved in the metabolism of deoxycortisol to cortisol. Deficiency of this enzyme leads to cortisol deficiency and, consequently, elevated ACTH levels without mineralocorticoid deficiency. This results in glandular hypertrophy, and the excessive diversion of unmetabolized substrate towards androgenic metabolism causes virilization in girls. The enzyme deficiency leads to the accumulation of 11-deoxycortisol and 11-deoxycorticosterone [13].

There are two isoforms of 3-βHSD (3-beta-hydroxysteroid dehydrogenase): type 1 and type 2, which differ by 23 amino acids. Type 1 is expressed in the liver, skin, placenta, or prostate gland, while type 2 is exclusively expressed in the adrenal glands and gonads. Moreover, 3-βHSD type 2 deficiency occurs in less than 0.5% of patients with congenital adrenal hyperplasia and is caused by impaired metabolism of Δ5-steroids into Δ4-steroids, affecting all three corticosteroid hormone lines, thus reducing the synthesis of mineralocorticoids, glucocorticoids, androgens [15].

Δ5-steroids (17-hydroxypregnenolone, DHEA, DHEAs) possess low androgenic activity, but their excessive accumulation leads to virilization of the external genitalia in patients with a 46, XX karyotype. *The protein ferrying POR* acts as an electron donor from NADPH to microsomal steroidogenic enzymes and influences the synthesis of glucocorticoids and sex hormones, affecting the action of enzymes encoded by CYP21A2, CYP17A1, or CYP19A1 [16]. Additionally, skeletal abnormalities may be observed due to insufficient interaction of POR with enzymes involved in sterol synthesis (CYP51A1, SQLE, CYP26A1, CYP26B1, CYP26C1). Thus, POR deficiency leads to impaired steroidogenesis (cortisol and sex hormones – causing DSD) and skeletal malformations, the phenotype of which resembles Antley-Bixler Syndrome. Glucocorticoid synthesis impairment is typically partial, with basal cortisol levels being normal but showing an anomalous response to stress, and elevated mineralocorticoid levels may also be observed, which are responsible for possible high blood pressure in these patients [17].

Glucocorticoid receptor deficiency is caused by loss-of-function mutations in the glucocorticoid receptor (NR3C1), leading to glucocorticoid resistance (elevated cortisol levels but no clinical signs of hyperfunction) and increased ACTH levels. This, in turn, stimulates the synthesis of adrenocortical hormones (aldosterone, cortisol, and androgens), manifesting clinically as hypertension, hypokalemia, virilization in females, and premature pubic hair and hirsutism [18].

Aromatase catalyzes the conversion of C19 androgens to C18 estrogens, playing a crucial role in the placenta and postnatally as a key enzyme in estrogen synthesis. Placental aromatase deficiency leads to elevated androgen levels, which return to the fetal circulation and cause virilization in patients with a 46, XX karyotype [18].

Consequences of 46, XX DSD

For 46, XX newborns with significant genital masculinization, sex determination initially evokes shock and doubt. In some cultures where males are traditionally preferred, such infants may be mistakenly assigned the male sex, and correcting this error later can be extremely difficult [19-21].

Considering data on the good adaptation of patients with 46, XX CAH raised as boys, as well as the risks of feminizing surgery for cosmetic and sexual function, some experts suggest intentionally raising such newborns as boys, despite the loss of fertility and the need for lifelong androgen therapy [22]. This approach is supported by the masculinizing influence of prenatal androgen excess on behavior and gender role preferences, which may lead to gender confusion and transgender identification [23-28]. However, the majority of adolescents and adults with 46, XX CAH raised as girls maintain a female gender identity; only 5.2% of 250 individuals reported serious issues in this area [29].

Atypical genital development is associated with severe psychosocial complications: the formation of awareness regarding the discrepancy between external appearance and registered sex, conflicting gender perception within the family environment, increased attention and stigmatization from society, and body image disturbance, which can be exacerbated by short stature, excessive body weight, and hirsutism [30]. The totality of these factors contributes to social self-isolation, avoidance of situations involving undressing (e.g., sports or medical examinations), and rejection of romantic and sexual relationships.

Adrenal neoplasms are detected in 1–4% of healthy men and women, and their incidence increases with age [31-32]. In the work by Jaresch et al., where computed tomography was used to examine adult DSD patients with CAH, a high frequency of benign adrenal tumors was noted, especially in the group receiving insufficient glucocorticoid therapy [33]. Adrenocortical carcinomas are rare in CAH patients; only one case in pediatric practice has been described in the literature [34-35]. Several adults with CAH developed massive adrenal myelolipomas, which required surgical removal to alleviate symptoms [36]. Children with CAH have a higher BMI than the control group due to increased fat mass [37]. Approximately half of pediatric patients are overweight, and 16% to 25% suffer from obesity [37-39]. Women with DSD secondary to CAH are often overweight [41-43], but in patients around 30 years old, fat mass was similar to that of the control group. Few of them had hypertension, cardiovascular disease, or diabetes. The most significant metabolic disturbance was a 20% prevalence of gestational diabetes, which is somewhat higher than the general population prevalence estimated at 7-10% but ranging from 1% to 25% [38].

Individuals with congenital adrenal hyperplasia (CAH) who did not receive intrauterine dexamethasone treatment may experience a reduction in working or short-term memory [44,45]. Furthermore, women with CAH show lower scores in tests of working memory, processing speed, digit span, and matrix reasoning compared to a control group [46]. Magnetic resonance imaging revealed structural changes in white matter, hippocampus,

thalamus, cerebellum, and brainstem; magnetic resonance spectroscopy also recorded a decrease in choline levels in the temporal lobe. Notably, these deviations were more pronounced in patients receiving higher doses of glucocorticoids [46].

46, XY DSD

Male pseudohermaphroditism (46,XY DSD) can be caused by the following main groups of reasons: disorders of testicular development (complete or partial gonadal dysgenesis, gonadal regression, ovotesticular DSD); defects in androgen synthesis or action, including enzymopathies (17-hydroxysteroid dehydrogenase deficiency, 5α-reductase deficiency), androgen insensitivity syndromes (complete — CAIS, partial — PAIS), LH receptor disorders (Leydig cell hypoplasia), as well as other anatomical anomalies such as severe hypospadias or cloacal exstrophy [4].

Androgen Insensitivity Syndrome (AIS), complete form (synonyms: Morris syndrome, testicular feminization syndrome, feminizing testes syndrome, male pseudohermaphroditism), is a genetic disorder characterized by a defect in the androgen receptor gene, located on the short arm of the X chromosome (Xq11-12) [47]. This condition is inherited in an X-linked recessive manner and often has a family history [48-49].

The pathogenesis of conditions caused by impaired androgen receptor function is linked to the absence or varying degrees of reduced sensitivity to male sex hormones secreted during the pre- and postnatal periods [50]. Gonadal differentiation proceeds along the male type, but the defect in androgen function implementation causes impaired masculinization and development of the genitalia along the male type. Concurrently, the function of anti-Müllerian hormone is not disrupted; its intrauterine secretion by Sertoli cells leads to the regression of Müllerian ducts (absence of their derivatives – uterus, fallopian tubes). At the same time, estrogens are still secreted by the adrenal glands and partially by the gonads, and due to this influence, a fetus of genetic and gonadal male sex develops a female phenotype [51]. Depending on the degree of androgen resistance, various clinical and morphological manifestations are observed with a 46, XY karyotype: a male phenotype with impaired spermatogenesis and infertility (in adulthood), a male phenotype with isolated micropenis or penoscrotal hypospadias, a female phenotype with partial labial fusion, clitoral hypertrophy and gynecomastia, or a typical female phenotype [52].

Numerous genetic studies have shown that various mutations in the androgen receptor gene AR/HUMARA are the cause of androgen insensitivity (resistance). The probands' mothers are carriers of the mutation in approximately 70% of all cases [53-57]; the remaining 30% of cases consist of de novo germinative mutations, as well as postzygotic mutations, which can lead to somatic mosaicism in patients with androgen insensitivity [58]. Furthermore, it has been noted that a condition similar to incomplete androgen insensitivity can be caused by mutations in the SF-1 (steroidogenic factor-1) gene [59].

Clinical Presentation of 46, XY DSD

Complete Androgen Insensitivity: Due to insensitivity to dihydrotestosterone, female external genitalia develop. In puberty, primary amenorrhea is observed, as the uterus and ovaries are absent. A characteristic diagnostic sign is sparse or complete absence of pubic and axillary hair (the so-called "smooth skin syndrome"), as androgens are responsible for hair growth in these areas. Breast development proceeds normally, explained by the normal estrogen levels formed by aromatization of testosterone. In the postpubertal period, individuals with the complete form of androgen insensitivity syndrome exhibit normal male testosterone levels, higher estrogen and luteinizing hormone (LH) levels, and normal or slightly elevated follicle-stimulating hormone (FSH) levels [60].

Women with the complete form of androgen insensitivity syndrome are typically tall and physically developed. The increased prevalence of this condition among female athletes who have achieved notable sporting success supports the notion that women with complete androgen insensitivity syndrome possess certain physiological advantages over their competitors. Currently, their participation in competitions is regulated by the rules of international sports federations (e.g., World Athletics), which set limits on testosterone levels for specific events, sparking widespread discussion in sports medicine and ethics [60].

Incomplete Androgen Insensitivity. In patients with the incomplete form of androgen insensitivity, reactivity of the body to androgens is partially preserved. Therefore, signs of masculinization are noticeable in the structure of the external genitalia: a hypertrophied clitoris, a funnel-shaped vaginal vestibule, and often vaginal aplasia [61]. The symptoms of the incomplete form of androgen insensitivity syndrome vary widely, which is likely why it has numerous historical names: incomplete AR deficiency, incomplete masculinization syndrome, male pseudohermaphroditism, Reifenstein syndrome, Gilbert-Dreyfus syndrome, and others. However, these do not represent distinct entities and should be considered as different phenotypic variants of the incomplete form of testicular feminization (partial androgen insensitivity). The phenotypic variant where the structure of the external genitalia is close to normal male development is described as Reifenstein syndrome [62].

Unlike the complete form, incomplete androgen insensitivity is typically diagnosed at an early stage of life due to an intermediate phenotype combining masculine and feminine features. In cases of significant pathology, the sex is determined as female; however, clitoromegaly and partial labial fusion are noted, and progressive masculinization may occur during puberty. A urogenital sinus and labial-scrotal fusion may be observed [60]. In cases of less pronounced pathology, such as Reifenstein syndrome, the patient's phenotype exhibits more masculine traits, with male external genitalia potentially presenting with perineoscrotal hypospadias; a small penis may be accompanied by cryptorchidism or testicular location in the inguinal region, and a split scrotum. Typically, gynecomastia develops during puberty. In mild forms of androgen insensitivity, the patient may exhibit all signs of the male sex but be infertile, with isolated hypospadias being the only noticeable sign [60].

46, XY DSD Metabolism

Androgen insensitivity syndrome is the most common cause of sex development disorders in individuals with a 46, XY karyotype. It arises from alterations in the androgen receptor gene, leading to a state of hormonal resistance and can manifest clinically in three phenotypes: complete (CAIS), partial (PAIS), or mild (MAIS) [63].

Type 2 5α-reductase deficiency impairs the conversion of testosterone (T) to its more active metabolite, dihydrotestosterone (DHT), which is essential for the normal development of the external genitalia, urethra, and prostate in the male fetus, whereas testosterone plays the primary role in Wolffian duct virilization. Although testosterone and DHT have specific roles in the process of sex differentiation, their actions are mediated by the same androgen receptor (AR) [64]. The diagnosis of 5α-reductase deficiency is suspected in a newborn with ambiguous genitalia characterized by penoscrotal hypospadias. In fact, the degree of undervirilization of the genitalia in patients with 5α-reductase deficiency has been reported to be highly variable [65-71]. This variability may be attributed to residual enzyme activity, genetic background, or the action of type 1 5α-reductase.

46, XY DSD Consequences

Histological examination of gonadal biopsies from patients with androgen resistance reveals atrophy and hyalinization of the seminiferous tubules, interstitial fibrosis with Leydig cell hyperplasia, indicating tubular damage in the postpubertal period. Furthermore, impaired differentiation and development of male germ cells and a block (arrest) of spermatogenesis are found in the convoluted seminiferous tubules [72]. In most patients with Reifenstein syndrome, impaired sensitivity to sex hormones leads to secretory azoospermia, therefore, male infertility is usually their sole complaint [73].

Androgen insensitivity syndrome often correlates with the occurrence of inguinal hernias, which is a typical diagnostic sign in girls when the process

is bilateral. Disruption of the negative feedback mechanism leads to excessive LH secretion, provoking Leydig cell hyperplasia and the formation of Pick's adenomas. Due to the high risk of malignancy in non-functional gonads in the complete form of the syndrome, bilateral laparoscopic gonadectomy is the standard treatment. The intervention is recommended to be performed after the completion of puberty, once breast development is complete and bone growth has ceased [60]. In a study by S. Steinmacher et al., 27 out of 35 patients with XY-DSD underwent gonadectomy, including 10 at the authors' clinic. In 4 of these 10 patients (40%), histological analysis revealed tumors: a seminoma was found in a 23-year-old patient with 5α-reductase deficiency; a seminoma and a Leydig cell tumor were found in a 40-year-old patient with complete androgen insensitivity (cAIS); and bilateral and unilateral Sertoli cell adenomas were found in a 19-year-old and a 20-year-old patient with cAIS, respectively. The average age of patients with tumors was 25.5 years compared to 14.5 years in the operated group, indicating an increased risk after puberty [74].

Conclusion

Summarizing the above, it should be emphasized that false hermaphroditism is a heterogeneous condition requiring thorough genetic investigation. The main trend in managing such patients today is to avoid hasty feminizing or masculinizing surgeries in favor of a watchful waiting approach and careful hormonal monitoring. The prospects for further research lie in studying the long-term quality of life of patients and improving methods of bioethical support for families. Only comprehensive diagnostics and cautious surgical tactics can ensure patients with disorders of sex development achieve full personal and social realization.

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