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Case Report

The Jacobs Syndrome: Clinical Case

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Abstract

This work describes a clinical case of a violation of sex formation in a newborn child with Y-chromosome dysomy. The diagnostic challenges related to Y-chromosome variability and associated anomalies in sex development are being considered. The work presents clinical and laboratory data for Y-chromosome dysomy. It is noted that the challenge in diagnosing disorders of sex development is associated with the polymorphic clinical manifestations of this syndrome. It is noted that the presence of Y-chromosome dysomy is one of the most common chromosomal abnormalities, ranking third after Down syndrome and Klinefelter syndrome. It is often found that this pathology results in anomalies in genital development. A Y-chromosome polysomy is associated with variable phenotypic manifestations in gonadal development disorders.

Keywords

The violation of sex formation; an Jacobs syndrome; the Y-dysomy

1. The Relevance

The violation of sex formation (VSF) is currently occurring with a frequency of 1 case per 4,500 live-born newborns. The most common cause of this pathology is congenital adrenal dysfunction. The second most common cause (VSF) is mixed gonadal dysgenesis. According to some data [1], VSF is detected in 50% of children with hypospadias and unilateral or bilateral cryptorchidism [2]. Only 20% of children with VSF are determined to have a genetic defect. Most newborns with VSF with chromosomes 46,XX and signs of virilization have congenital hyperplasia of the adrenal cortex. Only half of the children with VSF and a set of chromosomes 46,XY are finally diagnosed [1-4]. The problem of determining gender is relevant for forming psychological gender and further socialization.

2. Introduction

Modern ideas regarding sex development are founded on an understanding of the mechanisms of embryonic development. Initially, the formation of sex is determined at the time of fertilization and is associated with a set of sex chromosomes in the zygote (genetic sex). Genetic sex determines the formation of male or female glands (gonadal sex). The gonadal sex determines the formation of the genital ducts and external genitalia according to the male or female type (phenotypic sex). It is known that initially, the fetus has male (Wolf's) and female (Muller's) rudiments of the genital tract, and their differentiation begins only at 6-7 weeks of pregnancy [1]. Without specific influences, the body develops along the female path. This specific factor is the SRY gene, located on the short arm of the Y chromosome, and encodes a protein that activates gonad differentiation into the testicle. Hormones regulating the development of the male sex are testosterone (accelerates the growth of the wolf ducts) and anti-muller hormone (regression factor of the Muller ducts); in its absence, the uterus, fallopian tubes, and the upper part of the vagina are formed from the Muller ducts). The absence of the effects of testosterone and anti-Muller hormone leads to the involution of the wolf ducts and differentiation of the Muller ducts into the female internal genitalia [1].

The 47,XYY karyotype was first described in 1961 by the American internist and cytogeneticist Avery Sandberg with Koepf, Ishihara, and Hauschka at Roswell Park Memorial Institute in Buffalo, New York [3, 5]. In 1965, Patricia Jacobs, a British geneticist, described it in detail, going deeper into the study of this chromosome aneuploidy [2-4].

The initial researchers of the disease identified carriers of the syndrome among male prisoners and individuals treated in psychiatric clinics. This situation contributed to a stereotype linking the syndrome with criminal behavior within this patient category. However, more recent studies showed that the vast majority of carriers of the syndrome have never committed crimes or suffered from a mental illness. However, they may have an increased risk of learning difficulties [2, 6, 7].

Sexual differentiation can be disrupted at any stage and be associated with chromosomal abnormalities, mosaicism, and point mutations. This section only discusses genetics.

3. The Clinical Case

The child, at the age of 4 days, was sent from the maternity hospital to the neonatal pathology department of the Irkutsk City Children's Ivano-Matreninsky Hospital with signs of a violation of the formation of external genitalia.

The authors received the written consent of the patient's legal representative for the analysis and publication of medical data.

The local ethics committee approved the research protocol. The approval and procedure for the protocol were obtained according to the principles of the Helsinki Convention.

3.1 From Anamnesis

A child was delivered urgently during the mother's second pregnancy at 40-41 weeks of gestation. The mother was diagnosed with Rh-negative blood type without any antibody titer during pregnancy. In this regard, the mother received immunoglobulin. During the first trimester of pregnancy, anemia of the first degree of severity was detected, and iron supplements were prescribed. At the 13th week of ultrasound screening, an increase in the nuchal translucency (NT) thickness was noted in the fetus. Childbirth proceeded with complications: rupture of the posterior adhesions (due to a large fetus), necessitating suturing. The child screamed immediately. The Apgar score is 8-9 points. The baby is attached to the breast in the delivery room—birth weight 4000 g, length 53 cm, head circumference 35 cm, chest circumference 34 cm.

Immediately after birth, it was observed that the child's external genitalia were formed in an atypical manner: there was hypertrophy of the clitoris and "scrotum-like" labia majora. An ultrasound examination (ultrasound) of the abdominal cavity and pelvic organs was performed. It is noted that the uterus is rudimentary, and while the left ovary is visualized, the right one is not observed. There is a right kidney pyeloectasia (the expansion of the kidney pelvis associated with minor calyces).

From the 2nd day, jaundice increased to the 3rd degree, according to Kramer, with regression against the background of phototherapy. Electrolyte disturbances in the form of hyperkalemia and hypocalcemia were observed. Consequently, correction of these electrolyte imbalances was carried out. Congenital adrenogenital syndrome is suspected.

The child's mother is 28 years old and an economist by profession. She denies smoking and somatically considers herself healthy. According to laboratory tests, the mother is HIV-negative, and the lung fluorogram is normal. The child's father is 33 years old and an engineer by profession. Smokes, somatically considers himself healthy, HIV-negative, lung fluorogram is normal. The parents' first child is a full–term healthy girl. At the moment, she is 3.5 years old. When analyzing the genealogical history, it was found that heredity was not burdened.

3.2 Objectively

Upon examination of the child, it was noted that the external genitalia developed abnormally, with labia resembling the scrotum in size and appearance. The clitoris demonstrates enlargement, measuring up to 2 cm in length; the vestibule of the vagina is evident, and the external opening of the urethra is observed. Upon probing the opening of the urethra, a small amount of urine was obtained. Below the external opening of the urethra, very close to it, the entrance to the vagina is indistinctly visualized. A probing examination was conducted, revealing a vaginal length of approximately 2 cm, with no leakage of urine. The entrance is narrowed. There is no pigmentation of the skin of the external genitals. There is no discharge.

Upon admission to the Department of Pathology of Biology, material was immediately collected from the newborn for cytogenetic analysis using karyotyping and fluorescence in situ hybridization

(FISH). Both FISH and karyotyping methods were utilized for the study. Cytogenetic analysis was conducted on preparations of metaphase chromosomes using differential staining techniques by length (GTG and CBG staining). The drugs were obtained by culturing peripheral blood lymphocytes in vitro according to standard methods [8]. Cells were cultured in PB-MAX or RPMI-1640(T) nutrient medium. Computer image analysis was performed at 1150× magnification using a light microscope. Conclusion: 47,XYY. Abnormal male karyotype (Figure 1). Y-chromosome disomy. Heterochromatin regions of chromosomes are within the normal range. No clones of cells with different chromosomal sets were detected within the tissue.

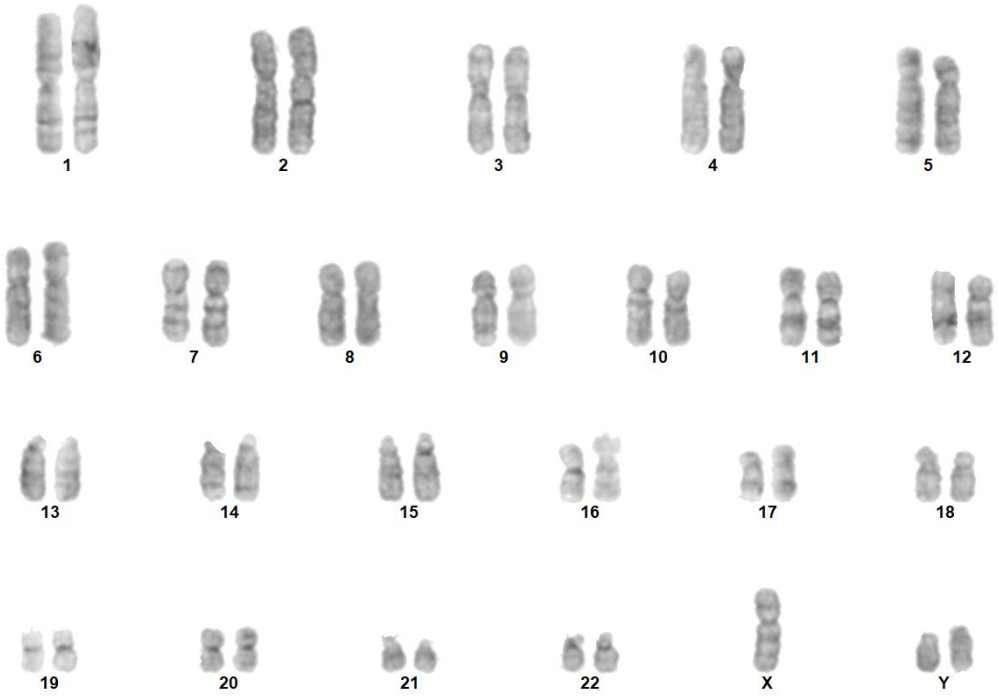

Figure 1 Karyotype: 47,XYY. Abnormal unbalanced male karyotype – disomy of chromosome Y. Material studied: lymphocyte culture.

DNA diagnostics (polymerase chain reaction method) of Y-chromosome genes detected the AZF locus and the SRY gene. Microdeletions in the AZF locus were not detected.

A second-look transabdominal ultrasound examination of the uterus and appendages revealed a visualized uterine rudiment measuring 2.4 cm in length and 0.65 cm in anteroposterior size. The ovaries were not visualized.

The consultation of the endocrinologist confirmed the violation of the formation of sex. The diagnosis of "congenital dysfunction of the adrenal cortex," namely the StAR-protein defect, is doubtful because there is no adrenal insufficiency but an abnormal karyotype. Planned follow-up examination for the levels of FSH (follicle-stimulating hormone), LH (luteinizing hormone), AMH (anti-muller hormone), inhibin B, a test with chorionic gonadotropin, followed by testosterone examination, MRI (magnetic resonance imaging) of the pelvis, diagnostic laparoscopy is recommended.

The laboratory studies of hormonal status showed: cortisol – 75 nmol/l (lower limit of normal), cortisol – 271 nmol/L (normal), testosterone – 1.6 nmol/L (reduced), 17-OH progesterone – 14.8 nmol/L (increased), 17-OH progesterone – 20.73 nmol/l (elevated), anti–muller hormone - 14.85 ng/ml (slightly below normal), LH – 6.31 mMEd/ml (normal), FSH – 24.14 mMEd/ml (significantly above normal), renin – 13.4 mmed/ml (normal), ACTH – 32.5 pg/ml (above normal), testosterone after a test with chorionic gonadotropin: after 24 hours – 10.7 nmol/l, after 48 hours – 10.8 nmol/l, inhibin B – 104.8 pg/ml (increased).

The MRI of the pelvic organs with contrast revealed the absence of testicles in the bifurcated scrotum. In the pelvic cavity, the testicles are also not visualized, but symmetrical cavernous bodies are revealed. Below the base of the cavernous bodies are symmetrically two oval formations with approximate dimensions of 8 × 11 × 7 mm each, which, according to the signal characteristics of similar cavernous bodies, is a split bulb of a spongy body. Conclusion: MR-signs of gonadal agenesis.

Ultrasound of the abdominal cavity and urinary tract showed minor pyelectasia on the right.

A medical consultation was held. Conclusion: Violation of the formation of sex. Gonadal dysgenesis syndrome. Chromosomal pathology: abnormal male karyotype – Y-dysomy syndrome. Considering clinical, instrumental, and laboratory parameters, the chromosomal sex is abnormal, the gonadal sex is unspecified (as no gonads were identified), the internal genital structure conforms to the female type (uterus, vagina), and the phenotypic structure of the external genitalia of the child remains unspecified.

4. The Discussion of the Results

The violation of sex formation is a serious violation of the development of the body. In the above clinical case, differential diagnosis is difficult. The child has an abnormal male karyotype 47,XYY, which causes the development of Jacobs syndrome (Jacobs syndrome, “Superman” syndrome); however, making a final diagnosis is difficult because there is a violation of intersex sex formation and minor electrolyte changes in the early neonatal period.

It is theorized that the presence of the second Y chromosome arises from nondisjunction in meiosis II following normal meiosis [3]. According to several authors, the incidence of Jacobs syndrome is about 0.1% of the male population [7], or with a frequency of 1-1.5 per 1000 newborns [8]. According to some data, Y-chromosome dysomy is one of humans’ most frequent chromosomal and gonosomal mutations, ranking third after Down and Klinefelter syndrome [9]. Often, due to the absence of pronounced gender disorders, he remains undiagnosed. The main manifestations of the syndrome are high growth, intellectual development is normal or reduced, learning problems (especially reading and writing), an increased risk of ADHD (attention deficit hyperactivity disorder), autism spectrum disorders, and a tendency to develop asthma and epilepsy [7].

Data from the literature indicate the examination of 4424 male children presenting with mental retardation, delayed speech and psychomotor development, congenital malformations, and/or minor developmental anomalies [8]. At the same time, regular and mosaic forms of Y-chromosome dysomy syndrome were found in 23 patients (frequency 0.52%). The average age of children from the cohort with syndrome 47,XYY was 6 years 6 months (from 9 months to 14 years). Every child with Y chromosome dysomy had genital abnormalities, such as disorders of sexual development, genital dysplasia, hypogonadism, cryptorchidism, scrotal hypoplasia, hypospadias, genital anomalies, gynecomastia [8].

It is known that with an increase in the number of chromosomes, including Y-chromosome polysomies, more pronounced phenotypic anomalies are noted, including dental anomalies, cryptorchidism, and hypogonadism [9].

The mutations of sex chromosomes themselves can have various phenotypic manifestations, from the normal phenotype and reproductive functions to severe forms of sexual development disorders and infertility. It depends on the type of mutation and its severity, the ratio of cells in mosaicism, the presence of certain types of structural rearrangements of gonosomes (isodicentric chromosomes X and Y with break points in the distal part of PAR1, isodicentric Yp chromosomes with breakpoints in Yq12 or the distal part of the long arm euchromatin, locus Yq11.23) [10].

The mosaicism by sex chromosomes can be explicit (detected by standard cytogenetic examination) and hidden (detected by FISH, micromatrix analysis and/or PCR, DNA hybridization, MLPA). In cases where one individual has three or more cell clones, mosaicism is complex. Mosaicism characterized by repeated (simultaneous) structural rearrangements of the same chromosome is called dynamic mosaicism. Dynamic mosaicism leads to the emergence of complex mosaicism with the presence of cells with various mutations (for example, with isochromosome Yp and with terminal deletion Yq) [11].

The structural abnormalities of sex chromosomes can be both balanced and unbalanced [12]. The genetic effects and phenotypic manifestations of such mutations can vary (from neutral to fertility disorders, severe forms of gender formation disorders, and multiple malformations) and depend on the type of restructuring, the presence and severity of mosaicism, and other factors.

The cytogenetic studies of Y-chromosome structural rearrangements conducted postnatally and prenatally in more than 600 patients showed differences in the phenotypes of pre- and postnatally diagnosed cases of Y-chromosome abnormalities, except regular Y dysomy (47,XYY) [13]. In almost all postnatal cases, phenotypic changes in disorders of sex formation or reproduction were noted, whereas in 90% of prenatal cases, normally developed male genitalia were noted in fetuses [13]. For several structural rearrangements of the Y chromosome, pronounced phenotypic variability (clinical polymorphism) is shown, which is due to the preservation of its short arm (Yp), in particular the SRY gene, and/or the long arm (Yq), as well as the presence, type, and severity of mosaicism [10].

The Y chromosome itself belongs to the most variable human chromosomes. Her heteromorphism is due to the polymorphism of her heterochromatin site Yq12, the size of which differs significantly among men of different ethnic populations [14]. Another type of Y-chromosome heteromorphism is inversion polymorphism. Most carriers of pericentric inversions of the Y chromosome are fertile, and their spermatogenesis and reproductive function are preserved [12]. In addition, various polymorphic microstructural rearrangements of the Y-chromosome (paracentric inversions, microdeletions, and microduplications) have been described, which cannot be detected only by molecular cytogenetic and molecular genetic methods [15]. Another type of polymorphism of the human Y chromosome is due to the difference in the number of copies of multicopy genes, for example, the presence of a TSPY cluster varying in the number of copies located at the GCY locus. The TSPY genes are arranged as a block of tandem copies (30-60 copies of the gene). It is shown that for normal sexual development, the number of tandem copies should not exceed the average values [16].

5. The Conclusion

Understanding the processes of sex formation is the basis for the diagnosis of patients with impaired sexual development. In the case of Y-dysomy, it is important to remember the pronounced polymorphism of the Y chromosome and the variability of phenotypic manifestations. At the moment, the polymorphism of the Y chromosome is insufficiently studied [14], so each new case should be thoroughly investigated using modern methods of genetics, both cytogenetic and molecular genetics [17].

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Dr. Elena Tkachuk is responsible for developing the project, collecting data to prepare the test, Dr. Galina Kurenkova collecting data.

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Competing Interests

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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