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SHERESHEVSKY-TURNER SYNDROME A MODERN VIEW

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Introduction. *Among newborns with chromosome abnormalities, about 50% are carriers of sex chromosome abnormalities. Sex chromosomes are the main carriers of genes that control sex determination and differentiation. Their numerical or structural abnormalities are compatible with life, but lead to defects and disturbances in sexual development. The most significant place among chromosomal diseases associated with X chromosome abnormalities is Turner-Shereshevsky syndrome (TS). The frequency of TS varies from 1:1500 to 1:5000 newborn girls [6, 42]. In 1925, N. A. Shereshevsky was the first to describe a 20-year-old patient with pronounced infantilism (underdevelopment of the gonads, primary amenorrhea, absence of secondary sexual characteristics) in combination with developmental abnormalities (short stature, wide skin fold on the neck, etc.). In 1938, G. Turner gave a detailed description of this condition, which was subsequently called Shereshevsky-Turner syndrome in Russian-language literature. N. A. Shereshevsky and G. Turner believed that the primary cause of the disease was a dysfunction of the pituitary gland and ovaries. In 1956, Polani and co-authors proposed a different explanation for the occurrence of the syndrome - the absence of one of the sex chromosomes. In 1959, the presence of the 45,X karyotype (44 autosomes + X) in patients with Turner syndrome was confirmed [42]. Later, it was shown that the Turner syndrome phenotype is caused by various structural anomalies of the X and Y chromosomes, as well as mosaicism of normal or aberrant sex chromosomes in combination with 45,X [4].*

Keywords: *Turner syndrome; karyotype 45,X; aberrations of X and Y chromosomes; mosaicism; parental origin of monosomy X.*

Clinical signs. Turner syndrome Features of the phenotype The phenotypic features of Turner syndrome are well known and include short stature, sexual infantilism, short neck, thyroid chest, widely spaced nipples, antimongoloid eye shape, high and narrow hard palate, etc. [6]. Patients have an increased risk of diseases such as diabetes, coronary heart disease, hypertension, arteriosclerosis, and many others. The incidence of mental retardation in patients with Turner syndrome is not higher than in the population. At the same time, they retain the ability to read, but most of them experience difficulties with social adaptation, memory, attention, and some other functions of the higher nervous system [31, 45]. It should be noted that the phenotypic picture of Turner syndrome is very polymorphic. Thus, short stature occurs in 94.5% of patients with TS, infertility in 95–99%, skeletal and cardiovascular anomalies in 40%, and renal anomalies in 33–70% [6]. The most serious disorders concern the reproductive system.

Reproductive functions. Monosomy X, partial or complete, is accompanied by anomalies in gonadal embryogenesis. In the absence of the Y chromosome, indifferent gonads develop into embryonic ovaries with first-order oocytes that are indistinguishable from the ovaries of normal XX embryos until the end of the 3rd month of development. Later, progressive degeneration of germinal cells and proliferation of connective tissue occur [46]. The gonads of adult patients are represented by connective tissue strands, where either completely undifferentiated rudiments are found, the sex of which is not established, or rudiments of female gonads without ovarian elements. Primordial follicles are extremely rare. Spontaneous development of secondary sexual characteristics is detected in 5–20% of patients (in 14% of patients with the 45,X karyotype and in 32% with the mosaic form of monosomy X or with structural rearrangements of the X chromosome) [50], whereas spontaneous menarche occurs only in 2–5% of patients [47]. Morphologically normal ovaries are visualized in 18% of patients [37], significantly more often in carriers of the 45,X/46,XX and 45,X/47,XXX mosaic karyotypes [37]. Isolated cases of normal ovarian function have been noted in patients with monosomy X [10]. Physiological pregnancy occurs in 3.6–7.6% of patients with Turner syndrome [22]. As a rule, these are women with structural rearrangements of the X chromosome [22] or with a mosaic karyotype 45,X/46,XX [3, 22]. A case of the presence of the 45,X karyotype in the mother and her daughter in blood cells, skin fibroblasts and ovaries has been described [10]. Genetic determinants of phenotypic features of Turner syndrome As early as 1965, it was suggested that the abnormal phenotype in Turner syndrome is due to the gene dosage effect, as well as the nonspecific influence of the aneuploidy itself [23]. In 1997, two independent groups of researchers mapped a regulatory transcription factor in the pseudoautosomal region of the short arm of the X chromosome: the SHOX

gene (short stature homeobox-containing gene), which is the main genetic determinant of growth. The SHOX gene is expressed in many tissues - skeletal muscles, heart, kidneys, pancreas, bone marrow and brain tissues [23]. In fetuses, gene expression is shown in the developing limbs, first and second pharyngeal vaults, which indicates the participation of the gene in the formation of the skeleton [51]. To date, it has been clearly determined that, firstly, genes are located on the short arm of the X chromosome, the deletion of which determines the development of almost all phenotypic features of SHTS; secondly, the genetic determinants responsible for the formation of any phenotypic feature are located not only on the short but also on the long arm of the X chromosome and the deletion of some can be compensated for by the presence of others; thirdly, the genes responsible for the development of the skeleton and lymphatic system exhibit incomplete expressivity and penetrance. Studies in recent years have shown that genetic determinants,responsible for the development of visual-spatial abilities, are localized in the pseudoautosomal region of the short arms of the sex chromosomes [45]. According to English researchers, there is a "critical locus of autism" in the region of Xp22.3 [54]. Reproductive dysfunction is the most characteristic sign of STZ. Currently, at least 9 genes are localized in the X chromosome that determine the normal development and functioning of the ovaries [55]. It is believed that reproductive dysfunction is associated not only with the dose effect of X-linked genes, but also with other causes. In particular, with disturbances in the pairing of homologous X chromosomes during meiotic recombination, changes in gene localization (position effect), changes in the replication pattern as a result of structural rearrangements of chromosomes [36]. Karyotype variants in patients with Turner syndrome Complete and mosaic forms of monosomy X The absence of the X chromosome is the only form of monosomy in humans that is compatible with both embryonic and postnatal development. Monosomy X has been shown to account for 1–2% of all human conceptions [28]. Among spontaneous abortions, the frequency of 45,X fetuses is the highest and reaches 17%. The survival rate of embryos with this chromosomal abnormality is extremely low: more than 99% are eliminated at different stages of development [14]. Most embryos stop developing by 6 weeks after conception. In 70% of cases, the amniotic sac contains elements of embryonic tissue and remnants of the yolk sac. In one third, a morphologically unchanged non-developing embryo is found, corresponding to 40–45 days of development. Monosomy X in fetuses of later stages of embryonic development is accompanied by specific signs: swelling of the neck, lungs, and generalized fetal edema. These signs are often combined with intrauterine growth retardation [12]. Often, fetuses have neural tube defects [15] and coarctation of the aorta [12]. The pathogenetic mechanism of early mortality of embryos with monosomy X is based on vascular anomalies and/or fluid

imbalance, which leads to impaired embryo-placenta circulation and excess fluid in the body [12], as well as placental dysfunction [47]. The consequences of these disorders in newborns are lymphedema of the hands and feet, a short wrinkled neck, low height and body weight. Why do 1% of fetuses with monosomy X survive? The results of cytogenetic and molecular studies have shown that the mosaic form of monosomy X was detected in 7.4% of spontaneous abortions, while in newborns, mosaicism of sex chromosomes can reach 82% [24]. These observations allowed us to hypothesize that chromosomal mosaicism (a combination of cell lines with different chromosome sets in an individual's tissues) is necessary for the survival of fetuses with monosomy of the X chromosome. According to this hypothesis, all live-born children with the 45,X karyotype are mosaics that have additional cell lines with normal or aberrant sex chromosomes in their organs and tissues [26].Based on theoretical calculations, approximately 60% of patients with the 45,X karyotype may be X-chromosome mosaics, and 40% - Y-chromosome mosaics. In reality, "latent", i.e., undetected by traditional cytogenetic methods, X-chromosome mosaicism in patients with Turner syndrome varies from 2.4 to 48% [3, 24, 35, 53]. The frequency of "latent" Y-chromosome mosaicism in the studied groups varied from 0 to 61% [3, 38, 39]. In one study, additional cell lines with X and Y chromosomes were detected in 90% of patients with monosomy X [21]. Some researchers believe that the survival of fetuses with monosomy X may be due to the existence of placenta-limited mosaicism and/or the presence of mosaicism in the early stages of embryonic development with subsequent loss of an additional cell line [34]. Data from different authors on the nature of mosaicism in patients with Turner syndrome show that in most cases (80–90%) mosaicism is true (present in all tissues regardless of origin), while mosaicism limited to cells of one tissue is detected in only 10–20% of cases. The karyotype established on peripheral blood lymphocytes objectively reflects the true karyotype of patients with Turner syndrome. In 70–80% of cases, the same cell line prevails in all tissues of the body. That is, the predominance of one of the cell lines in mosaicism is preserved in tissues of different origin [3, 4, 7, 34, 35, 43]. There is an opinion that the presence of additional cell lines increases the viability of fetuses [25]. The results of prenatal diagnostics do not confirm this assumption. Thus, according to our observations, X/XX mosaicism was detected in the lymphocytes of the umbilical cord blood of fetuses in two cases, with the aneuploid cell line predominating in one case and the euploid one in the other. In the third case, monosomy X was detected in the cytotrophoblast and X/XX mosaicism was detected in the lymphocytes of the umbilical cord blood of the fetus. All three pregnancies ended in fetal death [1]. To diagnose mosaicism, we have developed an algorithm for laboratory and genetic testing of patients with TS (Fig.). Considering that the presence of Y-chromosome material has a significant impact on

the patient management tactics, as it increases the risk of malignant degeneration of immature testicular tissue, at the first stage, the presence of Y-chromosome material is examined in DNA samples from peripheral blood in patients with monosomy X and signs of masculinization using PCR with primers to various loci of the Y-chromosome. If it is absent in blood samples, the search can be supplemented by an analysis of DNA samples of the buccal epithelium. If the result is positive, it is advisable to conduct FISH with Y-specific DNA probes on lymphocyte and buccal epithelium preparations to establish the der(Y) structure. It is important to note that not all patients with Y-chromosome material have signs of masculinization. Therefore, in the absence of signs of masculinization in patients with a karyotype of 45,X recommends FISH analysis on lymphocyte preparations and then buccal epithelium to detect additional X- and Y-chromosome material. Data on the frequency of phenotypic features in patients with different chromosomal constitutions are ambiguous. According to most authors, the phenotypic picture of Turner syndrome is most pronounced in carriers of the pure form of monosomy X [3, 4], but they are also characterized by a variety of clinical pictures. Literature data on the phenotypic manifestations of Turner syndrome in chromosomal mosaicism 45,X/46,XX; 45,X/46,XX/47,XXX; 45,X/47,XXX indicate significant polymorphism of the clinical picture of the disease. In general, the presence of the 46,XX cell line “softens” the manifestation of the phenotypic signs of Turner syndrome: the higher the proportion of cell clones with the 45,X karyotype in different tissues, the more pronounced and close to the main form - monosomy X - the clinical picture of the syndrome [7]. The phenotype of patients with the 45,X/46,XY karyotype is extremely diverse and varies from almost normal male to almost normal female with some signs of Turner syndrome [43]. Interestingly, 90% of 45,X/46,XY mosaics in the prenatal period have a normal male phenotype [13], while in the postnatal period, female patients with signs of Turner syndrome are most often encountered [43]. The predominance of cells containing the Y chromosome in the gonadal ridge during embryogenesis naturally leads to differentiation of the gonads according to the male type [43]. At the same time, no relationship was found between the somatic sex and the quantitative ratio of cells with the chromosomal constitution 45,X and 46,XY in the blood or in the amniotic fluid [13]. No relationship was found between the proportion of cells with the 46,XY karyotype in the blood and the presence of signs of masculinization. The female phenotype in patients with Y-chromosome material in their genome may be due to a deletion of the region containing the SRY gene, a mutation in the gene itself, or a deficiency of the SRY gene product. SRY activity can be suppressed by two doses of the DSS gene product [36]. It should be noted, however, that even the predominance of the X-monosomal cell clone with the 45,X/46,XY karyotype is not always accompanied by the formation of TS. In contrast to the

rudimentary gonads characteristic of complete monosomy of the X chromosome, the gonads in the 45,X/46,XY karyotype are asymmetrical and often look like underdeveloped testicles on one side and a connective tissue gonad on the other. The structure of the internal and external genitalia in this group of patients depends on the functional activity of the testis during the prenatal period [13]. Structural anomalies of gonosomes X chromosome aberrations Isochromosome X on the long arm i(Xq) can be represented by a complete or mosaic form and is the second most common chromosomal anomaly after monosomy X (15–20% in patients with TS and 0.002% among newborns) [17]. In spontaneous abortions, i(Xq) is very rarely detected compared to live births. The reason for such differences is unclear [44]. Xq isochromosomes can be of two types: mono- and dicentric.Patients with isochromosomes on the long arm of X have complete or partial monosomy of the short arm in combination with trisomy of the long and the remaining part of the short arm. Partial monosomy of the short arm causes the appearance of typical signs of TSS (short stature, underdevelopment of secondary sexual characteristics and infertility), while the presence of a triple dose of long arm material does not significantly affect the phenotype. At the same time, it is noted that only 66% of patients with i(Xq) have the characteristic TSS phenotype [2]. Data on the phenotypic manifestations of deletions of the long (Xq-) and short (Xp-) arms of the X chromosome are numerous and ambiguous. In general, it can be noted that deletions of the X chromosome lead to less pronounced phenotypic abnormalities than the complete form of monosomy X. Thus, only 65% of patients with Xp deletion and 93% of patients with Xq deletion have gonadal dysgenesis. Short stature is detected in 88% of Xp carriers and 43% of Xq carriers [52]. In this case, deletions of the proximal region of Xp (Xp11) in 50% of cases cause primary amenorrhea, while interstitial deletions of the central region of Xp and deletions distal to Xp21 cause secondary amenorrhea [44]. Deletions of the long arm of the X chromosome affect sexual development, but are not accompanied by serious somatic disorders [36]. In patients with identical deletions, the range of reproductive system abnormalities may vary from primary amenorrhea and gonadal dysgenesis to secondary amenorrhea and premature menopause. In addition, the size of the deleted Xq region does not affect the degree of gonadal dysfunction or the time of menopause [11]. Unlike deletions, duplications of material of both the short and long arms of the X chromosome, although accompanied by disorders of somatic, psychomotor, and sexual development, do not always lead to TSS. It is believed that differences in physical and psychomotor development can be explained by the size of the duplicated region, expression of recessive mutant genes on the active normal X chromosome, random or preferential inactivation of the normal and aberrant X chromosomes (in this case, some cells will carry two active copies of the genes located

in the duplicated region instead of one), tissue-specific differences in the inactivation pattern [19, 41]. Paracentric and pericentric inversions of the X chromosome can also lead to the formation of an abnormal phenotype, which can be caused by disturbances in the nucleotide sequence at the breakpoints, as well as changes in the sequence of the genes themselves [16]. The ring X chromosome (r(X)) is formed during gametogenesis or in the early stages of embryogenesis by the loss of the terminal sections of the long and short arms of the X chromosome and the closing of the remaining sections into a ring. This chromosomal aberration accounts for 20–23% of all X-chromosome anomalies and occurs only in mosaic form, which is explained by its extreme instability during cell division [17]. The phenotypic effect of r(X) is variable:Some patients have severe mental retardation, facial skeletal abnormalities, and soft tissue syndactyly, while many of the classic signs of Turner syndrome may be absent. The rest have characteristic signs of Turner syndrome (as in monosomy X). The differences in the severity of the disease are explained by the functional state of the genetic material of the ring X chromosome [8]. Y-chromosome aberrations About 6% of patients with Turner syndrome have a chromosome set containing a cell line with a structurally abnormal Y chromosome. Dicentric chromosomes are one of the most common structural aberrations of the Y chromosome in patients with Turner syndrome [27]. In most cases, the cell line with the aberrant Y chromosome is combined with the 45,X cell line. The phenotype of patients with the 45,X/46,X,der(Y) mosaic karyotype can vary from normal male to normal female. All patients with the female phenotype have short stature and gonadal dysfunction. However, the phenotypic features characteristic of Turner syndrome, signs of virilization, and gonadoblastoma may be present in some patients and absent in others [9, 27]. Such a diversity of phenotypes is explained by the fact that the somatic sex and phenotypic features of Turner syndrome in patients with Y-chromosome material are determined not only by the presence/absence of the intact sex-determining gene SRY, but also by the size of the 45,X cell line and the ratio of cell lines with monosomy of the X or Y chromosome in different tissues of the embryo [9]. The phenotype of patients with X/Y translocations depends on which region of the X or Y chromosome is deleted. Marker chromosomes of 20% of patients with Turner syndrome have a chromosome set that includes a cell line with a marker chromosome [30, 34]. Most of these marker chromosomes are derivatives of the X chromosome [30], about 6% are derivatives of the Y chromosome [24, 30]. Establishing the nature of the marker chromosome and its characteristics are important for diagnosis and treatment tactics due to the increased risk of malignant degeneration of the gonads in the presence of Y chromosome material. It should be noted that the presence of a marker chromosome including Y chromosome material is accompanied by a “milder” manifestation of Turner syndrome [49]. Parental origin of the X chromosome in the

45,X karyotype It has been shown that in 69–90% of cases of monosomy X, the maternal X chromosome is present [3, 30]. Data on the predominant loss of the paternal X or Y chromosome in individuals with monosomy X, as well as differences in the functional activity of homologous chromosomes during embryogenesis [5], have led to a hypothesis about the influence of the parental origin of the single X chromosome on the viability of the fetus [29]. Thus, it has been shown that in spontaneous abortions, the single X chromosome is more often of paternal origin, which may indicate a reduced viability of fetuses with Xp [29]. However, no developmental anomalies were found in abortions with Xp that differed from those in abortions with Xm. The results of other studies indicate the absence of reliable differences in the frequency of Xp and Xm between spontaneous abortions,fetuses of the second and third trimesters of pregnancy and newborns [24]. These observations indicate an insignificant contribution of X-chromosome gene imprinting to the prenatal period of human development. Literature data on the role of genomic imprinting in the phenotypic manifestation of Turner syndrome are also ambiguous. The results of many studies indicate the absence of phenotypic differences in patients with monosomy Xp or Xm. Thus, no correlation was found between the parental origin of a single X chromosome and the gestational age, height and weight of newborn girls. No effect was found on the parental origin of the X chromosome on such phenotypic features of Turner syndrome as anomalies of sexual development; thyroid chest; widely spaced nipples; deformation of the elbow joints; low hair growth on the neck; multiple pigment spots; hearing abnormalities; renal abnormalities; short IV metacarpal joints; lymphemia; blepharoptosis; autoimmune diseases; myopia; osteoporosis; spontaneous development of secondary sexual characteristics; spontaneous menstruation [3, 33, 40]. The data of some authors [40] that cardiovascular anomalies and cervical folds are detected only in patients with a maternal X chromosome are refuted by others [3, 33]. The data of English authors [20] were extremely interesting; they showed that girls with a single paternal X chromosome adapt better in society and have better scores on verbal psychological tests than girls with a maternal X chromosome. The results of similar examinations of healthy people indicate that men who have a single maternal X chromosome have worse social adaptation scores compared to women [48]. It has been shown that a disease such as autism has been detected only in girls with Turner syndrome with a maternal X chromosome [20]. These observations suggested that there is a genetic locus for “social cognition” that is imprinted and not expressed if inherited from the mother. At the same time, on the paternal X chromosome, this locus is functionally active and is not imprinted in meiosis. The locus is presumably located in the pericentromeric region of the long or short arms of the X chromosome (Xp11.23-Xq) [32]. Studies of the dependence of verbal and nonverbal memory on the parental

origin of the X chromosome have shown that girls with Turner syndrome with a paternal X chromosome do not differ in this indicator from the control group (girls with a normal karyotype 46,XX), and girls with a maternal X chromosome do not differ in visual-spatial (motor) memory. These data suggested that the X chromosome contains one or more imprinted genes responsible for the memory function [22].The results of many studies indicate the absence of phenotypic differences in patients with monosomy Xp or Xm. Thus, no correlation was found between the parental origin of a single X chromosome and the gestational age, height and weight of newborn girls. No effect was found on the parental origin of the X chromosome on such phenotypic features of Turner syndrome as anomalies of sexual development; thyroid chest; widely spaced nipples; deformation of the elbow joints; low hair growth on the neck; multiple pigment spots; hearing abnormalities; kidney abnormalities; short IV metacarpal joints; lymphemia; blepharoptosis; autoimmune diseases; myopia; osteoporosis; spontaneous development of secondary sexual characteristics; spontaneous menstruation [3, 33, 40]. The data of some authors [40] that cardiovascular anomalies and cervical folds are detected only in patients with a maternal X chromosome are refuted by others [3, 33]. The data of English authors [20] were extremely interesting; they showed that girls with a single paternal X chromosome adapt better in society and have better results in verbal psychological tests than girls with a maternal X chromosome. The results of similar examinations of healthy people indicate that men who have a single maternal X chromosome have worse social adaptation rates compared to women [48]. It has been shown that a disease such as autism has been detected only in girls with TS with a maternal X chromosome [20]. These observations suggest that there is a genetic locus for “social cognition” that is imprinted and not expressed if inherited from the mother. At the same time, on the paternal X chromosome, this locus is functionally active and is not imprinted in meiosis. Presumably, the locus is located in the pericentromeric region of the long or short arms of the X chromosome (Xp11.23-Xq) [32]. Studies of the dependence of verbal and nonverbal memory on the parental origin of the X chromosome have shown that girls with Turner syndrome with a paternal X chromosome do not differ in this indicator from the control group (girls with a normal karyotype 46,XX), and girls with a maternal X chromosome do not differ in visual-spatial (motor) memory. These data suggest that the X chromosome contains one or more imprinted genes responsible for the memory function [22].The results of many studies indicate the absence of phenotypic differences in patients with monosomy Xp or Xm. Thus, no correlation was found between the parental origin of a single X chromosome and the gestational age, height and weight of newborn girls. No effect was found on the parental origin of the X chromosome on such phenotypic features of Turner syndrome as anomalies of sexual development; thyroid chest; widely spaced

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Conclusion. Over the past 80 years since the first description of a patient with Turner syndrome, great strides have been made in studying the clinical picture, etiology, pathogenesis, treatment and social adaptation of patients. However, it should be acknowledged that many problems remain unresolved. Thus, information on the genetic determinants of Turner syndrome is still fragmentary, the contribution of imprinting to embryonic death of fetuses with the 45,X karyotype, as well as to the development of Turner syndrome symptoms, remains controversial, the correlation of the degree of expression and the combination of individual symptoms with a certain type of abnormal karyotype is discussed.

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