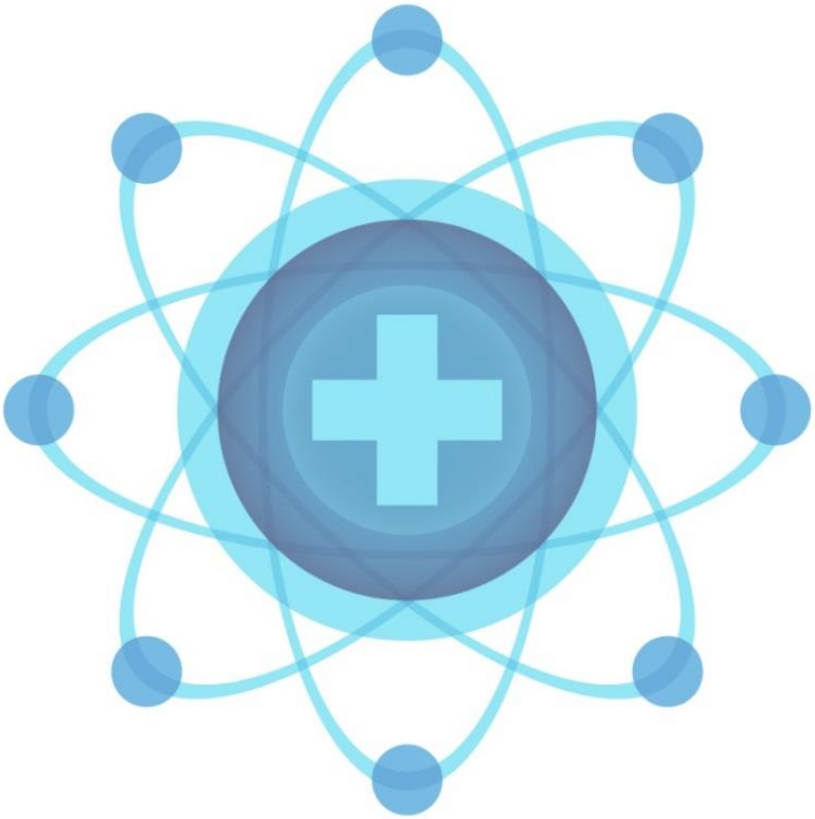

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Complex characteristics of disorders in Turner syndrome

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Turner syndrome (TS) is a genetic disease associated with the complete or partial loss of one X chromosome, often with a mosaic karyotype. TS is the only one monosomy life-compatible, and affects approximately 1 in 2000-2500-2500 newborn girls [4; 13; 15; 16].

Keywords: Turner syndrome, karyotype, mosaicism, isochromosome.

Type and frequency of chromosomal abnormalities in Turner syndrome [15].

Karyotype	%	Description
45, X	40-50	Monosomy X
45, X/ 46, XX	15-25	
45, X/47, XXX; 45, X / 46, XX/47, XXX	3	Mosaicism with a "Triple cross"
45, X/ 46, XY	10-12	Mixed gonadal dysgenesis
46, XX, del(p22.3); 46, X, p (X)/46, XX		Deletion Xp22. 3 Ring X chromosome
46, Xi(Xq); 46, X, idic(Xp)	(10%)	Isochromosome Xq; isodicentric Xp
X-autosomal translocation, unbalanced	Rare	Various
46, XX,del(q24)		Non-ST; premature ovarian failure
46, X,idic (X) (Q24)		Non-ST; Isodicentric Xq24

There are various variations of the karyotype for TS, such as monosomy X (45,X; the most common karyotype), mosaic karyotype, isochromosome X, ring X chromosome, or deletions. In all these cases, significant portions of the X chromosome are removed [3].

Mondal S. et al. [2-5] conducted a cross-sectional study to assess the prevalence of various karyotypic variants in the Indian population.

The majority (44.1%) of patients had classic TS, followed by karyotypes with 46, X, and iXq either in all cells or as part of mosaicism with 45, XO-containing cell lines [in 25(24.5%) cases, karyotypes contained an Xq isochromosome, of which 11 were 46,X ,iXq, 12-45, X / 46, X,iXq and 2-45,X/46,XX/46,X, iXq] and XO/XX are mosaics (17.6%). More half (56%) of isochromosomes-Xq were mosaics with XO cell lines, while 12 cases had mosaicism with X monosomy and two cases are complex mosaicism involving three cell lines, i.e., 45, X0, 46, XX and 46, X, iXq. Most girls with mosaic isochromosoma-Xq (mosaicism 46,X,iXq with XO or complex mosaicisms, n=14) had isodicentric-Xq (11 out of 14); the most common break point was q21, followed by q10 [2-6].

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Mondal S. et al. [2-5] finds it interesting that all those who had pure isochromosomes (46, X, iXq) had a break point at q10. Mosaicism of XO cell lines with marker chromosomes detected during karyotyping of peripheral blood leukocytes was revealed in four patients.

Interphase FISH with X-and Y-chromosomal probes was performed for these patients; in three subjects, the marker chromosome was derived from the X-chromosome; one patient had a Y-chromosomal origin.

The study also identified a number of extremely rare karyotypes, i.e., isochromosome-Xp and isodicentric chromosome Yp, which are rarely reported in the published world literature on TS. The authors believe that the predominance of various karyotypic variants in TS may have ethnic differences, with the predominance of isochromosomes and isodicentric chromosomes in India [22-5].

In China, Wu H.& Li H.[36] studied the karyotype, clinical manifestations, and natural and therapeutic outcomes of 124 patients with TS. Four types of karyotype were identified: monosomal (32.7%), mosaic with variants (27.4%), and variant (23.9%) and mosaic (15.9%). All patients were short in stature, with an average adult height of <145 cm. Spontaneous mammary glands development was observed in 16% of adolescent patients and spontaneous menstruation was observed in 8%. The rate of spontaneous sexual development was lowest in the monosomal karyotype [36].

From the general clinical signs: hallux valgus deformity of the cubitus and a wide chest space were observed in approximately 50% of patients, epicanthus and cutaneous nevus - in 30%, webbed neck and wide chest - in 10-20%. More than 10% of patients had concomitant abnormalities of the heart, thyroid, or kidney (highest in the monosomal karyotype). [36].

Darendeliler F. et al. [10] in a cross-sectional study that included 842 patients with TS younger than 18 years, it was found that the majority (50.7%) of patients had classic TS. The most frequently observed structural variation was 46Xi (Xq) (10.1%).

Turner syndrome is usually accompanied by hypergonadotropic hypogonadism and primary or secondary amenorrhea due to gonadal dysgenesis. Approximately one-third of girls with TS have spontaneous telarche, which is most common in girls with mosaicism. Regular menstrual cycles occur in no more than 6% of these subjects [15; 27; 34].

The TS phenotype includes a triad of symptoms: sexual infantilism, pterygoid skin folds on the sides of the neck, and deformity of the elbow joints.

Congenital cardiovascular malformations, such as bicuspid aortic valve (20-30%) and aortic coarctation (7-18%), are common in TS. Progressive aortic root dilatation or dissection may occur in 40-50% of CT patients, which is associated with morbidity and mortality. Also, patients with TS are at risk of developing urogenital abnormalities, congenital lymphedema, sensorineural hearing loss, and diabet, osteoporosis, obesity, and dyslipidemia [12].

The prevalence of aortic root dilatation and aortic dissection occurs in 32% and 1-2% of women with CT, respectively [14; 18].

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Cardiovascular diseases accounted for 41% of the increased mortality of British women with CT compared to the general population with a standardized mortality rate of 3.0 (95% CI, 2,7–3,4) [5; 32; 33].

In addition, there are a number of neurocognitive and psychosocial symptoms associated with TS. The frequency of anxiety (including generalized anxiety, social anxiety, specific phobias, and obsessive-compulsive behavior) or depression in TS reaches 52% over the course of life, which is a sharp increase compared to the prevalence of these conditions in women in the population. [21; 26].

In typically developing female embryos with a normal set of 46 chromosomes, one of the X chromosomes is inactivated during early embryonic development, a phenomenon known as dose compensation or lyonization. This epigenetic mechanism works to equalize the dosage of X-linked genes between female and male embryos. However, some genes on the" inactive " X chromosome in female individuals actually avoid inactivation at least to some extent. Therefore, TS can be considered as a result of partial or complete absence of these genes that avoid inactivation [7; 8; 23]. 20-30% of genes that avoid silence are candidates for a role in the Turner syndrome phenotype [30].

Clement-Jones M. et al. [9] believe that genes potentially associated with the TS phenotype avoid X-inactivation and have functional homologs on the Y chromosome. One such gene is the short-growth homeobox *(SHOX)*gene, located in the pseudoautosomal region of the X chromosome. *SHOX* has been identified as a candidate gene for short stature, as well as for skeletal abnormalities associated with TS, such as high arched palate, abnormal development of the auricles, hallux valgus deformity of the cubitus, hallux valgus deformity of the knee joint, Madelung's deformity and short metacarpal bones [9].

Day G. et al. [11] found that SHOX is expressed in the growth zones of vertebral bodies, which means that its expression may also be associated with scoliosis (and kyphosis) in TS.

Reduced expression of the SHOX gene is associated with all skeletal abnormalities in TS. Scoliosis in TS is clinically and radiologically similar to idiopathic scoliosis, although the phenotypes differ [11].

The European guidelines, published in 2017, specify how to monitor patients using magnetic resonance imaging (MRI) and/or echography. Various studies have shown that cardiovascular monitoring is necessary throughout life, and therefore training of patients with CT and their families is a serious challenge [12].

It is proposed to evaluate the hormonal status to determine the functional state of the reproductive system. In particular, the level of anti-muller hormone (AMH), which is stable from middle childhood to early adulthood, is normally high [35]. It is also necessary to study the level of FSH, normally it should be less than 10 mIu/ ml [1].

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During the first trimester, ovarian development in fetuses with CT is initially normal. Examination of the ovaries during pregnancy from 14 to 18 weeks revealed normal development of the sex glands. However, soon after this, oocyte loss accelerates in many girls with TS, with oocyte depletion becoming almost complete in utero or in the first few months after birth [14].

According to Reynaud K. et al. [31] in fetuses with karyotype 46,XX, oogonia was detected as early as 18 weeks, primordial follicles were detected in the ovaries starting from 20 weeks, and preantral and antral follicles were detected at 26 weeks. Some ovaries of fetuses with karyotype 45, X had oogonia, but primordial, preantral and antral follicles were not
found even in the ovaries from the third trimester of gestation.

There is evidence that some girls with TS preserves oocytes and functioning follicles after birth. In a study evaluating the presence of ovarian follicles in adolescent girls with TS in nine teenage girls with Turner syndrome was removed laparoscopically from 1/4 to 1 ovary and histological analysis was performed. Eight of the nine ovaries had follicles, with a higher number of follicles observed in younger adolescents and girls with mosaicism. The density of follicles is inversely proportional to the level of FSH [20].

Menarche rarely occurs in girls with TS. However, Hovatta O. [19] notes that 40-50% of girls with TS may experience puberty. Indicators are higher in girls with a mosaic karyotype, but up to 25% of girls with a 45,X karyotype have some signs of spontaneous puberty. Before 10% of girls with TS reach menarche.

Previously , Pasquino A. et al. [29] in a study of 522 patients with TS, spontaneous puberty was observed, and spontaneous menarche occurred in 84 (16.1%) patients. According to Aso K. et al. [1] spontaneous menarche was more common in patients with mosaicism 45,X/46,XX or 45,X/47,XXXthan in patients with a different karyotype. The authors believe that the extra X chromosome probably has a significant effect on the progression of puberty. In addition, serum FSH levels of less than 10 mIU/ ml at the age of 12 years indicate the onset of spontaneous menarche and regular cycles.

Spontaneous pregnancy is observed in a small number of patients with TS, mainly in women with mosaicism, as well as in those who report spontaneous puberty and regular menstruation. Although women with mosaicism are more likely to conceive spontaneously, women with monosomy can also be fertile. [6; 17].

In a study by Birkebaek N.. et al. [2] noted that the probability of physiological pregnancy in TS is 3.6-7.6%. A significant part of women with TS who gave birth to a child, have structural rearrangements of the X chromosome or a mosaic karyotype 45, X/46, XX.

Oktay K. et al. [2-8] believe that the probability of getting pregnant and giving birth to a genetically related child in women with mosaic TS is explained by the fact that they sometimes have spontaneous puberty and menarche, a regular menstrual cycle.

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Bryman I. et al. [6]note that 57 (12%) women out of 482 patients with TS reported 124 pregnancies that occurred either spontaneously or through in vitro fertilization (IVF). 27(47%) women became pregnant using their own oocytes, of which 23(85%) women became pregnant spontaneously, and 4(15%) – using either IVF or insemination, 30(53%) became pregnant as a result of oocyte donorship. The majority(92%) of women who have achieved pregnancy by autologous oocyte transfer have a mosaic karyotype.

According to Karnis M. [22] despite improved expectations for fertility in individuals with TS, pregnancy-related mortality remains higher than in the general population, at about 2% compared to 0.013% in healthy women. Hypertension and its consequences, including preeclampsia and eclampsia, are the main risks of cardiovascular complications during pregnancy.

The frequency of any hypertensive disorder associated with pregnancy in women with TS is variable and ranges from 35 to 67 % [14; 18].

During hormone therapy, growth increased by 7.6 cm and 6.7 cm in the first and second years of therapy, respectively, slowing down to 5.7 cm and 4.1 cm in the third and fourth years. Treated patients who reached almost adult height were 10.2 cm taller than untreated patients. The therapeutic effect correlated with the duration of GH therapy [36].

TS is one of the most common chromosomal abnormalities, the clinical manifestations of which affect many organ systems. Transition of young women with TS from pediatric to adult care is characterized by a high dropout rate and inadequate follow-up, which leads to an increase in morbidity and mortality. In women with TS who want to become pregnant, unique health problems must be considered, including height, risk of cardiovascular diseases, and endocrine disorders [14; 24]

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