# Turner's Syndrome

## Introduction

**Turner syndrome** is one of classical syndromes caused by numerical chromosomal aberrations, among which we include the Down, the Edwards, the Patau, the Klinefelter, the triple X and the XYY syndromes as well (the last two mentioned being formerly called the "Superfemale" and the "Supermale" syndrome respectively). Unlike these syndromes, which are (in most cases) caused by a trisomy of either a somatic or a sex chromosome, Turner syndrome represents likely the **only complete monosomia** whose bearers are capable of long-term survival.

Approximately a third of patients with Turner syndrome are diagnosed in the neonatal period based on a **congenital heart defect** (the coarctation of the aorta, bicuspidal aortal valve) and a **characteristic appearance** (pterygium colli, swollen hands and feet). Another third is diagnosed in childhood within the differential diagnosis of **stunted growth**. The remaining third is discovered during the maturation based on **primary amenorrhea and the insufficient development of secondary sexual characteristics**[1].

## History

The history of Turner syndrome as a singular pathological unit has more or less started in the 20$^{th}$ century, nowadays the syndrome is being linked to the American endocrinologist **Henry Turner** and his article – *A syndrome of infantilism, congenital webbed neck and cubitus valgus* – published in 1938[2]. In the name of the article itself the most significant symptoms of the syndrome are already described.

The most striking symptoms of this syndrome are summarized in the very title of the article. In the course of the following years, together with the development of cytogenetic and molecular genetic methods, the diagnosis of this syndrome improved, including prenatal diagnosis. Promising developments have also been noted in treatment, especially treatment with replacement of missing hormones. Today, women with Turner syndrome are no longer an exception, and thanks to a donated oocyte and hormone replacement therapy, they were able to give birth to a healthy child.

## Cytogenetic appearance

Turner syndrome is most often caused by the **X chromosome monosomy**, also called the **45,X** karyotype (the older description as 45,X0 is unacceptable since the ISCN 2009 norm). The lack of the Y chromosome directs the maturation towards female sex – thus the syndrome is typical for women. However, about 50 % of Turner syndrome cases are caused by a different karyotype – most often by **chromosomal mosaics**: 45,X/46,XX; 45,X/47,XXX; eventually even 45,X/46,XX/47,XXX, as well as structural aberrations – isochromosome X: 46,X,i(Xq); rarely 46,X,i(Xp), deletions of short or long arms of the X chromosome: 46,X,del(Xp); respectively 46,X,del(Xq); circular chromosome X: 46,X,r(X) or idiocentric chromosome X: 46,X,idic(X).

These structural aberrations and appear even in chromosomal mosaics – e.g. 45,X/46,X,r(X). Examples of rare chromosomal findings are the presence of the marker chromosome: 46,X + mar. or various reciprocal translations of the X chromosome.

Special attention should be given to cases connected to the presence of the Y chromosome in the karyotype. Not all of these cases can be considered a case of Turner syndrome in its proper sense. Moreover, they don't even have to be connected exclusively to the female phenotype. It is most notably the 45,X/46XY mosaic (linked to mixed gonadal dysgenesis) or the 46,XY karyotype linked to pure gonadal dysgenesis. The Y chromosome doesn't have to be present fully, it can even be a small translocated sequence, an idiocentric chromosome or a marker chromosome.

## Pathogenesis

From the cytogenetic point of view there is a certain link between Turner syndrome cases, it is the **absence** of the entire X chromosome or the **deletion** of some of its parts. Pathological is therefore the absence of certain genes which would otherwise be present. However, it is necessary to approach this problem more closely, because males (46,XY karyotype) also have only a single X chromosome and even in women with the complete karyotype (46,XX) is one of the two X chromosomes inactivated.

It is nonetheless important that some genes on the inactivated X chromosome continue being transcribed regardless (therefore they are exceptionally interesting in regards to the pathogenesis of Turner syndrome). These genes can be classified into three groups:

1. genes localized in the so-called **pseudoautosomal segments** of the X chromosome. These are two segments – the **PAR 1** (larger segment, circa 2,7Mb = millions of bases, 24 genes) at the end of short arms,

and the **PAR 2** (shorter segment, circa 330kb = thousands of bases, 5 genes) at the end of the long arms. Thanks to these areas (especially PAR1) the X and Y chromosomes can create a "homologous" pair during the meiosis; crossing-over is possible between genes in this area. The **SHOX** gene (Short Stature Homeobox; Xp22.32; OMIM: *312865 (https://www.omim.org/entry/312865)) is one example of a gene in the PAR1 area, as is his homologous gene **SHOXY** (Yp11.2; OMIM: *400020 (https://www.omim.org/entry/400020)).
2. Genes located outside the pseudoautosomal segments of the X chromosome that nonetheless have their homologous copies on the Y chromosome as well.
3. Genes located only on the X chromosome (without a homologous copy on the Y chromosome), but which don't undergo lyonization – for example the **SSDD** gene (Steroid Sulfatase Deficiency Disease; Xp22.32; OMIM: +308100 (https://www.omim.org/entry/308100); the gene is a code for the steroid sulphatase and its mutation causes the X-linked form of congenital ichthyosis).

Since the X chromosome doesn't have to be missing entirely – only some genes – the phenotype of the affected individuals can be different depending on which genes are missing. **The most severe is** exactly the **simple 45,X monosomy** (it is recorded that up to 99% of the fetuses with this karyotype are miscarried), forms with only specific structural aberrations of the second X chromosome or mosaic forms are clinically less severe (an opinion exists which states that simple 45,X monosomy is incompatible with survival and the living bearers of this karyotype are actually unrecognized mosaics).

# Clinical manifestation

Turner syndrome is complex and has a spectrum of clinical symptoms. Some are more typical than others.

## Growth and skeleton disorders

Growth disorder is likely the most common symptom of Turner syndrome. It is not simply the **stunted growth**, since various **skeletal abnormalities** (e.g. cubiti valgi) and **osteoporosis** may manifest as well. It is a complex disorder whose etiology isn't fully clear yet, though the role of one certain gene cannot be overlooked.

It is the above mentioned SHOX gene, aka PHOG (pseudoautosomal Homeobox Containing Osteogenic Gene). A homeobox gene localized in the PAR 1 region that plays a role during the ontogenetic development of a human. Thanks to the alternative splicing the gene produces two types of mature mRNA that are 1870 nucleotides (SHOXa – expressed in the skeletal muscle, placenta, pancreas, heart and bone marrow fibroblasts) and 1349 *[sic]* nucleotides long (SHOXb – expressed in the fetal kidney, skeletal muscle and especially in the marrow fibroblasts). The most significant is the role of the SHOX gene during the skeletal development, notably the middle and the distal segments of both upper and lower limbs – i.e. the forearm and the shin.

Due to the absence of one of the SHOX copies the skeletal development of the Turner syndrome patients is hampered to some extent (it is not solely responsible for the entire pathogenesis of the growth and skeleton disorders, though); similar (but very variable) phenotypic manifestation can be observed in other disorders caused by the SHOX (or the SHOXY) gene – one of the mutated / missing copies causes Léri-Weill syndrome (LVD; OMIM: #127300 (https://www.omim.org/entry/127300)), its severe form caused by a mutation in the homozygous state (or double deletion of both copies) is Langer syndrome (OMIM: #249700 (https://www.omim.org/entry/249700)); a special form causes the idiopathic growth retardation (OMIM: #604271 (https://www.omim.org/entry/604271)), which has a generally milder phenotypic manifestation and can be caused by a mutation of the genes for the growth hormone (GH), for its membrane receptor (GHR) or for its free receptor (GHSR). On the other had, a taller figure can be found in individuals with a multiplied SHOX or SHOXY gene – for example in Klinefelter syndrome, or in the 47,XXX and the 47,XYY syndromes.

Skeletal deviations further include symptoms like **cubiti valgi**, **genua valga**, **Madelung's forearm deformation**, **shortened metacarpal bones**, deviant shape of either jawbone and **anomalies of the ossicles and the ear canal** (abnormal ossicles can cause the **conductive hearing loss**; thanks to the unusual shape of the posterior cranial base, which is shorter and wider, the Eustachian tube becomes shortened and widened – infections like otitis media are more common).

Patients with Turner syndrome have somewhat **normal levels of growth hormone and the insulin-like growth factor** (IGF-I). Absence of the ovarian steroidogenesis also doesn't affect the resulting height at all, although the "pure estrogen" theory used to have many supporters. The latest theory is inclined to the idea that it is a result of the **disorder of paracrine and autocrine secretion of IGF-I on the fibroblast level** (especially in the growth zones of long bones); the **resistance to the growth hormone or the IGF-I** can be possibly present as well.

The resistance to insulin should be mentioned now as well, because, according to older studies, it can be found in a large number (up to a half according to some data) of Turner syndrome cases, often even since childhood. However, this demonstrably isn't related to the growth hormone therapy (growth hormone increases the blood sugar level), as recent studies have proven that patients can react to the increased glucose level by increasing the insulin production, which can cover possible resistance as well. Older studies showing that Turner syndrome patients develop type II diabetes, hypertension or hyperlipidemia have been toned down by newer studies, instead, the mechanisms associated with gained obesity are considered (effect of psyche – isolation – lack of activity?).

## Gonad disorders

Another basic symptom of Turner syndrome is the **gonadal dysgenesis** including all of its somatosexual and endocrine aftereffects. It is certain that the most severe form – **band-like, fibrous ovaries without gametes** – can be found in patients with the 45,X karyotype. On the other hand, the ovarian disorder can be limited (of

present at all) or present itself later in some structural aberrations or in mosaic forms.

Which genes are responsible for the development error is still not completely clear. Several "critical regions" (Xp11, Xq13-25, Xq26-28) and candidate genes exist: **ZFX** (Zinc Finger Protein X-linked; Xp22.2-21.3; OMIM: *314980 (https://www.omim.org/entry/314980)); **DIAPH2** (Homolog of Drosophila Diaphanous 2; Xq22; OMIM: *300108 (https://www.omim.org/entry/300108)) a **DFFRX** (Drosophila Fat Facets Related X-linked; Xp11.4; OMIM: *300072 (https://www.omim.org/entry/300072)). The ZFX gene codes a transcription factor of the "zinc finger" type; the DFFRX gene codes ubiquitin specific protease 9. All three genes are somehow connected to the development of gonads (it is necessary to acknowledge that some of these genes have been discovered on the basis of comparative genomic methods and their function was explored mainly on a model organism – the *Drosophila* in this case); the ZFX gene is implied in growth disorders as well.

In the case of pure chromosome X monosomia (and in germ lines with the 45,X karyotype in case of the mosaic form) another factor has to be considered, one which accelerates and aggravates the gonadal dysgenesis. It is the non-specific chromosomal effect, as cells with a solitary sex chromosome cannot enter meiosis, which leads to the **atresia of oocytes**.

Gonadal dysgenesis leads to the **absence of ovarian steroid hormones** manifesting as **hypergonadotropic hypogonadism**. Estrogen insufficiency is accompanied by multiply **higher gonadotropic hormone levels** (especially the FSH), whose secretion retains the biphasic course, nonetheless. The lack of estrogen then results in the **insufficient development of female sex organs and mammary glands**. Only 11–22 % of patients has high enough ovarian hormone levels to trigger menstruation (ovarian insufficiency has a tendency to develop gradually, however); **few patients (2–5 %) have an enduringly regular menstrual cycle** and are fertile. The morphological appearance of ovaries depends on the karyotype; the uterus remains poorly developed for a long time, of the so-called infantile type. Primary amenorrhea and the deficient development of secondary sex characteristics accompanied by the low growth are the exact most common reasons which lead the Turner syndrome patients to the practitioner.

Individuals with Turner syndrome having the Y chromosome or its part in their karyotype are exposed to a greater **risk of developing gonadoblastoma**. It is affected mainly by a region of the Y chromosome known as **GBY** (Gonadoblastoma Locus on the Y Chromozome), whose genes are responsible for physiological functions in men, but which can be oncogenic in the dysgenetic gonads. Probably the most influential gene in this group is the **TSPY** gene (Testis Specific Protein Y-linked; Yp11.2; OMIM: *480100 (https://www.omim.org/entry/480100)); it is assumed that it plays a significant role during the induction of meiosis in spermatogonia, but its erroneous or inappropriate expression can be oncogenic. Other "suspicious" genes are the **RBMY** (RNA Binding Motif Protein Y Chromozome; Yq11; OMIM: *400006 (https://www.omim.org/entry/400006)), the **PRKY** (Protein Kinase Y-linked; Yp11.2; OMIM: *400008 (https://www.omim.org/entry/400008)), the **PRY** (PTBL Related Gene on Y; Y; OMIM: *400019 (https://www.omim.org/entry/400019)), and the **AMELY** (Amelogenin Y Chromosomal; Yp11; OMIM: *410000 (https://www.omim.org/entry/410000)).

## Disorders of the lymphatic system

The abnormal development of the lymphatic system takes part in many disorders and complications in Turner syndrome, although the responsible genes on the X chromosome still avoid precise identification. The so-called "lymphogenic gene" is so-far being localized on the short arm of the X chromosome, further information isn't available yet. It is assumed that it doesn't undergo lyonization and has a functional homolog on the Y chromosome. Its absence is the cause for the developmental disorder of the lymphatic system that manifests as a dysfunction of the lymphatic drainage accompanied by the dilation of lymphatic vessels and lymphatic congestion. Widespread swellings appear – lymphedemas affecting the upper chest, neck, feet and other structures. These swellings deform neighboring soft tissues and are responsible for mane soft tissue dysfunctions in Turner syndrome. The **shield chest** forms this way, as well as the **low hairline** and the earlobe and nail abnormalities. Even the lateral webbing of the neck – pterygia (**pterygium colli**), typical of Turner syndrome, are formed on this basis.

## Disorders of the cardiovascular system

The pathogenesis of typical cardiovascular anomalies (coarctation of the aorta, arterial aneurysm, left heart abnormalities) are linked to the disorder of the lymphatic drainage in the prenatal age. Assumptions that even the defects of the urinary system (e.g. the horseshoe kidney) manifest based on the blocked lymphatic drainage exist as well.

## Neurocognitive disorders

It is often mentioned that Turner syndrome isn't connected with any deficiency of intellect. It is not entirely true in fact, although such disorders as those found in other chromosomal abnormalities (Down syndrome, Cri-du-chat syndrome) are definitely not present. The X chromosome has a special presence, since about a quarter of all genes linked with mental retardation are located on it. IQ levels in patients with Turner syndrome are almost equivalent as those in general populace. However, the **levels of nonverbal – perceptual IQ** (PIQ) can be **lower**. Turner syndrome patients may have **problems with short-term memory, concentration and** may show **indecisiveness** while solving simple tasks.

The phenomenon of genomic imprinting may play a role in the etiology of neurocognitive and psychosocial disorders in Turner syndrome. Although no concrete genes have been identified so far, it has been showing that it isn't so unimportant whether the X chromose (in the 45,X karyotype) is of maternal or paternal origin. The involved genes evidently don't have their homologous copy on the Y chromosome, still they don't undergo lyonization and they likely play a role in the sexual dimorphism of certain psychic processes. The entire process is still shrouded in

uncertainty, various anatomical variants of certain brain structures (amygdala, hippocampus) are being researched as well. The results of existing studies show that patients with a preserved maternal X chromosome have a greater tendency for neurocognitive disorders and tend to have problems with social adaptation. On the other hand, patients retaining a paternal X chromose have worse visual memory. Despite certain physical differences of Turner syndrome patients it is necessary to expect psychological complications also because of this reason (not just during the critical age of maturation, either).

# Diagnosis

Diagnostic methods can be classified into prenatal and postnatal diagnostics.

From the **prenatal** methods of **diagnostics** the most used ones are ultrasonography (its marker is notably hygroma colli cysticum) and karyotyping (after amniocentesis or chorion villus sampling). Recently the method of quantitative fluorescence polymerase chain reaction – **QFPCR** – is being employed as well, which is used for a numerical verification of selected chromosomes (including the X chromosome), but whose results must be verified through karyotyping nonetheless. Biochemical screening isn't specific in Turner syndrome. Turner syndrome (without more serious, visible developmental issues) isn't primarily indicated for interruption based on contemporary tendencies (the decision is left to the childbearer, nonetheless).

In **postnatal diagnostics** the karyotyping is being employed (it is necessary to confirm the diagnosis; differential diagnosis: Noonan syndrome, Léry-Weill syndrome, pure or mixed gonadal dysgenesis), which is indicated by the practitioner should the symptoms of the syndrome be present.

# Therapy

Nowadays, it is common to treat the syndrome with the recombinant **growth hormone**, which can improve the definite height to some degree, especially if it is administered since childhood. The effect of the treatment isn't equal to that in the growth hormone deficiency (the problem isn't caused by lower growth hormone levels, as has been noted above), but it can often mean at least psychological benefit, nonetheless. Because growth hormone can accumulate $Na^+$ (and water), the treatment by growth hormone can lead to a relapse of lymphedemas in Turner syndrome patients (notably because of low lymphatic drainage ability).

Another option is the **substitution hormone therapy**, whose goal is to improve the development of secondary sex characteristics and (depending on the severity of ovarian disability) attempt to achieve regular menstrual cycle, possibly even ovulation. Certain improvement can be expected in osteoporosis as well, though it is not primarily a result of estrogen insufficiency in Turner syndrome patients. It is necessary to estimate the biological age of the patients (it tends to be delayed) before administering the replacement estrogen therapy, because it causes the closure of epiphysal plates and disables further growth. During the first 21-23 days of the cycle estrogen is administered, gestagen is added since the 11. day of the cycle; the following 5 days are left without medication and the menstrual bleeding should become present.

Modern medicine can already partially solve the problem of infertility in Turner syndrome patients. Thanks to the **donated oocyte** and the methods of assisted reproduction it is possible to **become pregnant** even for patients with total gonadal dysgenesis. The embryo is implanted into the patient's uterus, which must be under substitution hormonal stimulation. Pregnancy of such patient must be supported by adequate hormonal treatment and must be considered high-risk.

# MKN-10 classification

Turner syndrome according to MKN-10:

- Q96 Turner syndrome:
  - Q96.0 Karyotype 45,X,
  - Q96.1 Karyotype 46,X iso (Xq),
  - Q96.2 Karyotype 46,X with abnormal sex chromosome, excluding iso (Xq),
  - Q96.3 Mosaic, 45,X/46,XX or XY,
  - Q96.4 Mosaic, 45,X/other germ line with abnormal sex chromosome,
  - Q96.8 Other variants of Turner syndrome,
  - Q96.9 NS Turner syndrome (non-specified).

# Links

## Related articles

- Disorders of the Sex Chromosomes


1. KLIEGMAN, Robert M. – MARCDANTE, Karen J. – JENSON, Hal B.. *Nelson Essentials of Pediatrics.* 5. edition. Elsevier Saunders, 2006. vol. 1. pp. 234-235. ISBN 978-0-8089-2325-1.
2. TURNER, Henry H. A syndrome of infantilism, congenital webbed neck, and cubitus valgus.. *Endocrinology.* 6-7/2005, vol. 23, p. 566-574, ISSN 0013-7227.