Nationwide study of Turner syndrome in children of Ukraine: analyses of the prevalence, genetic variants and phenotypic features

A short title: Turner syndrome in children of Ukraine

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What is already known on this topic
Turner syndrome (TS) is one of the most common genetic disorders associated with abnormalities of chromosome X. A significant delay at initial diagnosis of TS has been reported in all populations. The most serious malformations of TS include congenital and acquired heart diseases: aneurysm and aortic dissection, heart valves disease, hypertension, thromboembolic disease and myocardial infarction. Patients with TS are reported to have a higher frequency of autoimmune diseases including autoimmune thyroid and celiac disease.

What this study adds
The highest proportion of patients with TS had a karyotype 45,X. In Ukrainian population TS was accompanied by a lower frequency of malformations of internal organs compared to other countries.

Abstract
Background: We investigated the prevalence of Turner syndrome (TS) in Ukrainian population, the frequency of karyotype variants, the age of children at diagnosis, the degree of short stature and phenotypic features in TS girls.

Material and methods: A retrospective analyses was made in 538 TS girls aged 0.11–18.2 years old within the period of 2005-2015 with detailed examination of 150 patients.

Results and discussion: The prevalence of TS in Ukraine is 77.5 in 100,000 live births girls. The average age at diagnosis is 9.33±4.93 years old. In most cases TS girls had karyotype 45,X (59.32%), mosaicism 45X/46,XX (22.90%) and structural abnormalities chromosome X (17.78%). The most often findings were growth delay (98.82%), shortening of IV and V metacarpal bones (74.62%), abnormal nails (73.31%), broad chest (60.67%), short neck (58.63%), hypertelorism of nipples (51.37%), malformations of the cardiovascular system (19.62%), urinary system (13.82%), the pathology of vision (20.08%) and hearing (22.01%).

Conclusions: The highest proportion of patients with TS had a karyotype 45,X. In Ukrainian population TS was accompanied by a lower frequency of malformations of internal organs compared to other countries.

Key Words: Turner syndrome, prevalence, growth retardation, karyotype, phenotype, malformations.
Introduction

Turner syndrome (TS) is one of the most common genetic disorders associated with abnormalities of chromosome X (1). The incidence of this syndrome in a world has significant fluctuation between 25 and up to 210 per 100,000 live births in different populations because of the prevalence of mosaic forms and the lack of classical features of the disease (1-5).

A significant delay at initial diagnosis of TS has been reported in all populations (3, 6-8), thus the average age of TS diagnosis varies widely between 4.1 ± 5.1 years old in US (state Indiana) up to 13.74 years old in Albania (6, 9-11). The TS diagnosis in patients with karyotype 45,X is commonly determined earlier than other variants (9). Karyotype 45,X has been reported in 32-74% patients, whereas 9.2-31% patients are the carriers of different variants of chromosome X structural abnormalities or have a mosaic karyotype (9-56.3% of patients) (12-19).

The main manifestation of TS is the delay of growth of varying degrees: 20-30% of women who referred for help with the short stature were diagnosed with this syndrome (20). The definitive height in patients with karyotype 45,X, who do not receive treatment with recombinant growth hormone (rGH) is typically less than 142-145 cm, that is about 20 cm lower than the average growth in a healthy women population (21, 22).

The most serious malformations of TS include congenital and acquired heart diseases: aneurysm and aortic dissection, heart valves disease, hypertension, thromboembolic disease and myocardial infarction (23, 24). According to Sybert V. et al (24) in 56% of patients with TS has been revealed the pathology of cardiovascular system.

Defects of the urinary tract in patients with TS are observed in 30-40% of the cases, including pyelocaliceal system’s defects, horseshoe kidney and other anomalies of kidneys location (25, 26).

In patients with TS major stigmas of disembr yogenesis of eyes and eye appendages are epicanthus, palpebral ptosis and strabismus (20, 27). Pathology of hearing in patients with TS is characterized by a high frequency of otitis media. It is assumed to be caused by abnormalities in eustachian tube and middle ear (20, 28-29).

Patients with TS are reported to have a higher frequency of autoimmune diseases including autoimmune thyroid and celiac disease (30-33). According to the different researches in Europe 36-64.8% of patients with TS have increased levels of antithyroid antibodies (6, 30-35), and 21.2-70.4% patients out of that number have subclinical or clinical hypothyroidism (30, 31, 33-35).

The aim of our study was at first to investigate the prevalence of TS among children in Ukraine, to determine the age at initial diagnosis, the frequency of different karyotype variants, the degree of growth delay in girls (including those who didn’t receive treatment with rGH), and the prevalence of different phenotypic features of TS and malformations.

Materials and Methods

In this study the Ukrainian Pediatric TS Registry created in 2004 has been used. The Registry included children diagnosed with TS, aged 0.11-18.2 years old identified by regional Ukrainian pediatric endocrinologists. TS Registration cards contained the following information: date of child’s birth, age at diagnosis, karyotype, objective examination (height (cm), height SD (WHO, 2007) (36), weight (kg), body mass index (BMI (kg/m²) which was assessed using percentiles tables for girls of appropriate age (WHO, 2007) (36), stage of sexual development (by Tanner) (37), phenotypic features; biochemical and hormonal parameters (TSH, fT4, thyroid peroxidase antibodies (TPOAb), LH, FSH, estradiol, IGF-1, GH (results of clonidine stimulation test to exclude pituitary dwarfism); bone age (X-ray by Greulich and Pyle atlas); data of functional investigation with the annual update etc.

A retrospective analysis of 538 Registration cards of TS girls who were registered between 2005 and 2015 have been conducted.

 Besides this, 150 girls with TS were examined in Ukrainian Scientific Center of Endocrine Surgery Ministry of Ukraine and in the National Children's Specialized Hospital "OHMATDYT". Diagnosis of TS was confirmed by determination of karyotype in blood leukocytes. Depending on the karyotype’s variant patients were divided into 3 groups. The first group included patients with karyotype 45,X (n = 319); the second group – with the mosaic karyotype 45,X/46,XX (n = 123); the third group – girls with structural abnormalities of chromosome X: 46,Xi(Xq), 45,X/46,Xi(Xq), 45,X/46,X+mar, 46,X,del(X)(Xq) and 45,X/46,Xdel (n = 96). The physical
development of girls with TS were compared with healthy girls in the control group (n = 525) aged from 10 months to 18 years old. 

In these selected groups all parameters from TS Registration cards in 150 patients were re-evaluated. To study anomalies of internal organs patients underwent ultrasound of internal organs and heart ultrasound (echocardiography). Audiogram was performed to all patients with hearing loss. Also, all children were examined by an ophthalmologist and otolaryngologist to confirm the presence of any abnormal features. With the aim to study the thyroid function in patients with different TS karyotype, we analyzed levels of TSH, fT4 and TPOAb.

Statistical analysis of the results was performed by using Statistica 10 (StatSoft, USA). Standard non-parametric statistical tests, and Kruskal-Wallis test or Student’s t-test in the case of normal distribution were used. For the analysis of qualitative data (%) for two or more independent groups Pearson was used. One-Way ANOVA test was used for the quantitative data analyses in groups. Data is presented as mean value (M) and standard deviation (SD), as well as Me [25; 75], where Me - median and 25; 75 - interquartile value (25th and 75th percentile), the parametric and nonparametric distribution characteristics respectively. A (p<0.05) was taken as an indicator of significant difference.

Results

According to the Ukrainian Pediatric TS Registry, the prevalence of TS among children 0-18 years old was 77.5 per 100 000 live births. Over the last 5 years there had been 17-25 new registered cases with TS annually (38). Among girls with TS (n=538), different karyotype variants were found, however monosomy 45,X was identified more often – in 59.32% of patients (p<0.001), compared with mosaicism 45,X/46,XX (22.90%) and structural abnormalities of chromosome X (17.78% patients, including 46,Xi(Xq) – at 5.11%, 45,X/46,XX(Xq) – at 6.90%, 45,X/46,X+mar – at 3.16%, 46,X,del(X)(Xq) – at 1.87% and 45,X/46,X,del – in 0.74% of patients).

In Ukraine the average age of initial diagnosis of TS in children was 9.33±4.93 years old, however it depended on the karyotype: the lowest was in children with karyotype 45,X compared to children with structural abnormalities of chromosome X (p<0.05): 45,X(n = 303) - 8.96±5.28 years old, structural abnormalities of chromosome X (n = 87) - 10.49±3.95 years old, 45,X/46,XX (n = 111) - 9.50±4.41 years old.

In 1.62% girls the diagnosis of TS was revealed at the first year of life, in 3.60% - at age of 1-4 years old, in 9.46% - at 5-7 years old, in 18.92% - at early puberty (at 8-11 years old) and in 66.40% - at 12-17 years old.

Phenotypic manifestations of TS in children had significant variability. In the general population of TS girls, the growth delay was a constant feature (98.82% of patients). In addition, the shortening of IV and V metacarpal bones (74.62% patients) following by abnormal nails (73.31%), broad chest (60.67%), short neck (58.63%), sexual development delay (57.32%) and hypertelorism of nipples (51.37%) were most often findings. These manifestations of TS were most frequent in patients with karyotype 45,X and significantly less frequently had been observed in patients with 45,X/46,XX and structural abnormalities of chromosome X (p<0.05).

The most common pathology of internal organs, accompanied by TS was malformations of the cardiovascular system (19.62% of children). Mainly, it was aortic stenosis (5.32% of children), coarctation of the aorta and bicuspid aortic valve (2.63% and 2.02% of cases accordingly). Malformations of the cardiovascular system were found more often in children with mosaicism (26.18%) and in case of structural abnormalities of chromosome X (21.62%) compared to the karyotype 45,X (15.85% of patients) (p<0.05).

Less frequently were observed the urinary tract malformations (13.82% of patients), which were significantly more common in patients with karyotype 45,X (14.76%), and less – in case of karyotype 45,X/46,XX (8.28%) and structural abnormalities of chromosome X (2.75%), (p<0.05). The main malformations of urinary tract in girls with TS included doubling pyelocaliceal renal system (3.38%), renal hypoplasia (3.36%) and ureters malformations (3.31% of patients).

The pathology of vision was found in 20.08% of TS patients and pathology of hearing – in 22.01% (p>0.05, Table 1). The most common pathology of the ears was otitis which was observed with a maximum frequency in children with monosomy X (p<0.01), (Table 1).
Studies on frequency of autoimmune thyroid disease in TS girls have shown elevated levels of TPOAb in 48.45% patients regardless of karyotype (p>0.05). Among TS girls with elevated TPOAb levels more often subclinical (48.76%) and clinical hypothyroidism (29.14%, p<0.05) were found. The 11.87% of patients were euthyroid, but 10.23% of girls had subclinical hyperthyroidism.

Until 2013, in Ukraine there had been no state program providing the TS children free treatment with rGH, thus most patients were untreated. The analysis of indicators of growth in girls with TS, who did not receive treatment with rGH compared to the control group of appropriate age revealed a significant difference in the growth of children in all age groups (Table 2). The difference was noticeable in the first year of life, increased with age and was highest in 14 years old, more likely due to the lack of pubertal growth jump in patients with TS. As a result the difference between the final definitive height in TS girls was 24.4±1.7 cm compared to the control group (p<0.001).

Analysis of the definitive height in girls with TS, who did not receive treatment with rGH revealed no significant difference (p>0.05) between girls with different karyotype (Table 3).

In Ukrainian population of girls with TS we registered spontaneous (without hormonal stimulation) sexual development (which was assessed by the appearance of thelarche) in 14.62% (n=18) pubertal age girls. However, in groups with different karyotype there was no significant difference in the age of onset of puberty (p>0.05). The number of girls with different karyotype and spontaneous sexual development and the age of puberty is shown in Table 4.

We found spontaneous menstruations in 38.82% of TS girls having signs of true self-sexual development. It is noteworthy to say that among girls with spontaneous puberty and karyotype 45,X there were three girls with Tanner stage II, three girls with Tanner stage III after the age of 15 years old and three girls had even spontaneous menarche at age of 15±[14.30; 16.20] years.

The frequency of body weight disorders in TS girls was studied. BMI of TS girls was compared to BMI of girls with similar age in the control group. As a result, it was found that most of TS girls (68.1%) had a normal BMI (p<0.05), whereas 13.82% of patients had overweight, 6.88% were obese and 11.20% of patients had a lack of body weight (BMI<15th centile). The average BMI in patients with TS was within 53.23±27.06 percentile that was significantly higher (p>0.05) compared to the control group (50.62±27.63 percentile), (Table 5).

According to our data, BMI in patients with TS increased with age and reached a maximum in children over the age of 12 years old, but did not exceed the normal range, which may be considered as a reflection of the physiological process of growth with a similar trend in children in the control group. The highest BMI (p<0.05) was found in girls with structural abnormalities of chromosome X (Table 6).

**Discussion**

The current study was the pilot in Ukraine aimed to research the prevalence of TS, the age at initial diagnosis, the incidence of different variants of the karyotype, phenotypic characteristics, the presence of associated components of this syndrome, indicators of physical and sexual development in TS girls with different karyotype.

It has been found that in 2015 the prevalence of TS among children 0-18 years in Ukraine was 77.5 per 100 000 live births, that was more than in Denmark (3, 5), Germany (9), Albania (6) and Japan (2). In Ukraine, the age of initial diagnosis of TS was 9.33±4.93 years with a maximum frequency of initial registration of the disease in puberty, more likely because of the maximum referrals of patients with the growth delay or delay/absence of sexual development or menstruations in the puberty age. The highest proportion of early primary diagnosis of TS in Ukraine included patients with karyotype 45,X, who were diagnosed more early (an average at 8.96±5.28 years old), which can be explained by the presence of typical features of the disease in these girls. The earliest age of diagnosis in girls with this karyotype is similar to those in other countries (9, 11).

In Ukraine, the largest proportion of patients diagnosed with TS (59.32%) have karyotype 45,X, that is similar to Poland, UK and USA (17-19). Diagnostic of different karyotype’s variants depends on the different methods of analysis and the number of types of biological material that has been used. To determine the karyotype the cytogenetic analysis of peripheral blood lymphocytes was
only used. However, according to Hook and Warburton (39), all live births girls with karyotype 45,X, have a mosaic karyotype in fact, because some of their organs and tissues contain more cell lines with normal or aberrant sex chromosomes, which cannot be determined by conventional methods. This may be a rationale for further research of karyotype in other tissues in 45,X girls, especially in those who have signs of spontaneous puberty or mild growth delay.

In Ukraine there is a lower frequency of malformations of cardiovascular and urinary tract in children with TS, compared to the US (40-42), UK (43), Egypt (44), Denmark (45) and France (46). The lower frequency of malformations of the cardiovascular system in Ukraine may be explained by the lack of the routine magnetic resonance imaging (MRI) of heart in girls with TS in the absence of clinical symptoms. These results are in the need of the detailed and focused examination to detect the above mentioned pathology, even in the absence of clinical manifestations to evaluate the aortic dilatation and abnormalities associated with it in pediatric patients with TS.

The frequency of pathology of vision and hearing also was lower in Ukraine compared to other countries (20, 27-29). The fewer frequency of auricular pathology can be explained by the providing audiogram only to patients with hearing loss.

Basically children in Ukraine have lower frequency of malformations of internal organs despite of nationwide complex diagnostics and awareness between pediatric endocrinologists. However, the insufficient diagnostics of cardiovascular system and auricular pathology is being also present.

Studies on the frequency of autoimmune thyroid disease have showed increased TPOAb levels in 48.45% of patients with TS, that is similar to Italy (32), Denmark (33), but is less than in Albania (6) and Poland (35). However among girls with elevated TPOAb levels the number of patients with hypothyroidism (subclinical and clinical) was larger (77.9 %) than in other European countries (30, 31, 33-35).

Studies of the height of girls with TS, who did not receive treatment with rGH, compared with the control group, have shown that this parameter was significantly lower in all age groups which is consistent with other studies (21, 22). The progression of the degree of growth delay had been increased with age and was more pronounced in puberty. The definitive height of patients with TS who did not receive treatment with rGH was significantly lower, compared to women with normal female karyotype in Ukrainian population.

Most girls with TS (68.1%) had normal body weight, however overweight was detected in 13.82% of patients, obesity – in 6.88% and the lack of body weight – in 11.20% of patients. The frequency of overweight in children with TS was higher than in the general population of children in all age groups with a significant difference in puberty, which coincides with the findings of other authors (47-49). The highest BMI and the highest rate of overweight we observed in patients with structural abnormalities of chromosome X. To our knowledge, this data had not been thoroughly described previously.

In conclusion the lower frequency of malformations of internal organs in Ukraine that were found compared to other countries makes it necessary to widely use cardiac MRI and audiogram in all patients with TS. Additionally, the implementation of genetic testing to identify genes associated with malformations (ZFYVE9, TIMP1, PRKX, KDM6A) can lead to higher detection rate of aortic aneurysm formation, congenital urinary malformations and others (50).

Eventually, the early diagnosis of TS will allow providing timely the adequate medical, psychological and social assistance in children with TS and their families. It is assumed that pediatricians and family physicians should provide an active and targeted search of the reviewed disease among girls, especially in those with a delay of growth and sexual development in order to prevent short stature and late or insufficient diagnostic of malformations of internal organs.

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Conflict of interest: none declared.
Ethics Committee Approval: This study was approved by the Ethics Committee of Ukrainian Scientific Center of Endocrine Surgery MoH of Ukraine. All procedures performed in the studies involving patients were in accordance with the ethical standards of the institution on clinical practice and with the 1964 Helsinki Declaration, as amended.

Informed Consent: The parents or legal guardians of patients signed informed-consent forms in which they agreed to the treatment and all the diagnostic procedures required.

Peer-review: Externally peer-reviewed.

Authorship Contributions


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References


Table 1. The spectrum of pathology of vision and hearing in TS girls with different karyotype

<table>
<thead>
<tr>
<th>Pathology</th>
<th>In the general population of TS girls n=346</th>
<th>45.X n=200</th>
<th>45.X/46.XX n=84</th>
<th>Structural abnormalities of chromosome X n=62</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amblyopia, %</td>
<td>5.43 ± 4.91</td>
<td>5.26</td>
<td>4.62</td>
<td>p&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Strabismus, %</td>
<td>4.91 ± 5.32</td>
<td>5.20</td>
<td>8.11</td>
<td>p&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Myopia, %</td>
<td>8.65 ± 8.04</td>
<td>10.57</td>
<td>8.14</td>
<td>p&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Frequent otitis, %</td>
<td>12.62 ± 17.37</td>
<td>10.54</td>
<td>5.46*</td>
<td>p&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Hearing loss, %</td>
<td>9.39 ± 10.62</td>
<td>5.28</td>
<td>8.17</td>
<td>p&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

*= the difference between groups of patients with karyotype 45X and structural abnormalities of chromosome X.

Table 2. Girls height in TS girls without rGH treatment and in control group, including different age groups

<table>
<thead>
<tr>
<th>Age group</th>
<th>Height (cm) in TS group, mean ± SD, n = 502</th>
<th>Height (cm) in control group, mean ± SD, n = 525</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>before 1 year</td>
<td>61.45 ± 8.12</td>
<td>66.69 ± 7.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-3 years</td>
<td>82.06 ± 7.02</td>
<td>89.38 ± 8.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4-7 years</td>
<td>100.93 ± 8.42</td>
<td>114.21 ± 8.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8-11 years</td>
<td>120.72 ± 8.33</td>
<td>137.99 ± 8.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12-17 years</td>
<td>136.87 ± 7.83</td>
<td>160.58 ± 7.14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3. Definitive height in TS girls with different karyotype

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Definitive height (cm)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.X (n = 80)</td>
<td>140.90</td>
<td>-3.38 [-4.00; -2.70]</td>
</tr>
<tr>
<td>45.X/46.XX (n = 23)</td>
<td>142.02</td>
<td>-3.12 [-4.10; -2.20]</td>
</tr>
<tr>
<td>Structural abnormalities of chromosome X (n = 26)</td>
<td>140.75</td>
<td>-3.27 [-4.00; -2.60]</td>
</tr>
<tr>
<td>All TS patients with closed growth plates (n = 129)</td>
<td>141.09</td>
<td>-3.31 [-4.00; -2.60]</td>
</tr>
</tbody>
</table>
Table 4. The frequency of spontaneous sexual development and the age of puberty in TS girls with different karyotype

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Girls with spontaneous sexual development, %</th>
<th>Age of puberty, years Me [25, 75]</th>
</tr>
</thead>
<tbody>
<tr>
<td>45,X (n = 61)</td>
<td>11.56</td>
<td>15.76 [13.28; 16.65]</td>
</tr>
<tr>
<td>45,X/46,XX (n = 31)</td>
<td>25.82</td>
<td>14.20 [13.10; 16.20]</td>
</tr>
<tr>
<td>Structural abnormalities of chromosome X (n = 31)</td>
<td>9.62</td>
<td>16.11 [14.80; 16.60]</td>
</tr>
</tbody>
</table>

Table 5. Assessment of body weight using percentiles tables in children of all ages with TS

<table>
<thead>
<tr>
<th>Investigated groups</th>
<th>Age groups, mean ± SD</th>
<th>before 1 year</th>
<th>1-3 year</th>
<th>4-7 year</th>
<th>8-11 year</th>
<th>12-17 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>TS patients (n = 538)</td>
<td>65.33±29.54</td>
<td>56.48 ± 26.58</td>
<td>49.13 ± 28.25</td>
<td>57.38 ± 27.14</td>
<td>55.17 ± 27.28</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>control group (n = 525)</td>
<td>67.60± 27.03</td>
<td>52.06 ± 29.69</td>
<td>52.14 ± 28.40</td>
<td>50.16 ± 29.97</td>
<td>44.73 ± 22.62</td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td>0.84</td>
<td>0.58</td>
<td>0.04</td>
<td>0.06</td>
<td>0.0000013</td>
</tr>
</tbody>
</table>

*p – p-value between BMI in TS girls and the control group

Table 6. Body weight in children with TS and different karyotype

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>BMI, percentiles mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50.63±27.66</td>
</tr>
<tr>
<td>45,X</td>
<td>53.09± 26.73</td>
</tr>
<tr>
<td>45,X/46,XX</td>
<td>54.11±27.23</td>
</tr>
<tr>
<td>Structural abnormalities of chromosome X</td>
<td>62.16 ± 28.40</td>
</tr>
</tbody>
</table>

*p – difference among patients with TS karyotype 45,X and X chromosome structural abnormalities

1p – difference among patients with TS karyotype 45,X/46,XX and X chromosome structural abnormalities

2p – difference among control group (karyotype 46,XX) and X chromosome structural abnormalities