New insights into clinical features, karyotypes, and age at diagnosis in women with Turner syndrome

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Abstract

Introduction: Turner syndrome (TS) is due to a chromosomal abnormality in which only one normal X chromosome is present. The purpose of the study was to assess the prevalence of phenotypic differences in TS-women and monosomy-45,X and with other karyotypes as well as the possible relationship between the presence of differentiating features and age at final TS diagnosis.

Material and methods: The prevalence of anomalies and abnormalities from history taking/physical examination of 157 TS-patients was compared to 25 healthy controls (age 27.3 ± 4.5 years). The age at TS-symptom occurrence and final TS diagnosis was also analysed.

Results: Ninety-three TS women with 45,X (25.2 ± 7.1y) and 64 with other karyotypes (non-45,X) (age 24.1 ± 8.2 years) had lower growth than controls (144 ± 7.6 and 145.7 ± 6.8 vs. 165.8 ± 6.6 cm, respectively; p < 0.001). Only 15 and 12 out of 37 non-gynaecological features occurred more frequently in 45,X and non-45,X, compared to controls. 45,X and non-45,X women did not differ in terms of body height. Out of 60 study parameters, only nine differed significantly between 45,X TS women and those with other karyotypes. Mean age at TS-symptom occurrence (45,X: 6.8 ± 5.4 years; non-45,X: 10.3 ± 5.2 years; p < 0.001) and final TS diagnosis (45,X: 13.2 ± 8 years; non-45,X: 17 ± 8.2 years; p = 0.004) differed between TS groups.

Conclusions: 1. The prevalence of the majority of clinical manifestations of Turner syndrome does not differ between TS women with 45,X monosomy and non-45,X karyotypes. 2. Certain manifestations of Turner syndrome are more prevalent in women with non-45,X karyotypes compared to those with 45,X monosomy. 3. Clinical manifestations, the prevalence of which differs between TS-women with non-45,X karyotypes and 45,X monosomy, might help lower the age at diagnosis.

Key words: Turner syndrome; clinical features; phenotype; karyotype; age at diagnosis

Introduction

Turner syndrome (TS) is due to a chromosomal abnormality in which only one normal X chromosome is present. Its aetiology is still unknown [1, 2]. Turner syndrome includes a wide variety of chromosomal karyotypes and clinical phenotypes [3]. A majority of TS features are due to reduced dosage of genes on the short arm of the X chromosome (Xp) [4]. Because TS is associated with a wide variety of anatomical and physiological abnormalities, its phenotypic presentation is highly variable and has not been ultimately determined [5–7]. Physical stigmata can be quite subtle or absent, and this phenotypic variability of TS remains challenging for clinicians [8, 9]. Basic phenotypic abnormalities occur in the tissues of mesodermal origin [10]. Clinical manifestations found in TS females can either be attributed to chromosome X abnormality or gonadal dysgenesis. Treatment-related symptoms cannot entirely be excluded either. Because there are no pathognomonic features of Turner syndrome, the disorder should be considered in any female with short stature or delayed puberty [11].

Life expectancy of women with TS is shorter than that of the general population, mainly due to cardiovascular pathologies [12]. Despite progress in the diagnosis as well as treatment of organ abnormalities and clinical sequelae thereof, premature mortality remains a major problem. In adult females, the diagnosis of TS complications is frequently delayed [13]. There is also no clear-cut evidence to suggest that TS women with 45,X monosomy are at greater risk of morbidity or mortality than women with other karyotypes. Several investigations, including the present study, have focused on these issues [14]. For instance, Lebenthal et al. [15] analysed metabolic comorbidities in TS patients and attempted to determine whether their occurrence differed between 45,X monosomy and other karyotypes. Nevertheless, a range of issues regarding diagnosis, treatment, rehabilitation, and the overall approach to patients with Turner syndrome remain unsolved [16].
The aim of the study was to determine the following:
— the prevalence of phenotypic differences in TS patients with 45,X monosomy and those with other karyotypes as established on history taking and physical examination;
— the possible relationship between the presence of clinical features differentiating 45,X monosomy from other karyotypes and the age at symptom emergence and final diagnosis of TS.

The results may have practical implications. Nielsen and Wohlerl [17] studied sex chromosome abnormalities and found that TS occurred in one per 2130 girls. In Poland there are approximately 8000 females with Turner syndrome, of whom 5000 are over 18 years old. In a large proportion of this population the diagnosis was significantly delayed. Therefore the identification of clinical features that emerge early enough to facilitate diagnosis might help lower the age at final diagnosis of Turner syndrome and, consequently, accelerate treatment initiation, prevent complications, and improve quality of life and life satisfaction.

Material and methods

The study population comprised 157 patients with TS including 93 women diagnosed with 45,X monosomy and 64 women with other karyotypes (non-45,X). The control group comprised 25 healthy women of the general population. The study groups did not differ with respect to age (25.2 ± 7.14 and 24.1 ± 8.24 years, respectively), the proportion of participants who had received growth hormone therapy in their childhood (20.4 and 17.2%, respectively), or the proportion of women presently on hormone replacement therapy (HRT) (52.7 and 54.7%, respectively).

The diagnosis of TS was confirmed by karyotyping using cytogenetic and advanced molecular analysis [13]. Features to be assessed were selected based on literature descriptions of tissue and organ abnormalities seen in TS women (18-20). The following 36 non-gynaecological clinical features were evaluated prospectively based on each patient’s medical history and records: systemic diseases (history of thyroid diseases, arterial hypertension, diabetes mellitus — three features), ear, nose and throat (ENT) and maxillofacial surgery (feeding problems during infancy, low-set and/or deformed ears, hearing loss, otitis media, surgery for otitis media, oral cavity soft tissue abnormalities, third tonsil surgery, high-arched palate - eight features), dentistry (dental caries and tooth loss, dental braces, malocclusion, retrognathism — four features), ophthalmology (history of skin diseases, neck anomalies — the prevalence of webbed neck, — the prevalence of abnormal cervicovaginal cytology test and surgical interventions was assessed as well as the history of miscarriages, the occurrence of symptoms, and age at menopause. The study participants, from the whole of Poland, were examined from March 1995 to September 2015 in Poland’s only “de nomine” outpatient clinic for women with Turner syndrome. The investigations were conducted by the same group of investigators over a period of 20 years in Bytom and Katowice. All participants gave their consent to study procedures, all of which were approved by the Bioethics Committee. The prevalence of anomalies and abnormalities found on history taking/physical examination of women with Turner syndrome and 45,X monosomy or other karyotypes is presented in table form. There were 36 non-gynaecological parameters grouped according to the above-mentioned areas of interest. The prevalence of the majority of these features was compared between each of the study groups and the controls. These 36 parameters plus the above-mentioned endocrine-obstetric-gynaecological features (n = 23) and body height resulted in a total of 60 study parameters. An analysis of parameter prevalence and mean values (in the case of quantitative parameters, e.g. birth length and weight) enabled us to identify features differentiating between TS women with 45,X and those with other karyotypes.

The age at TS-symptom occurrence and final TS diagnosis was also noted. The mean age at symptom occurrence and final diagnosis of Turner syndrome was determined in TS women who exhibited the features differentiating between the 45,X and non-45,X karyotypes. This was done in an attempt to establish possible relationships between these features and age at symptom occurrence and final TS diagnosis. The statistical analysis was carried out using Statistica 12 software (StatSoft Inc., Palo Alto, CA, USA). The results are presented as the mean ± standard deviation (SD). The results were compared with the unpaired t-test. The bilateral test of differences between two structural indicators was applied to evaluate the number of occurrences of a particular value. The level of statistical significance was set at p < 0.05.

Results

Ninety-three (59.3%) women with TS had simple 45,X monosomy while 64 (40.7%) had other, non-45,X karyotypes. The following karyotypes were revealed in the non-45,X group: 18 (11.5 %) women with structural abnormalities of the X chromosome (e.g. isochromosome X, partial deletion of an arm of the X chromosome, ring X chromosome or translocation between the X chromosome and the autosomal material); another subgroup of 46 (29.3 %) patients had mosaic karyotypes [24 (15.3%) mosaicism without structural chromosome abnormality: seven with X monosomy and normal male cell line, 15 with X monosomy and normal female cell line, two with X monosomy and an aneuploid female cell line — trisomy] and 22 (14%) mosaicism with a second cell line with structural chromosome X abnormality.

**TS groups vs. controls**

TS women with 45,X monosomy and with non-45,X karyotypes had significantly shorter stature compared to the general population (144 ± 7.6 and 145.7 ± 6.8 cm vs. 165.8 ± 6.6 cm, respectively; p < 0.001). The controls and TS women with 45,X monosomy differed significantly with respect to the prevalence of webbed neck,
childhood lymphoedema, dense eyebrows and long lashes, drooping eyelids, epicanthal folds, abnormalities of the shape and position of the pinna, middle ear infections and hearing impairment, feeding problems during infancy, unusual palatal configurations, and retrognathism. TS women also showed a lower prevalence of dental anomalies. TS women with non-45,X karyotypes did not differ significantly with respect to arterial hypertension (two parameters) and the history of childhood lymphoedema compared to the control group. Compared to the controls, only 15 and 12 out of 37 non-gynaecological features under analysis were found in TS-women with 45,X monosomy and non-45,X karyotypes, respectively (Tab. I).

Table I. Abnormalities revealed on history taking and physical examination in women with Turner syndrome and 45,X (A), other karyotypes (B), and the control participants (C)

<table>
<thead>
<tr>
<th>Feature</th>
<th>A (n = 93)</th>
<th>B (n = 64)</th>
<th>C (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>28 (30.1)</td>
<td>30.1</td>
<td>0 (0)</td>
<td>0.017</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (5.5)</td>
<td>3 (4.7)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>History of thyroid diseases</td>
<td>17 (18.5)</td>
<td>10 (15.6)</td>
<td>6 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Feeding problems during infancy</td>
<td>50 (55.6)</td>
<td>38 (64.4)</td>
<td>3 (12.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low-set and/or deformed ears</td>
<td>77 (82.8)</td>
<td>56 (87.5)</td>
<td>5 (20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>29 (31.2)</td>
<td>22 (34.3)</td>
<td>2 (8.3)</td>
<td>0.024</td>
</tr>
<tr>
<td>Otitis media</td>
<td>64 (68.8)</td>
<td>42 (66.7)</td>
<td>9 (37.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Surgery for otitis media</td>
<td>11 (11.8)</td>
<td>4 (6.3)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Oral cavity soft tissue abnormalities</td>
<td>2 (2.2)</td>
<td>3 (4.7)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Third tonsil adenoidectomy</td>
<td>24 (25.8)</td>
<td>15 (24.6)</td>
<td>4 (16.7)</td>
<td>NS</td>
</tr>
<tr>
<td>High-arched palate</td>
<td>83 (89.3)</td>
<td>53 (82.8)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dental caries and lost teeth</td>
<td>6 (6.5)</td>
<td>4 (6.3)</td>
<td>13 (54.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dental braces</td>
<td>17 (18.3)</td>
<td>9 (14.1)</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>Malocclusion</td>
<td>41 (44.1)</td>
<td>226 (40.6)</td>
<td>13 (54.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Retrognathism</td>
<td>58 (62.4)</td>
<td>36 (56.3)</td>
<td>5 (20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of vision defects</td>
<td>52 (56.5)</td>
<td>37 (57.8)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Drooping eyelids</td>
<td>48 (51.6)</td>
<td>30 (46.9)</td>
<td>2 (8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Epicanthal folds</td>
<td>30 (32.3)</td>
<td>22 (34.4)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dense eyebrows, long eyelashes</td>
<td>63 (67.7)</td>
<td>47 (73.4)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Squint</td>
<td>11 (11.8)</td>
<td>17.2</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Daltonism</td>
<td>0</td>
<td>3.1</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Childhood lymphoedema</td>
<td>35 (37.6)</td>
<td>14.3</td>
<td>1 (4)</td>
<td>0.0012</td>
</tr>
<tr>
<td>History of skin disease</td>
<td>22 (23.9)</td>
<td>20.3</td>
<td>1 (4)</td>
<td>0.026</td>
</tr>
<tr>
<td>Neck anomalies (short/webbed)</td>
<td>61 (65.6)</td>
<td>43.8</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low posterior hairline</td>
<td>59 (64.1)</td>
<td>46 (74.6)</td>
<td>1 (4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Facial hypertrichosis</td>
<td>8</td>
<td>8.6</td>
<td>6.3</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Fingernail anomalies</td>
<td>48 (51.6)</td>
<td>44.4</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>Heart defect(s)</td>
<td>14 (15.1)</td>
<td>7.8</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>History of cardiosurgery</td>
<td>2</td>
<td>2.2</td>
<td>4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure ≥ 140/90 mm Hg</td>
<td>30 (32.3)</td>
<td>32.8</td>
<td>0 (0)</td>
<td>0.014</td>
</tr>
<tr>
<td>Urinary system malformations</td>
<td>18 (19.4)</td>
<td>12.5</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>Urologic surgery</td>
<td>3</td>
<td>3.2</td>
<td>3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Conservative kidney management</td>
<td>26 (28.3)</td>
<td>42.2</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>Posture defects</td>
<td>49 (52.7)</td>
<td>28.1</td>
<td>–</td>
<td>0.002</td>
</tr>
<tr>
<td>Finger/toe deformity</td>
<td>29 (31.2)</td>
<td>15.9</td>
<td>–</td>
<td>0.03</td>
</tr>
</tbody>
</table>

V — absolute values; % — percentage; NS — not significant; (–) no data
45,X monosomy vs. non-45,X karyotypes

Our TS-participants with 45,X monosomy were not significantly shorter than those with non-45,X karyotypes (144 ± 7.6 and 145.7 ± 6.8 cm, respectively; p = 0.133). The respective birth lengths were 51.6 ± 2.9 and 49.7 ± 4.9 cm; the birth length of women with 45,X monosomy was significantly greater (p = 0.038). Birth weight (2849.1 ± 508.8 and 2738.2 ± 649.3 g, respectively), age of puberty (15.7 ± 1.6 and 15.7 ± 3 years, respectively), age at menarche (16.6 ± 1.9 and 17.2 ± 5.2 years, respectively), and age at menopause onset (21.1 ± 8 and 19.7 ± 6.5 years, respectively) did not differ significantly between the groups. Out of 60 parameters analysed, nine differed significantly between TS women with 45,X monosomy and those with other karyotypes. TS women with 45,X monosomy more frequently had: 1. clinical records of childhood lymphoedema, 2. short and webbed neck, 3. low posterior hairline, 4. postural defects, and 5. finger/toe deformities (all compared to TS women with other karyotypes). The prevalence of 19 out of 23 endocrine-obstetric-gynaecological features (Tab. II) did not differ significantly between the two groups of women with TS. The differentiating features were: 1. pubertal induction, 2. menarche induction, 3. proportion of gynaecological surgeries, and 4. birth length. Only the first two features were more prevalent in 45,X monosomy.

The mean age at TS-symptom occurrence and final diagnosis of Turner syndrome

The mean age at TS-symptom occurrence (45,X monosomy 6.8 ± 5.4 years vs. other karyotypes 10.3 ± 5.2 years; p < 0.001) and final diagnosis of Turner syndrome (45,X monosomy — 13.2 ± 8 years vs. non 45,X - 17 ± 8.2 years; p = 0.004) differed significantly between both study groups. The mean age at symptom development and final diagnosis of Turner syndrome in patients from both study groups with: clinically documented childhood lymphoedema, short and webbed neck, low posterior hairline, postural defects and finger/toe deformities was 17.2 ± 5.2 years.

Table II. The prevalence and severity of endocrine-obstetric-gynaecological features in 157 women with TS and 45,X monosomy or non-45,X karyotypes

<table>
<thead>
<tr>
<th>Feature</th>
<th>45,X (n = 93)</th>
<th>non-45,X (n = 64)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental consanguinity</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Intoxication during pregnancy</td>
<td>56</td>
<td>44</td>
<td>NS</td>
</tr>
<tr>
<td>Premature birth</td>
<td>8</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>51.6 ± 2.9</td>
<td>49.7 ± 4.9</td>
<td>0.038</td>
</tr>
<tr>
<td>Body weight at birth (g)</td>
<td>2849 ± 509</td>
<td>2738 ± 649</td>
<td>NS</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>8</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Age at puberty (years)</td>
<td>15.7 ± 1.6</td>
<td>15.7 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Induced puberty</td>
<td>55</td>
<td>26</td>
<td>0.023</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>16.6 ± 1.9</td>
<td>17.2 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Induced menarche</td>
<td>75</td>
<td>39</td>
<td>0.006</td>
</tr>
<tr>
<td>Abnormal cervicovaginal cytology test</td>
<td>16</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Tanner stage &lt; IV</td>
<td>55</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>Gynaecological surgeries</td>
<td>7</td>
<td>11</td>
<td>0.008</td>
</tr>
<tr>
<td>Loss of menstrual cycle</td>
<td>24</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>No GH treatment in childhood</td>
<td>71</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>No oxandrolone therapy</td>
<td>68</td>
<td>44</td>
<td>NS</td>
</tr>
<tr>
<td>No history of HRT</td>
<td>7</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>8</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>5</td>
<td>0</td>
<td>0.059 (NS)</td>
</tr>
<tr>
<td>Menopause symptoms</td>
<td>21</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Menopause onset (years)</td>
<td>21.1 ± 8</td>
<td>19.7 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>No current HRT</td>
<td>40</td>
<td>25</td>
<td>NS</td>
</tr>
</tbody>
</table>

GR — growth hormone; HRT — hormone replacement therapy; NS — not significant
Karyotype and phenotype in Turner syndrome
Jakub Frelich et al.

-found in TS females can be attributed to chromosome X-

symptoms are highly variable. Clinical manifestations
arises: why not all 37 features? As mentioned in the

features occurred more frequently in the TS-women

study revealed that only about 41% and 33% of these

between TS women and the general population. Our

fields. Although this kind of message prove to be

subjective or sketchy, it should convey the general

impression obtained during a patient-doctor encounter.

The results obtained by the same medical team should

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Thirty-seven non-gynaecological TS features (in-
cluding body height) were selected for analysis based
on literature determinations regarding differences
between TS women and the general population. Our
study revealed that only about 41% and 33% of these
features occurred more frequently in the TS-women
with 45,X monosomy and other karyotypes, respec-
tively, compared to the controls. The question therefore
arises: why not all 37 features? As mentioned in the
Introduction section, the prevalence and severity of TS
symptoms are highly variable. Clinical manifestations
found in TS females can be attributed to chromosome X

Discussion

Despite the progress in diagnostic techniques, the
findings elicited on history taking and physical ex-
amination remain the common ground of information
exchange between specialists in different medical
fields. Although this kind of message prove to be
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with 45,X monosomy and other karyotypes, respec-
tively, compared to the controls. The question therefore
arises: why not all 37 features? As mentioned in the
Introduction section, the prevalence and severity of TS
symptoms are highly variable. Clinical manifestations
found in TS females can be attributed to chromosome X

abnormality or gonadal dysgenesis. Treatment-related
symptoms cannot be excluded either.

Hormone therapy in TS patients comprises not only
a treatment for short stature (growth hormone) and
compensation for sex hormone deficit (sex hormones),
but also a counteraction to the effects of this deficit,
including the reduction in the risk of cardiovascular
disease [12, 21]. Long-term pleiotropic effects of the
growth hormone should be kept in mind as well as
the fact that they are not always predictable [22]. The
proportion of patients acknowledging childhood ap-
lication of growth hormone and current use of HRT
was much lower than expected (as already noted in
our previous publications) [23]; nevertheless, the con-
sequences thereof cannot be ruled out. Comparable
proportions of patients admitting paediatric growth
hormone and current HRT application indicated that
differences in the occurrence of some clinical features
in 45,X monosomy and other karyotypes might result
from the loss of the genetic material from the X chro-
mosome. The longitudinal study by Lebenthal et al.
provides unique insights into the evolution of weight
gain and metabolic disorders from childhood to early
adulthood in TS patients. The occurrence of metabolic
comorbidities was similar in 45,X monosomy and other
karyotypes, while co-occurrence of multiple metabolic
comorbidities was significantly higher in 45,X mono-
somy. Because overweight and increasing age aggravate
the risk of metabolic comorbidities, careful surveillance
is warranted to prevent and control obesity from child-
hood through adulthood. The authors concluded that
the more prominent clustering of metabolic comorbid-
ities in 45,X monosomy underscores the importance of
a more vigorous intervention in this group [15].

We are now going to analyse the parameters whose
prevalence or mean values were significantly different
between the study groups. Prior to that, however, the
non-occurrence of statistically significant differences
in body height should be commented upon. Short stature
phenotype is characteristic of TS. The average height
of adult women with 45,X and 45,X/46,XX karyotype is
140–142 cm and 147 cm, respectively [24, 25]. Our study
participants with 45,X monosomy were not shorter
than those with non-45,X karyotypes. It can therefore
be speculated that, in women with 45,X monosomy or
some of them at least, growth impairment does not
necessarily result from the loss of genetic material.
The lack of differences regarding the prevalence of the
non-differentiating clinical features (ENT, ophthalmic,
maxillofacial, dermatological, urology and nephrology,
cardiology, endocrine-obstetric-gynaecological) in the
two TS groups could be similarly interpreted. However,
the magnitude of X-chromosome material deficit in
45,X patients is hard to determine. Genetically, pure

Table III. Mean age at Turner syndrome (TS) symptom
occurrence and final diagnosis of TS, in TS women with 45,X
monosomy — A, TS women with other karyotypes (non-
45,X) — B, as well as in TS women with phenotypic features
differentiating between TS women non-45,X and 45,X (1-7)

<table>
<thead>
<tr>
<th></th>
<th>Age at TS symptom occurrence (years)</th>
<th>Age at final TS diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A — TS women with</td>
<td>6.81 ± 5.43</td>
<td>13.16 ± 7.97</td>
</tr>
<tr>
<td>45,X monosomy (n = 93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood lymphoedema</td>
<td>5.81 ± 5.77</td>
<td>11.43 ± 8.05</td>
</tr>
<tr>
<td>Finger deformity</td>
<td>6.79 ± 4.94</td>
<td>15.13 ± 11</td>
</tr>
<tr>
<td>Posture defects</td>
<td>7.5 ± 5.29</td>
<td>13.33 ± 7.41</td>
</tr>
<tr>
<td>Low posterior hairline</td>
<td>7.45 ± 5.64</td>
<td>13.71 ± 8.92</td>
</tr>
<tr>
<td>Neck anomalies</td>
<td>7.42 ± 5.6</td>
<td>13.76 ± 8.72</td>
</tr>
<tr>
<td>Induced puberty</td>
<td>7.28 ± 5.66</td>
<td>13.1 ± 6.65</td>
</tr>
<tr>
<td>Induced menorrhoea</td>
<td>7.96 ± 5.64</td>
<td>14.15 ± 7.29</td>
</tr>
<tr>
<td>B — TS women non-45,X</td>
<td>10.27 ± 5.18</td>
<td>17 ± 8.19</td>
</tr>
<tr>
<td>(n = 64)</td>
<td></td>
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</tbody>
</table>
45,X monosomy is considered lethal. Although not yet proven, it is believed that patients with 45,X karyotype have some degree of mosaicism to maintain viability. According to some authors, clinical features are approximately in parallel with the magnitude of the deficit of X-chromosome material [14].

As presented in the Results section, TS-women with 45,X monosomy more frequently exhibited webbed neck, postural defects, finger/toe deformities, and low posterior hairline; childhood lymphoedema was also more frequently reported (all compared to TS women with other karyotypes). The prevalence of 19 of 23 endocrine-obstetric-gynaecological features (Tab. II) did not differ significantly between the two groups of women with TS. The differentiating features were: 1. pubertal induction, 2. menarche induction, 3. birth length, and 4. proportion of gynaecological surgeries.

Previous attempts to associate clinical features of with particular karyotypes did not lead to unambiguous conclusions. It should be emphasised that our study comprised 157 female participants examined by the same research team over a period of 20 years.

Webbed neck
Excess skin folds around the neck cause it to seem broad (webbed neck) and/or short [26, 27]. This anomaly is believed to result from subcutaneous nuchal oedema during foetal life, leading to nuchal skin redundancy, which can persist throughout life.

Similar to other dysmorphic features, webbing of the neck may be more or less prominent. Excess skin folds can be barely noticeable or of considerable width extending from the mastoid process and laterally to the acromion. Webbed neck was observed in over a half of our TS participants, which is consistent with literature data [11]. However, twice as many women with 45,X monosomy exhibited this feature compared to non-45,X TS women — a finding unaccounted for by any other reports.

Childhood lymphoedema
Abnormal development of the lymphatic system may lead to lymphatic insufficiency, and, consequently, to hand and feet swelling. Lymph fluid stasis in the peripheral tissue typically produces chronic inflammation. Congenital lymphoedema occurs in over 80% of TS-girls. Savendahl and Davenport used lymphoedema as the key to diagnosis in 97% of the girls diagnosed with TS in infancy, while short stature was the key to diagnosis for 82% of the girls diagnosed in childhood or adolescence [28, 29]. The proportion of our study participants who had clinically documented childhood lymphoedema was markedly lower. This clinical feature should be interpreted with caution because there were no medical records to verify the patient’s statement. The significantly more frequent occurrence of childhood oedema in 45,X monosomy (Tab. I) could be attributed to the loss of some genetic material from the X chromosome.

Finger/toe deformity
Many of physical stigmata of TS result from structural bone defects [3]. Typically, females with TS have disproportionately short legs and an abnormal upper-to-lower segment ratio. Cervical vertebral hypoplasia contributes to short stature. Scoliosis may be present in approximately 10% of TS females, and approximately half have cubitus valgus or a wide carrying angle as a result of a developmental defect of the ulnar head. Similar abnormalities of the medial tibial and femoral condyles may also be present. Short metacarpals and metatarsals can result in finger and/or toe deformities. Around 20% of our TS participants exhibited finger and toe deformities, which again was consistent with literature data [11]. However, the feature was significantly more prevalent among women with 45,X monosomy.

Postural defects
Postural defects can be attributed, at least in part, to abnormalities in the growth of long (limbs) and short (spine) bones. The average height of adult women with 45,X and non-45,X tends to differ significantly [24]. Forty per cent of the Turner syndrome population examined by Elder et al. [27] had excessive kyphosis. In our study faulty posture was found in a similar proportion of the TS participants but significantly more frequently in women with 45,X monosomy.

Low posterior hairline
Individuals with Turner syndrome have a broad webbed neck and a low posterior hairline. Co-occurrence of these features might indicate a common underlying mechanism. Cabrol [5] observed low posterior hairline in approximately half of girls with TS, which is consistent with our results. However, the feature was significantly more prevalent in women with 45,X monosomy.

Pubertal induction and menarche induction
Gonadal dysgenesis is a type of hypogonadism found in Turner syndrome [18]. Girls with TS typically present with primary amenorrhoea. Only a small proportion (approximately 10–16.5%) are likely to have spontaneous menarche; subsequent menstrual cycles become irregular and tend to stop within 2–3 years. The mean age at menarche is 14 years [30]. In another study, 71% of TS women with pubertal induction had menarche at the mean age of 17.2 years [31]. Hagen et al. examined
66 patients with TS; the prevalence of spontaneous puberty was 6% for 45,X and 54% for other karyotypes [32]. It is believed that spontaneous pubertal development is more common among girls with mosaic karyotypes compared to those with 45,X monosomy. This is consistent with our findings. Puberty and menarche induction turned out to be among endocrine-obstetric-gynaecological features differentiating between our TS-groups.

**Gynaecological surgeries**

It should be noted that the proportion of gynaecological surgeries in TS-women with 45,X monosomy was lower than in those with other karyotypes.

**Birth length**

No statistically significant difference in body height was revealed between TS women with 45,X monosomy and those with other karyotypes. However, it should be emphasised that TS women with 45,X monosomy had greater birth length than non-45,X participants, but despite this initial advantage the lack of significant differences in adult body height between our study groups indicates slower growth and more severe short stature in TS women with 45,X monosomy.

Summing up it should be noted that although the above discussed abnormalities differ in prevalence or mean values (quantitative parameters), they all develop in tissues of mesodermal origin, which become the most affected by the loss of the genetic material. The molecular defect has not been characterised yet, but it has been hypothesised that deletion of a gene on the X chromosome may be responsible for such connective tissue abnormalities [33]. Out of 60 parameters analysed, nine were significantly more prevalent among TS women with 45,X monosomy compared to their counterparts with other karyotypes. The majority of researchers report that more pronounced phenotypic features are associated with greater loss of genetic material observed in 45,X monosomy [14].

Gawlak et al. suggested that phenotype severity had an impact on time to diagnosis; hence, it is essential to emphasise the phenotypic variability of Turner syndrome [34].

Is it then worthwhile to try to identify clinical features differentiating between TS patients with different karyotypes? The mean age at symptom occurrence and final diagnosis of Turner syndrome differed significantly between the two subgroups of TS women. Hence, a question arises concerning the relationship between the presence of these differentiating symptoms in TS women and the age at final diagnosis of Turner syndrome [35].

The mean age at occurrence of TS symptoms and final diagnosis in all TS participants exhibiting the differentiating symptoms (presented in Tab. III) was comparable with the mean age at symptom occurrence and final diagnosis in TS patients with 45,X monosomy. Hence, the presence of the differentiating symptoms allows earlier diagnosis of Turner syndrome irrespective of the patient’s karyotype.

**Conclusions**

1. The prevalence of the majority of the clinical manifestations of Turner syndrome does not differ between TS women with 45,X monosomy and those with non-45,X karyotypes.
2. Most clinical features differentiating women with TS with different karyotypes are more frequent in monosomy, but there are also those that are more common in women with TS, non-45,X.
3. Clinical manifestations, the prevalence of which differ between TS women with non-45,X karyotypes and 45,X monosomy, might help lower the age at diagnosis.

**Conflict of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. The results presented in this paper have not been published previously in whole or part, except in abstract form.

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