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Selected clinical features of the head and neck in women with Turner syndrome and the 45,X/46,XY karyotype

Wybrane cechy kliniczne w obrębie głowy i szyi u kobiet z zespołem Turnera i kariotypem 45,X/46,XY

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Abstract

Introduction: A 45,X/46,XY karyotype in women with Turner syndrome (TS) is very rare. The presence of a Y chromosome in the karyotype causes phenotypic differences and increased risk for neoplastic disease, compared to TS-women with other karyotypes. Our study addresses an issue: non-genital phenotypic differences between TS-patients with a Y-chromosome of their karyotype and TS-women without it.
Material and methods: Results from patient history/physical examinations of the head and neck of eight TS-women and the 45,X/46,XY karyotype were compared with those observed in 164 TS-women and 30 controls. The heights of TS-groups: 142.5 ± 7.2 and 144.9 ± 7.2 cm were lower than controls (165.2 ± 6.6 cm). Participants were examined from 1995 to 2014.
Results: Among 28 study parameters, 15 were more frequently observed in TS women with the 45,X/46,XY karyotype compared to controls. Only abnormalities in the oral cavity and a history of childhood lymphoedema, differed significantly in the TS groups.
Conclusions:
1. With respect to the head and neck, the patient history and physical examination results of TS-women and the 45,X/46,XY karyotype and TS and other karyotypes revealed similar differences compared to controls.
2. Compared to others TS patients, 45,X/46,XY individuals might more frequently have oral cavity soft tissue abnormalities and more rarely a history of childhood lymphoedema. **(Endokrynol Pol 2017; 68 (1): 47–52)**

Key words: *Turner syndrome; 45,X/46,XY karyotype; head; neck*

Streszczenie

Wstęp: Kariotyp 45,X/46,XY u kobiet z zespołem Turnera (TS) występuje bardzo rzadko. Obecność chromosomu Y w kariotypie powoduje różnice fenotypowe i wzrost ryzyka chorób nowotworowych. Celem badania jest ocena różnic fenotypowych, nie związanych z układem rozrodczym, pomiędzy pacjentkami z TS i chromosomem Y w kariotypie, w porównaniu do pozostałych kobiet z TS.
Materiał i metody: Występowanie tych wybranych cech w obrębie głowy i szyi, które często występują u kobiet z TS, w oparciu o wyniki badania podmiotowego i przedmiotowego, określono u ośmiu kobiet z TS i kariotypem 45,X/46,XY, a następnie porównano z odpowiednio u 164 kobiet z TS i innymi kariotypami oraz u 30 kobiet grupy kontrolnej. Średnie wysokości ciała obu grup kobiet z TS wynosiły odpowiednio 142,5 ± 7,2 i 144,9 ± 7,2 cm i były znamiennie niższe niż w grupie kontrolnej (165,2 ± 6,6 cm). Badania przeprowadzono w latach 1995–2014.
Wyniki: Spośród 28 badanych parametrów, 15 częściej obserwowano u kobiet z TS i kariotypem 45,X/46,XY niż w grupie kontrolnej. Częstość występowania nieprawidłowości w obrębie tkanek miękkich jamy ustnej oraz obrzęku limfatycznego w dzieciństwie różniły istotnie obie grupy kobiet z TS.
Wnioski:
1. Różnice pomiędzy wynikami badania podmiotowego i przedmiotowego w odniesieniu do głowy i szyi, kobiet z TS i kariotypem 45,X/46,XY i kobiet z TS i innymi kariotypami a grupą kontrolną są porównywalne.
2. W porównaniu z kobietami z TS i innymi kariotypami, u pacjentek z TS i kariotypem 45,X/46,XY częściej występują nieprawidłowości w obrębie tkanek miękkich jamy ustnej i rzadziej w dzieciństwie obrzęk limfatyczny. **(Endokrynol Pol 2017; 68 (1): 47–52)**

Słowa kluczowe: *zespół Turnera; kariotyp 45,X/46,XY; głowa; szyja*

Introduction

Turner syndrome (TS) bears the name of Henry Turner, who, in 1938, described seven patients characterised by short stature, underdevelopment of reproductive organs, neck-webbing, and elbow deformity [1]. Turner syndrome affects women and results when all or part of one of the X chromosomes is missing or altered. In addition, the Y chromosome or part of it might be present [2]. TS includes a wide range of chromosomal karyotypes and clinical phenotypes [3]. The patients exhibit a wide variety of anomalies and pathologies within different organs. Nevertheless, the clinical features of TS have not been fully resolved [4]. Basic phenotypic

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abnormalities occur in the tissues of mesodermal origin. TS is characterised by the expression of different phenotypes, and physical stigmata can be mild or absent [5]. A study of sex chromosome abnormalities carried out in Denmark revealed that 1 in 2130 newborn girls had TS [6]. A 45,X/46,XY karyotype is rare; its incidence is estimated to be 1:50,000 live-born female infants [7]. Mosaicism for a cell line with a normal or abnormal Y chromosome is identified in 6% to 11% of TS-patients with standard cytogenetic techniques [8]. But Y chromosome material may be present in some patients in whom standard karyotype of white blood cells fails to demonstrate this. A meta-analysis of studies reporting a total of 541 patients with Turner syndrome without Y chromosome material on routine cytogenetic analysis found 5% mosaicism for a Y-containing cell line using molecular techniques [8]. The presence of a Y chromosome in the karyotype causes a wide variety of phenotypes [9] and an increased risk for neoplastic disease compared to TS-women but other karyotypes [10–13].

Our study addresses an issue: non-genital phenotypic differences between Turner patients with a Y-chromosome component of their karyotype and TS-women without it. A large number of anomalies in women with TS occur in the head and neck, which are the most visible portions of the body.

Literature on patients with Turner syndrome and the 45,X/46,XY karyotype is scarce. Only 20 studies have been identified, and of those, only a subset have information about clinical features of the head and neck.

As such, this study was carried out to determine the following:

1. The differences in head and neck anomalies from patient histories and physical examinations of women with Turner syndrome and the 45,X/46,XY karyotype compared to women from the general population.
2. Differences in the above mentioned anomalies between TS women and the 45,X/46,XY karyotype and other women with TS.

The results can answer the question: is it possible to verify, relying on the patient history/physical examination of the head and neck of women with Turner Syndrome, whether a TS patient has some Y chromosomal material? These findings may be most useful in patients in whom the standard karyotype (which must be performed in all patients thought to have Turner syndrome) does not show Y chromosome material. Such patients may be candidates for karyotyping of skin or other tissue (in addition to white blood cells) and/or for extensive FISH studies for Y chromosome material. Because the presence of Y chromosomal material increases the future oncogenic risk potential for the patient, obtaining a karyotype is critical for the management and education of the patient and family.

Material and methods

The study population included eight women with TS and the 45,X/46,XY karyotype, aged 22.4 ± 4.9 years, 164 with other TS-karyotypes (25.1 ± 7.8), and 30 controls. Karyotype was identified using routine cytogenetic analysis. The group of TS-women without Y consisted of 104 women with simple X monosomy, 17 with structural aberrations of the X (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). The TS-women group with mosaic karyotypes consisted of 36 TS persons (14 with X monosomy and normal female cell line, two with monosomy and second aneuploid cell line (trisomy), and 23 with monosomy and second cell line with structural aberration of chromosome). Four TS-persons had karyotypes and markers. Features assessed on patient history and physical examination were selected based on literature reports on tissue and organ anomalies seen in TS-women [14, 15].

The following were evaluated as a prospective study, based on the patient's medical history and documentation: childhood lymphoedema, feeding problems during infancy, a history of skin diseases, thyroid diseases, diabetes mellitus, hypertension, hearing impairment, recurrent otitis media, and surgery for otitis media, third tonsil adenoidectomy, and vision defects. On the physical examination, we paid close attention to the density of eyebrows, length of eyelashes, drooping eyelids, epicanthic folds, squint, and daltonism. The low set and/or deformed ears, high-arched palate, oral cavity soft tissue abnormalities, retrognathism and other types of malocclusion, dental caries, and tooth loss were also checked. Neck anomalies were evaluated (short or webbed). We also paid attention to low hairline on nuchae, hypertrichosis on the face, goitre, and pigmented nevi. The participants were examined from March 1995 to September 2014. All participants consented to the procedures. All study procedures were approved by the Medical University of Silesia Bioethical Board. A statistical analysis was performed using the mean ± SD with an unpaired t-test to compare the results. A bilateral test of differences between two structural indicators was applied to evaluate the frequency of occurrence of particular values. The level of significance was set at $p < 0.05$.

Results

The mean height of TS-patients with the 45,X/46,XY karyotype (142.5 ± 7.2 cm) was similar compared to TS-women with other karyotypes (144.9 ± 7.2 cm). Heights of TS-participants were significantly lower than controls

Table I. *Head and neck anomalies revealed on history taking: V — absolute values, (%) — per cent, in women with TS and the 45,X/46,XY karyotype (A), other TS karyotypes (B) and control participants (C)*

Tabela I. *Występowanie cech klinicznych typowych dla zespołu Turnera (ZT) w obrębie głowy i szyi, uzyskanych podczas badania podmiotowego (wywiadu): V — liczba bezwzględna, (%) — odsetek u kobiet z ZT i kariotypem 45,X/46,XY (A), z innymi kariotypami (B) i w grupie kontrolnej (C)*

Parameter	A (n = 8)		B (n = 164)		C (n = 30)		p =	
	V	(%)	V	(%)	V	(%)	A *vs.* C	A *vs.* B
Childhood lymphoedema	0	0	43[a] n = 162	26.5	1	3.33	0.302	0.046
Feeding problems during infancy	5[a] n = 7	71.4	90[a] n = 157	57.3	3[a] n = 29	10.3	0.000	0.233
Skin diseases	2	25	40[a] n = 162	24.7	2	6.7	0.067	0.492
History of thyroid diseases	0	0	29[a] n = 162	17.9	6[a] n = 29	20.7	0.081	0.095
Diabetes mellitus	0	0	9[a] n = 161	5.6	1	3.3	0.302	0.248
Hypertension	3	37.5	42	25.6	0	0	0.000	0.227
Impairment of hearing	2	25	54	32.9	2[a] n = 29	7.4	0.078	0.319
Otitis media	7	87.5	109[a] n = 163	66.9	9[a] n = 29	31	0.002	0.111
Surgery for otitis media	0	0	115	9.2	1[a] n = 29	3.5	0.298	0.184
Third tonsil adenotomy	1[a] n = 7	14.3	47[a] n = 161	29.2	4[a] n = 29	13.8	0.367	0.195
History of vision defects	5	62.5	95[a] n = 163	58.3	11	36.7	0.095	0.405

[a]data were not obtained from all participants in a given group

(165.2 ± 6.6 cm, $p < 0.001$). The results of head and neck anomalies revealed in patient histories and upon physical examination are presented in Table I and Table II.

An analysis of 28 study parameters (27 and height) revealed significant differences in the frequency of 15 of them between 45,X/46,XY individuals and controls. Only two: soft tissue abnormalities in the oral cavity and a history of childhood lymphoedema, differed significantly between women with the Y chromosome and those with other TS-karyotypes.

Discussion

The 45,X/46,XY karyotype is very rare in TS-females. There are few reports on 45,X/46,XY women with Turner syndrome, they are primarily focused on reproductive organ pathologies [9–18], and they rarely refer to others, e.g. the cardiovascular system [19]. In available publications, we could not find correlations between clinical manifestation and the proportion of mosaic cells for peripheral blood karyotypes [20]. The percentage of 46,XY cells in peripheral blood may be extremely low (less than 0.2%) in patients with sexual development disorders and was not detected by FISH analysis. This finding suggests that an imbalanced distribution could occur in 45,X/46,XY cases [21, 22]. Only three reports refer to our area of interest (head and neck anomalies). Soares described a young girl with the mosaic karyotype 46,X,idic(Y)(q11.2) [23]/45,X [6] but no signs of virilisation. This girl presented with reduced growth, facial anomalies, and a melanocytic nevus [23]. Knudtzon and Aarskog reported 10 patients with 45,X/46,XY mosaicism. Three girls presented with short stature, delayed sexual development, or Turner-like stigmata without signs of virilisation. Two of them had bilateral gonadoblastoma; the gonads of one also contained mucinous cystadenoma. The remaining seven patients were raised as boys. The authors concluded that 45,X/46,XY mosaicism resulted in a wide spectrum of phenotypic manifestations ranging from females with Turner-like phenotypes, phenotypic males and females with mixed gonadal dysgenesis, male intersex to almost phenotypically normal males [24]. El-Bassyouni reported a female with a TS phenotype and an isodicentric Y chromosome

Table II. *Head and neck anomalies revealed on physical examination (V — absolute values, % — per cent) in women with TS and the 45,X/46,XY karyotype (A), other TS karyotypes (B) and control participants (C)*

Tabela II. *Występowanie cech klinicznych typowych dla zespołu Turnera (ZT) w obrębie głowy i szyi, uzyskanych podczas badania przedmiotowego (fizykalnego): V — liczba bezwzględna, (%) — odsetek u kobiet z ZT i kariotypem 45,X/46,XY (A), z innymi kariotypami (B) i w grupie kontrolnej (C)*

Parameter	A (n = 8)		B (n = 164)		C (n = 30)		p =	
	V	%	V	%	V	%	A *vs.* C	A *vs.* B
Dense eyebrows, long eyelashes	4	50	114[a] n = 160	69.5	0	0	0.000	0.123
Drooping eyelids	4[a] n = 7	57.1	76[a] n = 163	46.6	2[a] n = 29	6.90	0.001	0.291
Epicanthic folds	4	50	51[a] n = 163	31.3	0	0	0.000	0.134
Squint	1	12.5	21	12.8	1	3.3	0.152	0.492
Daltonism	0	0	1[a] n = 163	0.61	0	0	1.000	0.413
Low-set and/or deformed ears	7	87.5	140	85.4	7	23.3	0.000	0.433
High-arched palate	7	87.5	143[a] n = 163	87.7	0	0	0.000	0.492
Oral cavity soft tissue abnormalities	1	12.5	4	2.44	0[a] n = 29	0	0.027	0.049
Retrognathism	4	50	95[a] n = 157	60.5	6[a] n = 27	22.2	0.063	0.278
Malocclusion	4	50	73	44.5	16[a] n = 29	55.2	0.397	0.382
Dental caries and lost teeth	0	0	10[a] n = 163	6.1	11[a] n = 29	37.9	–0.041	0.236
Neck anomalies (short, webbed)	4	50	74[a] n = 145	51	0	0	0.000	0.480
Goitre	0	0	22	13.4	4[a] n = 29	13.8	0.134	0.134
Low hairline on nuchae	4[a] n = 7	57.1	91[a] n = 159	57.2	2	6.7	0.006	0.227
Hypertrichosis on the face	0	0	12	7.3	1	3.3	0.302	0.215
Pigmented nevi	8	100	159[a] n = 161	98.8	20	66.7	0.029	0.375

[a]data were not obtained from all participants in a given group

46,X,idicYq a combination. The patient presented with bilateral lymphoedema of upper and lower limbs since birth. Craniofacial anomalies (epicanthic folds, broad nasal bridge, long philtrum, protruded tongue, low-set ears, short neck), genital ambiguity, with variable Turner stigmata and normal height were detected. The authors concluded that further elucidation to pinpoint the level of the defect of the major Y genes is of great clinical significance for better phenotype/karyotype correlations [25].

Considering the phenotype of our 45,X/46,XY, TS-patients, we expected male-pattern hair growth, which was not observed. As many as 15 out of 28 study parameters differed between the 45,X/46,XY TS-participants and controls. Only two differed significantly between women with the Y chromosome and those with other TS-karyotypes. We would like to emphasise the differences between TS-women and the 45,X/46,XY karyotype and those with other TS-karyotypes regarding childhood lymphoedema and the occurrence of isolated soft tissue abnormalities within the oral cavity.

Lymphoedema is common in children with TS; under some circumstances it might signal a need for diagnostic tests for the disorder [5]. It is interesting that lymphoedema does not occur, or occurs more rarely, in girls with the XY karyotype. Because no literature data are available, it could be hypothesised that information on this type of pathology is not located in the genetic material of the Y chromosome. Anomalies within the oral cavity are also of interest, including extensive

adhesion of the tongue to the floor of the mouth, lip shortening, protruding, large, and fissured tongue, uvula deformity, fibrous growth of the gingiva, and epulides. The above-mentioned anomalies were observed significantly more frequently in the 45,X/46,XY participants (12.5%) compared to those with other TS karyotypes (2.44%). Anomalies within the oral cavity were similar in both compared groups. Again, however, it is not possible to compare these observations to other studies. The female phenotype indicates that women with TS might lack the SRY fragment [26]. Thus, it may be presumed that the remaining part of the genetic material on this chromosome did not have any effect on the parameters studied. In order to establish the extent to which the fragment of the Y chromosome determines other phenotypic traits in TS-women, a study with a larger population and examination of many other body parts (not addressed in this paper) would be necessary.

Turner syndrome is a common cause of short stature referred to paediatric endocrinologists. Our results demonstrate that phenotypic features do not distinguish the child with 45,X/46,XY Turner syndrome from the child with other karyotypes, although there is a statistical difference in the incidence of oral cavity and chronic lymphoedema abnormalities/features. It is important to distinguish between these two patient groups because of the higher incidence of carcinoma in the females with Y chromosomal material. Basically, what this review tells us is that we CANNOT tell by head and neck exam whether a TS patient has some Y chromosomal material. The absence of lymphoedema and presence of oral cavity abnormalities do not give assurance that the patient's karyotype does not include Y genetic material.

Conclusions

1. With respect to the head and neck, the results of patient histories and physical examinations of women with TS and 45,X/46,XY karyotype differed from those of the general population control women to a similar degree as did those from TS women with other karyotypes.
2. Compared to other patients with Turner syndrome, 45,X/46,XY individuals might more frequently have oral cavity soft tissue abnormalities and more rarely a history of childhood lymphoedema.

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