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The occurrence of ocular diseases in patients with Turner syndrome

Research Article

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Abstract: Turner syndrome is among the most common chromosomal aberrations.It is caused by a missing or anomaly of one X chromosome,alternatively a chromosomal mosaicism. It is often connected with a more frequent occurrence of some ocular diseases.In our study 81 girls and women with Turner syndrome from the age of 5 to 23 years old were examined. The occurrence of ocular diseases and their possible connection with karyotype was the main focus of our attention.Myopia had the highest incidence in these girls, further there were hyperopia,epicanthus,colour vision deficiency,amblyopia, strabismus and ptosis.The occurrence of colour vision deficiency was higher than in the general population where it differs in sexes.The occurrence of strabismus and ptosis was higher than in the general population.The total range of refractive errors was slightly higher than in the general population, with a different distribution according to karyotype.Hyperopia was recorded more often at the 45,X karyotype, namely 28 %, while for chromosomal mosaicism it was only in 18%.For myopia the ratio was reversed - chromosomal mosaicism in 31% and in 45,X karyotype in 26 %.In total,while comparing individual eye defects incidence in 45,X karyotype and chromosomal mosaicism, similar findings were recorded.These results were also assessed with the help of statistics.

Keywords: *Turner syndrome • 45, X karyotype • Chromosomal mosaicism • Refractive errors • Colour vision deficiency • Ptosis • Strabismus • Amblyopia • Epicanthus*

1. Introduction

Turner syndrome is a chromosomal aberration where phenotypic differences in afflicted girls and women are conditioned by missing or by abnormalities of one X chromosome, alternatively a chromosomal mosaicism. It occurs in 1: 2000 to 2500 live born girls [9,30]. Henry Turner, an American internist and endocrinologist, described the clinical manifestations of the syndrome for the first time in 1938 [25]. Etiology was not known at the time of the first clinical reports of Turner syndrome. Assumptions about the possibility of chromosomal aberrations appeared in 1954 when the absence of Barr body in the cellular nucleus was detected in female patients with Turner syndrome [23]. The hypothesis was confirmed by chromosomal analysis in 1959 [11] which detected a missing X chromosome. A genetic foundation for the impairment in connection with the female population was proved definitely as late as in the sixties of the last century when karyotype started to be examined routinely [24].

A whole range of clinical manifestations can occur in patients with Turner syndrome, however their level of expression is quite variable. Phenotype has some correlation to a karyotype, with a genotype more precisely, although a different clinical model is observed in girls and women with the same chromosomal abnormality. At the present time there is no unified opinion about how to determine the karyotype in girls with Turner syndrome.

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Different cytogenetic methods are used for karyotype determination. A large variability in the resulting ratio of 45, X karyotype to mosaic forms of Turner syndrome appears during their comparison in quite large cohorts of female patients [17,28,29].

Some authors state that pure 45, X monosomy is not compatible with life and therefore it is always a hidden, unrecognized chromosomal mosaicism in patients with a 45, X cytogenetic finding. This hypothesis is not possible to be verified in a reliable way at the moment, but findings during karyotype determination from the cells of other tissues (for example from dermal fibroblasts) and assessment of high mitotic rate support it. The development of new cytogenetic and molecular-genetic methods enabled the reassessment of the original cytogenetic findings and gradually enabled the revealing of mainly mosaic forms of Turner syndrome.

Deviations in the karyotype in patients with Turner syndrome can be divided into 2 basic groups:

1. missing one X chromosome, which is 45, X karyotype (about 55% girls)
2. chromosomal mosaicism, for example 45, X/46, XX, or 45, X/47, XXX and other structural and numerical aberrations of X chromosome, for example 46, X, X p- or 45, X/46, X, i (Xq) and others [22].

Lymphadens and poor growth rate in newborns, growth retardation in childhood, absence of puberty manifestations at the time of adolescence and infertility caused by the dysfunction or ovarian agenesis in adulthood dominate clinical manifestations. At the present time dysmorphic features such as a low hairline on the back of the neck, a limited ability to extend arms at the elbow (cubiti valgi), heart anomalies (atrial septal defect and coarctation of aorta), kidney and urinary ways anomalies (a horseshoe kidney, dystopic kidney), hearing impairment and numerous pigmented nevi on the skin are described besides generally known small growth (untreated girls with Turner syndrome are 22 cm shorter on average in adulthood than the general population) and a typical webbed neck (pterygium colli). Girls with Turner syndrome suffer also from some autoimmune disorders more often. Celiac disease and Hashimoto thyroiditis are most common, glucose intolerance disorder and osteoporosis appear in some of them in adulthood more often than in the general population [9,17,28,29].

Antimongoloid slant of eyes, hypertelorism, epicanthus, ptosis, exophtalmos, keratoconus, dysplasia and coloboma of the iris, blue sclera, congenital glaucoma, congenital cataracts, colour vision deficiency and last but not least refractive errors, strabismus and amblyopia are the ocular defects which occur more often in girls with Turner syndrome than in the general population [2,7,9,12,14,21].

Not only some somatic deviations but also a specific social-neurocognitive phenotype (problems with short term memory, bad concentration, indecisiveness while performing easy tasks and difficulties in interpretations of abstract mathematical terms) are typical of Turner syndrome. However, generally it is true that they are as intelligent as the rest of the population. Only the female patients who have a so called ring chromosome contained in their karyotype are the exception, with a rather high prevalence of mental retardation [17,28,29].

In the Czech Republic there are more than 2000 girls and women with Turner syndrome and about 20-25 little girls are born every year [28].

Due to the various health problems these girls have, they see a doctor on average more often than others. This implies that almost every doctor meets a female patient with Turner syndrome during his or her practice, including ophthalmologists.

2. Materials and methods

81 girls and women with Turner syndrome were examined repeatedly at the Clinic of Pediatric and Adolescent Medicine of the Faculty hospital Kralovske Vinohrady and later at the Ophthalmology clinic of the Faculty hospital Kralovske Vinohrady. Their age was in a range from 5 to 23 years old.

Chromosome examination for karyotype determination was performed at the Department of Biology and Medical Genetics of the Motol Faculty Hospital.

Distance visual acuity (with the help of Snellen optotypes) and near distance acuity (with the help of Jaeger´s test types) were examined with and without correction during the eye examination. Cycloplegic refraction was measured with the help of an autorefractometer in each female patient. Eye and eyelid position were examined with a cover test for distance as well as for near vision and a possible size of deviation of strabismus by prismatic glasses on a troposcope was measured, ocular motility examination of the eye moving muscles was performed in all view directions including the examination of the elevating muscle of upper eyelid function. Binocular functions were assessed using a stereoscope and with the help of Randot Stereotest.

The anterior eye segment was examined using a slit lamp, the fundus of the eye in artificial mydriasis with the help of a direct ophthalmoscope.

Corneal topography was performed on the female patients with a higher astigmatism.

Colour vision test was performed with the help of Lanthony Desaturated 15 D test (15 Hue) based on Farnsworth.

3. Results

3.1. Chromosomal examination

42 girls (52%) had 45, X karyotype and 39 girls (48%) had a chromosomal mosaicism or another structural or numerical chromosome X abnormality. Chromosomal mosaicism 45,X/46,XX (5 girls), 45,X/46,XY (4 girls) or 45,X/47,XXX (2 girls) were the most frequent, mosaicism with an X chromosome structural abnormality occurred often as well (45,X/46XrX karyotype in 6 girls or 45,X/46 XiXq karyotype in 3 girls).

Both the groups were approximately the same size which reflected also the ratio of individual karyotype representation in girls with Turner syndrome in the general population.

3.2. Refractive errors

Refractive errors were the most common in the girls in our cohort from the point of eye symptomatology. Refractive error was diagnosed in 42 patients (52%). It was hypermetropia in the range from +0.5 to +7.5 diopthries (D) in 19 female patients and myopia in the range from –0.25 to –5.5 D in 23 patients. They were recalculated to a spherical equivalent during the combination with astigmatism. 38 out of 42 female patients with a refractive error (90%) were corrected. More frequent representation of hypermetropia was found at 45, X karyotype by comparison of refractive error based on karyotype (Table 1). It was contrary in chromosomal mosaicism where myopia was represented more distinctively.

Table 1. Summary of ocular symptoms at 81 patients of our group and their relationship to the karyotype

	45, X (n=42)	Mosaicism (n=39)	TOTAL (n=81)
Hyperopia	12 (28%)	7 (18%)	19 (24%)
Myopia	11 (26%)	12 (31%)	23 (29%)
Strabismus	4 (9%)	4 (10%)	8 (10%)
Amblyopia	5 (12%)	5 (13%)	10 (12%)
Ptosis	2 (5%)	2 (5%)	4 (5%)
Epicanthus	9 (21%)	7 (18%)	16 (20%)
Red-green color deficiency	3 (11%) (n=26)	4 (13%) (n=31)	7 (12%) (n = 57)

3.3. Strabismus and amblyopia

Strabismus was revealed in 8 girls (10%) during an all-embracing eye examination in our cohort. Esotropia with or without minimum accommodation was represented 6 times and a basal exotropia occurred twice. Amblyopia was detected in 10 eyes, there were anisometropic 8 cases accompanied by the above mentioned one strabismus and 2 cases were meridional hypermetropic in both eyes accompanied by one patient with hypermetropic astigmatism (+3,0 and +1,75 D). The findings of strabismus and amblyopia were not connected with karyotype (Table 1).

3.4. Ptosis

Ptosis was detected in 4 girls (5%) in our cohort, where two of them were with 45, X karyotype and two of them with chromosomal mosaicism.

Only one girl had been operated on (45, X karyotype) for ptosis of both eye lids which had already overlapped half of the pupil and forced the girl to lean her head backwards. A method of front tarsal fixation based on Fox was performed using deeply frozen fascia, the operation was performed on both eyes. The other three girls are being checked by a doctor continuously and examined once a year.

3.5. Epicanthus

A vertical skin fold overlapping the inner eye corner, or epicanthus, was detected in 16 girls (20%). 9 girls were with 45, X karyotype and the other 7 girls had chromosomal mosaicism

3.6. Colour vision deficiency

Colour vision test with the help of Lanthony Desaturated 15 D test (15 Hue) based on Farnsworth is fast, sensitive and relatively undemanding. Only patients older than 12 years old can be assessed though according

Table 2. The distribution of color vision deficiency, depending on the type of chromosomal disorders

	45, X karyotype (n=26)	mosaicism (n=31)	TOTAL (n=57)
Protania	2 (7,7%)	3 (9,7%)	5 (8,5%)
Deuterania	1 (3,8%)	1 (3,2%)	2 (3,4%)
Tritania	1 (3,8%)	2 (6,5%)	3 (5,2%)
All color vision deficiency	4 (15,4%)	6 (19,4%)	10 (17,1%)

Table 3. A comparison of the percentage of ocular diseases at patients with Turner syndrome in our study with available published files

	Adhikary, 1981 (n=24) [1]	Chrousos,1984 (n=30) [13]	Masters, 1990 (n=177) [18]	Our study (n=81)
Strabismus	37%	33%	33%	10%
Hyperopia	41%	16%	27%	24%
Myopia	N.A.	N.A.	13%	29%
Amblyopia	41%	13%	31%	12%
Ptosis	29%	16%	21%	5%
Epicanthus	46%	10%	40%	20%
Red-green color deficiency	N.A.	10%	7%	12%

to the advice of the producer. Therefore only 57 (70%) girls of our cohort were examined with the help of this test. In 47 of them (83%) colour vision was within the norm. Seven girls had a colour vision deficiency in the area of the red-green spectrum and three girls in the area of the blue spectrum. Comparison of colour vision deficiency in individual karyotypes (Table 2) shows that the representation of colour vision deficiency is only slightly higher in chromosomal mosaicism.

3.7. Statistics

To evaluate possible influence of karyotype on the frequency of occurrence of different types of ocular diseases, statistical testing was used. In the case of refractive errors, a chi-squared test was used, while Fisher's exact test was employed for the remaining types of ocular diseases.

Figure 1 shows a standard box-and-whisker plot of the variance of patient age within the two karyotype groups. The difference of age is statistically significant (p= 0,0068)

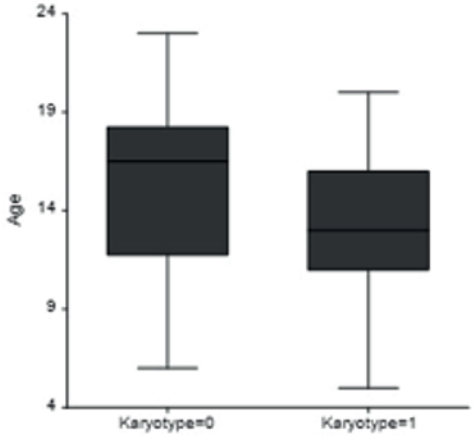

Figure 1. Box-and-whisker plot of the variance of patient age within two karyotype groups (0 is karyotype 45,X and 1 is chromosomal mosaicism)

Statistical analysis of data was performed using software GraphPad Prism version 6.03 (http://www.graphpad.com) and NCSS.

4. Discussion

A collection of 6 publications is the most numerous study of female patients with Turner syndrome [7] which was found by us in literature, and it is a collection of ocular defects of 274 female patients with Turner syndrome. However, none of the works filed here nor the total conclusions were interested in the relationship between eye symptomatology and karyotype, additionally, and, furthermore, the observations should be considered with care as studies with different numbers of female patients (from 7 do 177), from different authors and at various time periods (1974-1990) were compared. We ourselves have not found any considerable differences between individual ophthalmic findings and karyotype. The ratio was reversed between hypermetropia and myopia at 45, X karyotype and chromosomal mosaicism was the only significant difference.

It is interesting that after 4 years of examining female patients with Turner syndrome, when there were 59 girls in the cohort, the occurrence of strabismus, both refractive errors and ptosis in the probands with 45, X karyotype exceeded the findings of these ocular defects in girls with mosaic form of chromosomal aberration by a factor of two. But after 7 years when there were as many as 81 girls in the cohort [4], ocular diseases found by us were represented in nearly the same ratio in girls both with 45, X karyotype and with mosaic form. Both in our original cohort and in the cohorts published earlier in the 80´s of the last century where there were only 24 [2], and 30 [14] female patients with Turner syndrome, the inaccuracy of using a small sample size was shown.

Significant differences in the numbers of individual eye impairments were found during comparison of results from our study and accessible studies (Table 3).

So far the most numerous independent studies from the turn of the 80´s and 90´s which include 177 female patients [21] from the age of 4 months up to 44 years old have more significant representation of strabismus, amblyopia, ptosis as well as epicanthus in comparison with our study. On the contrary, the representation of refractive errors in the ratio was reversed and there are fewer red-green association disorders as well.

It was confirmed in our study that the occurrence of strabismus in girls with Turner syndrome is higher than in the general population where the average is 4 to 6% [8,12]. Our 10% observation of crossed eyes occurrence in Turner syndrome seems to be more realistic than the high figures of 33% [14], or 37% [2] in the above mentioned smaller sample sized studies. In the separate cohort of 177 probands with Turner syndrome [21] strabismus was observed in 58 of them in total in various forms. The set included for example microstrabismus, intermittent forms of horizontal tropia, vertical deviations, fully accommodative esotropia, acute forms of esotropia and exotropia, convergence excess etc. which were not revealed in our cohort even with a detailed orthoptic examination. Our afflicted cohort suffered from single eye esotropia and exotropia always accompanied by amblyopia which was represented only in 16 cases in the mentioned cohort [21] which meant 9% from the total number of female patients and which is in accordance with our 10% observation of girls with strabismus.

Myopia is not stated in the two quoted studies and the occurrence of hypermetropia has a large range 16% [14] to 41% [2]. Again, it can be as a result of using a small sample size as well as of age during the examination. The ratio is reversed in the cohort of 177 girls and women [21] between hypermetropia and myopia than in our cohort with half the number of patients. A low number of mentioned myopias will probably be dependant on the age composition as the cohort includes infants and toddlers in its listing. It is known from eye development that ametropia can turn into school myopia. Representation of hypermetropia, on its own or with astigmatism, occurs about 23% till the age of 15 in Europe and similarly, myopia is represented approximately 25% [12]. The proportion of these impairments is slightly higher in our cohort.

A high number of amblyopia in the above mentioned study [21], can be caused by failure or late diagnosis at an earlier age (with respect to the maximum age of female patients) and, on the other hand, by more complicated diagnostics in very small children as arises from the wide age range of the cohort. Yet, a quite low number of amblyopia in our cohort is very serious in reality and it shows belated diagnosing of this eye impairment which can be treated rather easily.

Certainly, the age of examination plays an important role as well during observing the incidence of individual eye impairments. The situation during comparison of epicanthus and ptosis occurrence in individual cohorts is an example. Epicanthus was discovered in 20% and ptosis only in 5% girls in our cohort of 81 girls. 26 girls are younger than 7 years out of 42 female patients in the cohort with 177 girls [21] which then can mean physiological infant epicanthus [12,21] which disappears with growth of the face. Ptosis was found in 16% [14], 21% [21], or in 29% [2] in compared studies. These figures are surprisingly high in comparison with 5% representation in our cohort. The problem consists probably in judging the real drop of the upper lid, not in the change of shape and narrowing eye slit at all. A significant epicanthus with antimongoloid slant of eyes which makes it optically narrower is often combined in Turner syndrome. Most ptosis of a congenital basis are of myogenic origin, more rarely of neurogenic origin [11] and their number does not exceed the total number of paralytic strabismus which is of a stated maximum of 2% of all strabismus [8].

Colour vision deficiency is described mainly in the forms of impairments in the area of the red-green spectrum in the literature in Turner syndrome [7,14,24] which reflects the reality that red and green retinal photo pigment is localized on the long arm of the X chromosome. The change of colour vision is described in 8% in men and 0,5% in women in the general population [27]. Therefore the incidence of colour vision deficiency in girls with Turner syndrome is the same as in healthy men who also have one X chromosome [22,24]. This was confirmed in our cohort which was in real agreement with the previous cohorts [14,21] where a lower portion of colour vision deficiency in the most numerous set afflicted with Turner syndrome was probably caused by its age composition (an assessable colour vision examination is only really possible to be performed as late as at school age, after 12 years old). Tritanopia was also detected in our cohort which has not been described in this nosologic unit yet.

Some ophthalmologic works concentrate on eye symptoms which occur in Turner syndrome less often [10,13,18,19]. They are anterior eye segment dysgenesis [1,18], keratoconus [19], juvenile glaucoma [10] and retinal neovascularization [13]. The authors tried to find correlation between eye impairment and karyotype. In their opinion female patients with mosaic form of Turner syndrome have a higher risk of anterior eye segment dysgenesis than female patients with 45, X karyotype because the presence of two or more different cell

lineages during mosaic karyotype could lead to neuronal cell migration defects and thus to anterior eye segment dysgenesis in mosaic phenotypes. Girls with mosaic form of karyotype can escape detection during a routine eye examination because of insignificant expression of individual symptoms of Turner syndrome even if they have a higher risk of anterior eye segment dysgenesis [18]. We have not met any of these accompanying disorders in our cohort. Both intra-ocular melanoma [6] and Coats disease [5] were described in Turner syndrome which could possibly be just a co-occurrence of two diseases independent of each other.

Hormonal replacement therapy influence on visus of girls with Turner syndrome is discussed as well [3,15,26]. Changes on retina simulating diabetic changes were observed in a non diabetic female patient with Turner syndrome treated with growth hormone [15], however, they were not proved in the cohort of 61 patients treated by growth hormone [3]. Neovascularization of retina are described also in female patients without growth hormone therapy [13]. The unambiguous influence of hormone therapy on the visus of female patients with Turner syndrome has not been proved yet [3,26].

Patients with Turner syndrome need multidisciplinary care which a pediatrician-endocrinologist together with a cardiologist, nephrologist, psychologist and other specialists should coordinate. Ophthalmologists, who can accelerate its potential confirmation by reporting suspicion of this syndrome and thus also start early treatment, can play an important role as well in making the diagnosis of Turner syndrome. For example, in the study with 177 female patients [21], diagnosis of strabismus in 33% proceeded the identifying of Turner syndrome.

5. Conclusion

There are different manifestations of clinical symptoms in Turner syndrome. It is true, generally, that impairments are expressed more in a typical form which is a 45, X karyotype. Oligosymtomatic manifestations are typical more for mosaic forms of karyotype [17,28,29].

These links were looked for also during comparison of karyotype and eye symptoms (Table 1).

Causal connections of some ocular diseases with a certain karyotype have not been confirmed though. During examination of girls with Turner syndrome a higher occurrence of strabismus and ptosis were confirmed in comparison to the general population, no significant difference was found in the incidence of refractive errors.

Statistically at the standard 95% confidence level, no statistically significant relationship has been found between karyotype and any type of ocular diseases. Therefore, it can be concluded that at least within the studied sample group, karyotype has no influence on the occurrence of any specific eye defect.

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Conflict of interest

The authors declare that they have no conflict of interest.

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