

EAR AND HEARING PROBLEMS IN TURNER SYNDROME.

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Abstract

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Hearing problems are frequent among women suffering from Turner Syndrome. The syndrome is due to loss of one X chromosome resulting in a female phenotype with a short stature, loss of ovaries with no estrogen production and infertility. Autoimmun diseases are common. The outer-, middle- and inner ear are affected. In Sweden a Turner Academy have been established consisting of a Turner team at each University Hospital. This has promoted joint projects with a huge material of 325 audiometrically tested Turner females in Sweden. Statistical mean values were calculated. Karyotype testing were performed in all cases. Immunohistochemical staining of inner ear specimens were undertaken with antibodies against estrogen receptors of both human Turner fetuses and middle-aged women.

Among younger females otitis media is extremely common lasting longer than in otitis prone individuals in general. The sensorineural dip can be found as early as at the age of 6, is progressive over time and related to karyotype. An early "aging" of the ear is found. A questionnaire distributed among 143 Turner females revealed that hearing impairment are rated # 4 of all problems related to the syndrome.

Since estrogen is missing in Turner Syndrome there are indications that estrogens may have an effect on the ear and hearing, but the relationship is not fully investigated. Estrogens acts through intracellular receptors α and β .

The present immunohistochemical study could confirm estrogen receptors in the inner ear of humans. The animal experiment showed estrogen receptors at an almost equal amount in rats, mice, Turner mice, β knockout mice and ovariectomized rats and at the same localization as in the human inner ear.

Key words: audiometric testing, estrogen receptors, hearing, Turner Syndrome, mice

Introduction

One X chromosome is totally or partially missing (mosaicism) in Turner Syndrome, seen in 1:2000 female births, giving the main characteristics of a female with short stature (not >150 cm) and loss of ovaries with no estrogen production resulting in infertility. No mental retardation is found. Since the early 80ies these patients are substituted with growth hormone and estrogen.

Estrogen – the female sex hormone - is classically known to influence growth, differentiation and function of the reproductive tract and plays a significant role in the maintenance of bone mass and also in the cardiovascular system and in the brain, where estrogens have certain protective effects (1,2). In Turner syndrome ear and hearing problems are common and loss of estrogens is one of the major characteristics, which can indicate that estrogen might also have an effect on the ear. For example in the normal population elderly males have a 10-25 decibel worse hearing loss in the high frequencies than the females in the same age (3). There are also well documented ABR differences between women and men, with shorter latencies for the females (4). These differences

cannot only be explained by occupational noise or anatomical variations. Henry Turner first described the syndrome in 1938, but overlooked the connected ear problem (5). Later frequent otitis media and an early hearing loss have been described (6,7,8). These girls suffer during adolescence for a prolonged period of time than commonly seen among otitis prone children (9). Even if these ear problems are meticulously taken care of, some ears develop into chronic otitis media.

A sensorineural dip in the midfrequencies is found but as a young Turner girl, this seldom leads to hearing impairment. Over time the dip broadens and the depth progresses which leads to hearing problems. The dip seems to be correlated to the karyotype. A high frequency hearing loss (presbycusis) is also added to the dip at the age of >35 leading to rapid hearing loss and social hearing problem (7).

Most of the actions of estrogens are believed to be mediated through estrogen receptor α (ER α) and the more recently discovered estrogen receptor β (ER β), which are intracellular receptors. The expression of ER α and ER β varies in different tissues and also in-between species, and no definite statement regarding ER expression pattern has yet been made. Up to this moment, the biological significance of the two ER subtypes is unclear.

In order to report the hearing results from the Swedish Turner women, to describe the recommendations for handling of these patients from the Swedish Turner Academy,(otologic section) and to discuss the eventual effect of estrogen and hearing in animal studies the present survey was performed.

Materials and methods

Turner females audiometrically measured and having an accepted karyotype testing emanating from 4 different regions in Sweden were included. Totally 325 women aged 4-68 years were tested at four University Hospitals in Sweden. Values have been calculated in the whole material as such, but also broken down in three age groups: <16, 16-34 and >34 years.

A medical report of otitis media, hearing problems and hearing aids were recorded. The outer ear and the eardrum of each patient were inspected. Hearing measurements were performed according to standard audiometric tests (8 frequencies 125Hz - 8kHz) and pure tone hearing thresholds (dBHL) were determined for both air and bone conduction. The mean value (pure tone average (PTA)) of frequencies 0.5, 1, 2 and 3 kHz were calculated and compared to an age-matched control material in Sweden. The frequency of a present dip was noted and correlated to karyotype.

A questionnaire was mailed to all known patients in the Stockholm area with the diagnosis Turner syndrome. The 143 patients were between the age of 4 and 68 years and the mean age was 34,6 years. The questionnaire consisted of 46 questions, 11 of which were open-ended single statement questions, 15 had a YES / NO answer format, 15 were answered in a 5-point scale format, two in a 2-point scale format and three were ranking questions.

Immunohistochemistry

Paraffin embedded temporal bones attained from human adults postmortem and fetuses spontaneously aborted were harvested at the University Clinic in Innsbruck, Austria, according to the laws of the country. Paraffin sections (5 μ m) of the temporal bones from adult humans and of two normal fetuses and two Turner fetuses (45,X0) from the 14th gestational week were used.

Temporal bones from Sprague Dawley rats and normal CBA mice, a special Turner mouse (X,0) and a receptor β knock-out mouse (produced by insertion of a neomycin resistance gene into exon 3 of the coding gene by using homologous recombination in embryonic stem cells) were used, paraffin embedded and sectioned. Also temporal bones from rats, ovariectomized and substituted with estrogen were added.

A standard immunohistochemical technique (avidin-biotin-peroxidase) was used to visualize ER α and ER β immunostaining distribution. A polyclonal rabbit anti-human antibody was used for detection of ER α (ZS08-0174, Zymed Laboratories, INC., San Francisco, CA), and a polyclonal rabbit anti-rat antibody (PA1-310, Affinity Bioreagents, INC., UK), was used for detection of ER β . Negative controls were treated in the same way as mentioned except for leaving out the primary antibody. As positive control served tissue from uterus (ER α) and ovaries (ER β).

Results

Mild malformation of the outer was found in 30-50% of the Turner women. Sixty-one % of the Turner females had suffered from otitis media and 32% had as young had ventilation tubes inserted one or many times. Sequelae of the tympanic membrane were seen in almost all women. Hearing aids were worn in 27% of all women, but among women >35 years of age 44% wore hearing aids.

Audiometric data

A result of the calculated pure tone average is seen in Fig.1 in the three different age groups. Both the bone and air conduction is shown. The air conduction exceeds the bone conduction in the younger age group. In the older age group with elderly Turner females, who never as young children having been carefully attended concerning the otitis media or never substituted with estrogen or growth hormones, the sequelae of middle ear problems (chronic ear problems, running ears, chronic infections, cholesteatoma) is extensive leading to hearing impairment.

The sensorineural dip

In the total material the dip is present in 83%. Sixty-nine % among the girls younger than 16 years of age, 85% among the middle aged and 88% among the elderly showed a dip. As noted in Fig.2 the dip is progressive over time and the depth increases with increasing age. The dip was most frequently found in the 2 kHz region. A correlation is also seen between the dip and the karyotypes (Fig.3) where 45,X and 45,X/46,X,(i),X(q) (isochromosome) almost always presented with a dip.

When comparing different age groups with the normal control material in Sweden the Turner females of >36 years of age have almost the same hearing as the control group of women >60 (Fig. 4).

Questionnaire

The 80 %, who answered the questionnaire, rated hearing problems as # 4, after infertility, being short and looking different. The non-participants were in the same age and had the same hearing capacity as the participants. The worst thing with having hearing loss was mentioned in a falling scale as 1) difficulties in hearing when many people are talking, 2) difficulties in hearing radio

and TV, 3) misunderstandings due to communicating problems and 4) a non-understanding surrounding. Being tired after a day of work due to intensive listening was common.

Immunohistochemistry

A. Human.

Adult tissue: ER α and ER β appeared to be expressed in the organ of Corti, in the nuclei of the in the inner and outer hair cells. Ganglion cells were heavily labeled.

Fetal tissue

No certain ER α or ER β immunostaining was seen in Kollikers organ in both Turner and normal fetus but there was a positive staining in the immature ganglion cells.

B. Animal.

Heavy labeling in the inner ear was found of ER α in the Organ of Corti in the inner hair cell, in the stria vascularis in Reissners membrane and in also in the ganglion spirale in both the type I (mostly) and type II cells (infrequently) (Fig. 5). This was true in all specimens and in all animal species. The staining was however stronger in the Turner mouse.

ER β appeared to be expressed in a more subtle way and was most frequently seen in the ganglion spirale cells.

Discussion

In this huge Swedish material consisting of 325 females with Turner Syndrome, hearing problems were common and in agreement with earlier reports. Otitis media is a great problem among the younger Turner patients. So typical that those small, short girls, undiagnosed for Turner Syndrome, have been diagnosed due to repeated otitis media. It is important to attend to these girls carefully to prevent future sequelae like eardrum pathology and middle ear problems. The extensive problems today among the older women is probably due to unawareness earlier of the coupling of the syndrome to otitis media, but also lack of treatment like penicillin at that time. What impact the estrogen replacement therapy today might have on ear problems in the future for the younger females can only be speculated upon.

The dip in the 1.5-2 kHz region is probably of genetic origin following a specific pattern with a high correlation to the 45,X and the 45,X/46,X,(i),X,(q). It can be seen as early as at the age of 6, but do not give hearing problems early in life since the dip still is within the level of normal hearing (above 20dB) and the high and low frequency regions are still intact. Since the dip progresses over time and the correlation to karyotype is verified, both the dip and the karyotype can be used to prognosticate (10). It could be useful to early know about a future developing hearing impairment and eventually take that in account when choosing profession.

There are indications that the hearing impairment could be located to the short arm (p arm) of the X chromosome since this part is missing in both groups (45,X and 45,X/46,X,(i),X,(q)) where dip is most common. Since there are no total correlation there are probably more than one loci involved (11).

Increased hearing problems develop rather rapidly when the high frequency presbycusis is added to the loss of the dip. At this point many females are unaware of the developing hearing problems and the extensive listening all day makes them very tired. It is important to support these women with all help, to inform them about the origin of the hearing problems and tiredness and support them with adequate hearing aids.

In the present study estrogen receptors α and β were present in the adult human inner ear cell nuclei at specific locations, implying that estrogens may have an effect on the inner ear. Labeling of the receptors is a prerequisite for estrogen influence on the ear and hearing.

ERs was found in the nuclei of the inner and outer hair cells and in the nuclei of the ganglion type I cells, locations where auditory impulses are transmitted.

Wharton and Church (12) demonstrated that ABR latencies in younger women were shorter than those of younger men, but this relationship changed with age, and the older postmenopausal women almost presented the same values as the men. The young women also showed larger amplitudes than the young males, but interestingly the amplitude values of postmenopausal women closely approached the male values, proposing a hormonal effect accompanying menopause. The male amplitude values essentially stayed the same regardless of age. It has recently been shown in rats that were ovariectomized and resubstituted with estrogen change their ABR latencies (13). The animal studies show that there are estrogen receptors present in the inner ear of both the Turner mouse lacking estrogen production, in the β knock-out mouse, lacking one receptor and in the ovariectomized and substituted rat. This might indicate that there is not a lack of receptors that lead to at least some of the ear related problems in Turner syndrome.

There are soforth indications that estrogen might have a beneficial effect on hearing, but further investigations are needed.

Conclusions

- Outer ear malformation, otitis media and the hearing loss correlates well with the karyotype, which can help to prognosticate future hearing problems.

-Otitis media is frequently seen (61%). Generosity with ventilation tubes and careful follow up is important. Chronic middle ear problems should be operated on without delay to prevent future sequel. Small, short girls with extensive Otitis media problems and without a diagnose, should be referred to an endocrinologist.

-The majority of women with Turner Syndrome has sensorineural hearing loss (50-90%). These problems are shown as a sensorineural dip in the 1.5-2 kHz region, a sensorineural high frequency loss or both. The hearing loss is progressive over time and gives an early aging with presbycusis requiring hearing aids. When the rather rapid inset of hearing problems develop, refer the woman to an otologist. If only a dip is present (without middle ear problems or hearing loss) check ups every 3rd to 5th year is recommended.

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Legends

- Figure 1. Pure tone average calculated in the three age groups. Among the younger girls a conductive ear problem is more frequent due to their otitis media problems. This is not seen in the middle-aged group, while the elderly women suffer from sequelae from chronic middle ear problems earlier in life.
- Figure 2. The dip is progressive over time and deepens with increasing age.
- Figure 3. Correlation between the dip and karyotype. Almost all females with the chromosome aberration 45,X and 45,X/46,X,(i),X(q) show presence of a dip while the mosaics show lesser percentage.
- Figure 4. Turner females of different age groups as compared to age matched control women in the normal population of Sweden. Note that a Turner woman in the age group 40-49 have the same hearing level as the normal controls in the age group 60-69.
- Figure 5. a. Immunological staining with receptors α and β in the inner ear ganglion of the normal CBA mouse as compared to controls. Note the heavy staining in the type I ganglion cells. b. Immunological staining of receptor α and β in human inner ear tissue.
- Figure 6. Immunostaining for ER α in the Organ of Corti in the β knock-out mouse. The inner hair cell nucleus is heavily stained.