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TÍTOL: Hearing loss in Adult Women with Turner Syndrome

Hipoacúsia en dones adultes amb Síndrome de Turner

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Índex:

HEARING LOSS IN ADULT WOMEN WITH TURNER SYNDROME

SUMMARY

Hearing loss (HL) is often reported in patients with Turner Syndrome (TS). The aim of this study is to define the patterns of HL in these patients and all the possible factors that can promote the onset of sensorineural hearing loss (SNHL) in adult TS women. Three cohorts study of 31 TS women, 15 patients with congenital hypogonadism (OCH) and 41 healthy controls were identified. A detailed medical history was taken with special attention given to karyotype, age at diagnosis, previous history of oestrogen use and otorhinolaryngological history. Pshysical examination and hearing evaluation with pure-tone audiometry and brain auditory evoked potentials (BAEP) were performed.

We found that the incidence of HL was higher in TS women compared to other groups, mainly in frequencies equal or higher than 1000Hz. According to previous studies, SNHL was the mostfrequent type of hearing impairment among middle-aged TS women, suggesting a premature presbyacusia. TS patients with previous history of recurrent otitis also had an increased incidence of HL. No statistically significant differences were found between groups in BAEPs latencies and amplitudes. Some autors suggested that HL related genes may be located on the short arm of the X-chromosome and we found that monosomies and isochromosomes presented a significant higher hearing threshold. The lack of endogenous oestrogens has been also proposed as a contributing cause for SNHL, we didn't find statistically significant differences between TS women with normal and low oestrogen levels or between TS women and other congenital hypogonadisms.

INTRODUCTION

Turner syndrome (TS) is one of the most common human genetic disorders, occurring in approximately 1:2500 live females. Affected subjects have a range of problems associated with loss of an entire sex chromosome or a portion of it, specially, the distal part of the short arm. Gonadaldygenesis and short stature are the main characteristics of TS. However, other medical conditions such as cardiovascular abnormalities, hypothyroidism, osteoporosis and non-verbal learning disabilities are linked with this syndrome[8,11,13].

Hearing loss (HL) and middle ear disease are often reported in some patients with TS[19,21,23,27]. Young and middle-aged women with TS have a progressive type of hearing impairment, deteriorating rapidly in adult age. The conductive hearing loss (CHL) seems to be a consequence of several episodes of otitis media during infancy. The cause for the infection is related to the deformity in the pinna, more pronounced in patients with a total delection of the short arm of the X chromosome, as monosomy 45X0 or isochromosome[33]. The literature characterizes the sensorineural hearing decline as two patterns: a mid-frequency dip, and a high frequency loss resembling age-related hearing impairment (presbyacusia)[21,22,27,33]. Therefore, the conductive loss may have a genetic origin, while the pathophysiology of sensorineural lesions is not yet fully understood. Some studies indicate that cochlear dysfunction is the cause of the sensorineural impairment, and it is possibly influenced by oestrogen deficiency [22,29].

The relation between otologic disease and karyotype[23,33], the impact of oestrogen deficiency on hearing[10,17,20], the physiopathology of the sensorineural hearing loss (SNHL) or the identification of otolaryngologic markers for the early diagnosis of TS[24], are questions pending resolution.

The aim of the present study was to define better the patterns and causes of HL associated to TS, using subjective and objective diagnosis tools. Remarkably, to the best of our knowledge, no previous studies exist where TS women were compared with OCH in terms of hearing loss. On the above evidence, the current investigation was undertaken to deal this subject using TS patients, but also two appropriate comparator groups: OCH and a reference control group taking exogenous hormones.

METHODS

Study design and population

An analytical study of three independent cohorts was designed. The first cohort corresponds to 31 TS patients recruited by the Gynaecological Endocrinology Unit of the Hospital Clinic of Barcelona. The diagnosis of TS was confirmed by blood karyotype showing a total or partial absence or alteration of X chromosome in at least, more than 10% of cells. Inclusion criteria were TS subjects between 20 and 50 years of age receiving hormone replacement treatment.

A total of 15 women with congenital hypogonadism and wild-type karyotype, receiving hormone replacement treatment, composed a second cohort. This cohort includes subjects with pure gonadal dysgenesis (hypergonadotrophic hypogonadism), and with idiopathic hypogonadotrophic hypogonadims. Kallman's syndrome patients were excluded because of its possible association with sensorineural hearing loss [5,15]. The aim to include this group was to define the role of congenital hypooestrogenism in hearing decline associated with TS.

The third cohort included 41 non-exposed age-matched cases, as controls, were all treated with oestrogen and progestagens with the aim of contraception. The gynaecological department recruited them. None of them took any other drug that could interfere with the study results. Animal [16,29,31] and human [28,30]studies indicate that oestrogens could have and impact on hearing. Moreover, cycling hearing alterations have been described in women with normal menstrual cycle. High pure-tone thresholds have been found during the menstrual phase, when the levels of circulating estrogens are at their lowest[22,32]. This was not seen in women using oral contraceptives. Therefore, a control group receiving exogenous hormones was selected for the present study, in order to mimic as much as possible the hormone status of the main study group.

Exclusion criteria were the presence of acute or chronic pathologies non-related with the syndrome being studied which could interfere with the analysis, such as head injury, Meniere's disease or cerebellopontine angle or intracanalicular tumors[20]. The study protocol was reviewed and approved by the Ethics Committee of the HospitalClinic of Barcelona, and it was performed in accordance with the Helsinki II Declaration

and the ICH Guidelines for Good Clinical Practice. All patients were informed about the study and the interventions that would be performed and signed informed consent was obtained from all of them at the time of inclusion.

Interventions

Clinical history: blood karyotype, age at diagnosis of hypogonadism and previous history of oestrogen use were collected. Patients with spontaneous menarche before 16 years of age (and consequently, spontaneous development of secondary sexual characteristics) or age at diagnosis before 16 years old (and consequently, with the beginning of oestrogen replacement therapy before 16 years) were considered as patients with normal puberty. Additionally, data of otorhinolaryngological (ENT) history was recorded, as history of recurrent episodes of otitis media, tubes insertion, tonsillectomy or adenoidectomy, or family history of hypoacusia.

Physical examination: measurement of height and weight. Microotoscopy in order to evaluate the external auditory canal and the eardrum was carried out by two experienced ENT specialists without knowing which of the three study groups the patients belonged.

*Standard pure tone audiometry*was performed to all participants, according to standards audiometric methods (ISO 389), using a clinical audiometer at octave intervals from 250 to 8000 Hz. All hearing test were carried out by the same trained audiologist in a soundproof booth, with background levels well-below the accepted standards. As always, there can be a 5 dB machine error rate associated with audiogram measurement.

Audiometry results were categorised as *normal* if the air conduction (AC) thresholds were equal to or lower than 20 dB across the frequency range of 250 to 8000Hz. However, if there was an apparent loss of only 5 dB HL at only one frequency, the ear audiometry was also considered normal for the purposes of this analysis. Hearing loss (HL) was defined as AC thresholds higher than 20 dB at one or more frequencies in the range of 250 to 8000 Hz. In these cases, bone conduction was performed in order to classify the type hearing loss. *Conductive hearing loss* (CHL) was defined as AC thresholds higher than 20 dB with an air-bone gap (ABG) of at least 10 dB at one or more frequencies, being bone conduction (BC) thresholds less than 20 dB at any frequency. Patients with a pure *sensorineural hearing loss* (SNHL) resented the AC thresholds worse than 20 dB HL at one or more frequencies in the range of 250 to

8000 Hz, with ABG lower than 10 dB. Finally, subjects with a *mixed* (MHL) conductive and sensorineural hearing loss were defined as BC thresholds worse than 20 dB HL at one or more frequencies with an ABG of at least 10 dB at one or more frequencies[31].
Degree of hearing loss was based on a four frequency (500, 1000, 2000 and 4000 Hz) pure-tone air conduction average, following the schemes adapted from the European Working Group on the Genetics of Hearing Impairment[23]. Mild hearing loss includes pure-tone air conduction average from 20 dB to <40 dB; moderate, from 40dB to <70dB; severe, from 70 dB to< 95dB; and profound, equal or higher than 95 dB[20].
HL was also assessed using the American Academy of Otolaryngology 1979 (AAO) equation. This equation is broadly used in occupational hearing decline and is obtained as follows; The average of 500, 1000, 2000 and 3000 Hz threshold was calculated per ear. From the average 25dB were subtracted, and the result was multiplied by 1.5. This result gave the percentage of HL of the ear. To calculate the binaural score the following formula is applied:

% binaural score = (5 x (best ear score) + 1 x (worst ear score))/6

Brain Auditory evoked potentials (BAEP) were performed to TS patients and OCH group. BAEP results were compared to the reference population data of our hospital. BAEP were registered using a two-canal recording device of a Medelec Synergy EP machine. The lower filter was 100Hz, and the upper one 3000Hz. The stimulus consisted of alternating clicks, presented monaurally with a rhythm of 20 times per second. The medium response of 1500 stimuli was registered for 10 ms. First of all, the latency of V wave was recorded at different intensities of the stimulus, between 30dB and a maximum of 110dB in order to find out the threshold of hearing and to establish with the best accuracy the type of deafness. Auditory brain response (ABR) was done afterwards. The intensity of the stimulus applied was 60dB higher than the threshold of hearing. Morphology, latencies of peaks I, III and V, as well as interpeaks I-III, III-V and I-V were recorded. Two replications, each to 1500 stimuli, were obtained for each stimulus intensity for each ear tested. Each recording was individually analyzed by the testing audiologist and by two neurologist of the hospital.

BAEP have been extensively validated as an objective diagnostic tool for sensorineural hearing loss, monitoring the pathway from the cochlea to the level of brainstem. Wave I is the result of the volley generated by the click stimulus in the distal part of the eight nerve. Consequently, changes in the amplitude or latency of this wave suggest damage of the coclea or the distal part of the eight nerve. Nevertheless, abnormal absolute

latencies of waves II-V or interlatencies I-III, III-V are strongly indicative of retrococlear hearing loss. In conductive deafness the hearing threshold is high, wave I to V are usually shifted to the right but the I-V interval is normal and the latency-intensity curve for wave V runs above the normal curve and is parallel to it. However, in sensorineural deafness the threshold of hearing may be high, the latency-intensity curve is of recruiting type so at high intensity, the curve is normal, but at lower intensity the wave V latency is prolonged disproportionately. Latencies in cases with sensorineural hearing loss are within the ranges seen in normal hearing individuals[6].

Statistical analysis:

Statistical analysis was performed using the the software SPSS v19 (SPSS 19.0, SPSS Inc. Headquarters, 223 South Wacker Drive, Chicago, IL 60606, USA). Qualitative variables were described using frequency tables, whereas quantitative variables were described by their average and standard deviation. A T-student test was performed to compare averages between groups in those variables following normality, according to Kolmogorov-Smirnov. Conversely, when the variables did not fit into normality, a Mann Whitney U-test was carried out. A binomial test was used to compare frequency variables. All statistical hypotheses to be testes were carried out considering an alpha error of 5%.

RESULTS

Clinical and anthropometrical characteristics of the subjects are shown in *Table 1*. As expected, controls and OCH were taller than TS patients. More than one third of TS patients underwent tonsillectomy and adenoidectomy, and only a quarter did not suffer from recurrent otitis media in childhood. However, a low percentage of TS women have deformed external acoustic meatus or affected eardrum.

Analysing pure tone audiometry results, 27 (87%) of TS patients suffer some degree of HL, compared with 3 OCH (20%) and 11 controls (27%). When outcomes of the AAO equation were compared between groups, TS women bear a significant HL in respect to OCH group and control group ***(Figure 1).*** Statistically significant differences were found between TS and controls considering the right ear ($p=0.001$), left ear ($p<0.02$) and binaural loss ($p<0.001$). Equally, differences were found between TS and OCH in right ear ($p=0.015$), left ear ($p=0.002$) and both ears (0.009). ***Figure 2*** shows air conduction (AC) hearing thresholds across the frequency range from 250 to 8000 Hz of the three study groups. Again, statistically significant differences were found in frequencies equal or higher than 1000 Hz between TS and OCH ($p<0.05$) and TS and controls ($p<0.01$), both in the right ear or left. Comparing the results of both ears, no differences were found between right and left ear.

Patients were divided considering the degree of HL ***(Figure 3).*** The majority of patients of the control group and OCH presented normal hearing function, with a low proportion of females with mild hypoacusia. Conversely, much more number of patients suffering moderate, severe or profound hypoacusia were found in TS group than in controls or OCH.

Following the classification criteria described previously, SNHL was the most frequent type of defect found in TS group (11 patients in the right ear, and 13 in the left), followed by CHL (8 patients in the right ear, and 8 more in the left) and MHL (4 affected right ears, and 4 left ears). The low percentage of affected controls was diagnosed by CHL (3 in the right ear, and 7 in the left ear), while OCH suffered SNHL (2 in the right ear, and 3 in the left ear) ***(Figure 4).***

The latency-intensity curve for wave V concluded that hearing threshold was improper in 33 ears (54.1%), which accounts for 19 TS patients (61%); in 14 TS patients bilaterally and in 5 cases one sided. According to pure tone audiometry results, just the

20% (6 ears affected) of OCH patients presented HL. Nevertheless, up to 8 TS patients with impaired audiometry results presented normal BAEP.

Following the classification criteria described previously, mild hearing loss was detected in 18 ears (29.5%); moderated hearing loss in 12 ears (19.7%); severe hearing loss in 2 ears (3.27%) and profound hearing loss in only one ear (1.63%). CHL was present in 4 ears (6.55%), mixed hearing loss in 3 ears (4.9%) and SNHL in 26 (42.6%). Type of HL evaluated by BAEP was in accordance with audiometry, except in a group TS patients analysed as mild CHL in the audiometry, which was evaluated as normal in BAEP; probably due to its greater objectivity.

Finally, the results of BAEP were analyzed. ABR-wave I was reliable indentified in 27 cases, wave III in 29 and wave V in all cases (31 TS patients). Mean and standard deviation of latencies, amplitudes and interpeaks of waves I, III and V are shown in ***(Table 2)***. No statistically significant differences were found either between TS and OCH, or TS and values of reference population.

Several sub-analysis between groups of TS patients were performed in order to explore possible associations of HL with karyotype, hormonal status, history of recurrent otitis media and age.

First of all, TS patients were divided considering the presence of the short arm of X chromosome. Complete absence sub-group included patients with pure monosomy (45X0) or isochromosome (45X0/46i(X)). The rest of mosaicisms or structural anomalies formed the second sub-group. Statistically significant differences were found between groups in 8000 Hz, where monosomies and isochromosomes presented higher threshold than the others ($p=0.01$ in T-student test).

The second sub-analysis divided TS patients considering the hormonal status during puberty. Patients with normal puberty (as defined in methods section) and TS women without normal oestrogen levels at the end of the puberty were compared. No statistically significant differences were found between groups.

Two groups of TS females were performed considering age: patients from 20 to 35 years, and women from 35 to 50. As expected, statistically significant differences were found between groups, with higher threshold in mid and high frequencies (2000, 4000 and 8000 Hz) in the oldest group ($p<0.05$).

The last sub-analysis was carried out dividing TS patients with a history of recurrent otitis media during childhood, and those without history. HL was statistically significant higher among patients with recurrent otitis at 250, 500, 4000 and 8000 Hz ($p<0.05$).

DISCUSSION

The main findings of the present study are: more than a half of TS females presented HL in pure-tone audiometry, confirmed by BAEP; SNHL is the most frequent type of hearing impairment among middle-aged women with TS; and age, karyotype and history of recurrent otitis media are likely to be factors that promote hearing loss among TS patients.

In the present study, we observed HL in almost 90% of females with TS evaluated by audiometry. Nevertheless, improper hearing analyzed by BAEP was found in approximately one-half of TS patients, in concordance with previous reports[17,23]. These differences may be due to an upper normality threshold in BAEP (30dB *vs* 20dB in audiometry) and the higher objectivity of this neurological technique. However, direct comparisons with other works are difficult due to the disparities in how HL is defined and categorized. The majority of the studies are performed in children with TS[17,26,27,33], with a high percentage of them showing CHL. The aetiology of this increased incidence of middle ear pathology in TS is thought to be due to early defects in lymphatic channels and aberrant anatomic shaping of structures derived from the first and second brachial arches, causing abnormally horizontal Eustachian tubes and palatal dysfunction[18]. Worse quality of epithelium is also reported in those patients[17]. All this factors predisposed to otitis media. Twelve TS females presented CHL (pure or mixed) in the present study, according to these data.

Otherwise, older population has an increased incidence of SNHL[27]. Taking into account that our TS patients studied are from 20 to 50 years of age, comparison should be done with other studies performed in populations of similar ages. Hederstierna and coworkers[20] studied 30 TS women aged 40-67, with mild to moderate HL, aimed at localizing the lesion causing the SNHL and assessing central auditory function. As already mentioned, ABR-latencies in the present study were within reference mean +/- 2SD in all 31 TS cases. No ABR amplitudes and absolute and interpeaks latencies of our TS-cases were not significantly prolonged compared to the reference population, in accordance with Hedestierna study. Fifteen of the thirty-one TS cases had mild to moderate hearing loss and three of them showed an absence of wave I, suggesting cochlear dysfunction as the cause of this hearing loss impairment. The last case of unilaterally absence of wave I suffered from a severe hearing loss. Unlike Hedesternia's results, shorter V latencies were not found in our study. There are contradictory

reports in literature, nevertheless. Other previous studies[17,18] also showed prolonged absolute ABR latencies, but interpeak latencies were completely normal in all cases.

The most frequent type of HL found in our sample was SNHL. The literature characterizes the SNHL in TS women as two patterns: a bilateral symmetrical mid-frequency dip, maximal at 2 Hz. and a high-frequency down-sloping SNHL[21]. No cases of clear mid-frequency dip were found in TS females in the present study. This could be due to the fact that a majority of TS women develop a moderate to profound high-frequency loss[20], leaving only the low-frequencies spared. This audiometric pattern was the most frequently observed in our TS population.

A cell cycle delay has been explained as a possible cause of SNHL in TS. Whereas in healthy subjects the density of hair cells in the Organ of Corti is highest in the middle turn of the cochlea, a lack of sensory hair cells within the cochlea exists in TS patients. This defect has been hypothesized as the cause of the mid-frequency hearing loss, while the apoptosis attributable to age has been suggested as the responsible of the presbyacusia. Therefore, both CHL and SNHL could be explained by developmental period alterations in TS women[17]. The severity of TS dysmorphology is related to karyotype[8,14,24]. There are suggestions that the hearing impairment related genes may be located on the short arm of the X-chromosome[22]. According to this hypothesis, a higher ocurrence of ear and hearing defects is expected in TS patients with monosomy or isochromosome compared to those with a mosaicism or structural anomaly[33]. The results of the sub-analysis perfomed in the present study between monosomy or isochromosome *versus* the rest of karyotypes are in accordance with this hypothesis: worse results in high frequencies were found.

Additionally, the lack of endogenous oestrogens has been proposed as a contributing cause for SNHL. Oestrogens receptors have been found in the inner ear in rats and mice[29], and also in human fetuses, adults and TS fetus[30]. Coleman and coworkers[7] proved improvement of BAEP latencies scores in ovariectomised rats after hormonal replacement therapy. A lack of appropriate hormonal treatment during childhood has been suggested as one cause of the extensive hearing problems found among older TS women[22,26]. Following this line, TS patients were divided again in two sub-groups: with normal hormonal status at 16 years of age, or lack of sexual development. No statistically significant differences in hearing status were found between groups in the present study. Furthermore, it is worth to note that no statistically significant differences were found between controls and OCH in any hearing test, while

differences were found between OCH and TS patients. TS is a suitable human model for the assessment of physiological processes in organs that have matured in a deficient oestrogen environment[20], but also are indeed patients with congenital hypogonadisms having normal karyotype. No hearing decline was found among patients of this second group (OCH group), which additionally suffered an even more delay than TS in the oestrogen deficiency diagnosis due to the lack of dysmorphology *(Table 1).* This new group of study suggests a minor role of oestrogens in HL, although further studies are needed to solve such issue.

Hearing decline in women, in general, fairly slow up until the age around 50 years, but accelerates after the menopause. TS patients suffer a rapidly progressive hearing decline with age. The rate of progression in young and middle-aged women with TS is on a level comparable to that seen in 70-89 year-old women in the general population, especially in high frequencies[19]. After dividing TS patients in two groups, considering age, higher threshold values were observed in the oldest group in mid and high frequencies, in agreement with previous studies[19,21,23]. This decline in hearing may reflect a premature loss of sensory function, residual cochlear sequelae of otitis media, or both[21]. It is important to note that the hearing impairment becomes more socially handicapping when a high-frequency loss joins the the mid-frequency dip developed previously[19].

Last sub-analysis was carried out sorting TS patients with and without history of otitis media during childhood. Interestingly, statistically significant differences were found between groups, with worse results in TS with history of otitis, in the lowest and the highest frequencies. Mid-frequency dip pattern seems to be independent of otitis media and it is typically present in TS adolescents[17,32]. No differences were found between groups at mid-frequencies, probably due to the alterations of these frequencies in a high percentage of TS adolescents, with and without history of middle ear infection.

Some limitations exist in the present study. The low sample size, especially in the case of TS sub-groups analyses, should make these results interpreted with caution. However, some selection biases have been avoided with the recruitment through a gynaecological unit instead of specialty otorhinological referral clinics, giving a more realistically prevalence of hearing disorders in TS women. In addition, the comparison between TS and OCH adds absolutely new type of data for the study of the role of oestrogens in hearing function.

CONCLUSION

A progressive hearing loss is associated with TS, being SNHL the most frequent pattern of hearing decline. The etiology of HL is no doubt heterogeneous, with a strong genetic influence, but also recurrent history of otitis media. However, the role of the lack of endogenous oestrogens becomes less important, although further studies are needed to define it. Regular audiometric test in adults patients with TS are required due to their much earlier development of presbyacusia with low percentages of complains about subjective hearing deterioration[17]. However, the single medical intervention to reduce hearing loss in women with TS is restricted to otitis media prevention.

Table 1. Clinical and antrhopometrical characteristics of the three study groups. Comparisons between groups were performed using student T-test for continuous variables, while binomial test was used to compare percentages. BMI = Body Mass Index. HRT = Hormone Replacement Treatment.

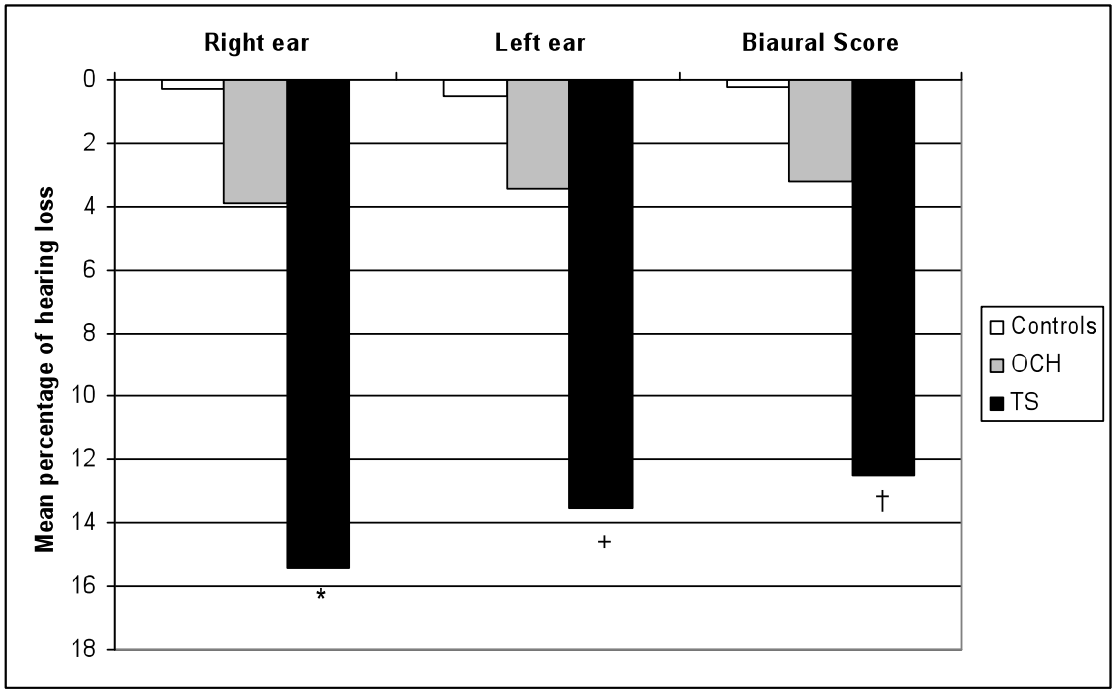
	Controls (n = 41)	Other congenital hypogonadisms (n = 15)	Turner's syndrome (n = 31)
Age, years (Mean ± SD)	34.6 ± 7.6	32.7 ± 8.5	36.6 ± 8.1
Height, cm (Mean ± SD)	163.4 ± 5.2	162.1 ± 8.7	148.8 ± 7.5**
BMI, kg/m^2 (Mean ± SD)	22.7 ± 4.0	22.3 ± 13.8	25.1 ± 3.8*
Age at diagnosis (Mean ± SD) years	-	16.7 ± 3.0	10.5 ± 10.2†
Age at beginning of HRT, years (Mean ± SD)	-	17.8 ± 3.7	17.8 ± 5.3
Spontaneous menarque. N (%)	41 (100)	9(60)**	10 (32)*
Hearing history			
Familial hipoacusia history. N (%)	6 (15)	3 (20)	5 (16)
Adenoidectomy. N (%)	4 (10)	1 (6)	10 (32)*
Tonsilectomy. N (%)	4 (10)	1 (6)	11 (35)*
Recurrent otitis media. N (%)			
No	13 (87)	13 (87)	8 (26)*
Bilateral.	2 (13)	2 (13)	12 (39)
Only right.	0 (0)	0 (0)	5 (16)
Only left.	0 (0)	0 (0)	6 (19)
Deformed external acoustic meatus. N (%)			
No	15 (100)	15 (100)	27 (87)
Bilateral.	0 (0)	0 (0)	3 (10)
Only right.	0 (0)	0 (0)	0 (0)
Only left.	0 (0)	0 (0)	1 (3)
Affected eardrum . N (%)			
No	15 (100)	15 (100)	24 (77)
Bilateral	0 (0)	0 (0)	3 (10)
Only right.	0 (0)	0 (0)	1 (3)
Only left.	0 (0)	0 (0)	3 (10)

*p <0.05 comparing with control group.
**p <0.01 comparing with control group.
†p <0.05 comparing with other congenital hypogonadisms.

Table 2 – Results of Brain Auditory Evoked Potentials (BAEP) of Turner's syndrome patients and other congenital hypogonadisms. Values of the reference Spanish population are shown. No statistically significant differences were found between groups using an ANOVA test.

BAEP values (Mean ± SD)	**Reference population**	**Other congenital hypogonadisms (n = 15)**	**Turner's syndrome (n = 31)**
Hearing threshold (dB).	<20dB	23.37 ± 8.48	36.00 ± 18.17
Latency Wave I (ms)	1.7 ± 0.15	1.62 ± 0.31	1.80 ± 0.23
Latency Wave III (ms)	3.9 ± 0.19	3.67 ± 0.74	3.86 ± 0.18
Latency Wave V (ms)	5.7 ± 0.25	5.43 ± 1.10	5.75 ± 0.30
Amplitude Wave I (μV)	0.28 ± 0.14	0.35 ± 0.16	0.19 ± 0.10
Amplitude Wave III (μV)	0.23 ± 0.12	0.31 ± 0.14	0.22 ± 0.10
Amplitude Wave V (μV)	0.43 ± 0.16	1.44 ± 5.01	0.35 ± 0.14
Interpeak I-III (ms)	2.1 ± 0.15	1.98 ± 0.57	2.05 ± 0.18
Interpeak III-V (ms)	1.9 ± 0.18	1.68 ± 0.51	1.85 ± 0.17
Interpeak I-V (ms)	4.0 ± 0.23	3.66 ± 1.07	3.89 ± 0.25

Figure 1. Percentage of hearing loss according to the equation of American Academy of Otolaringology (AAO).

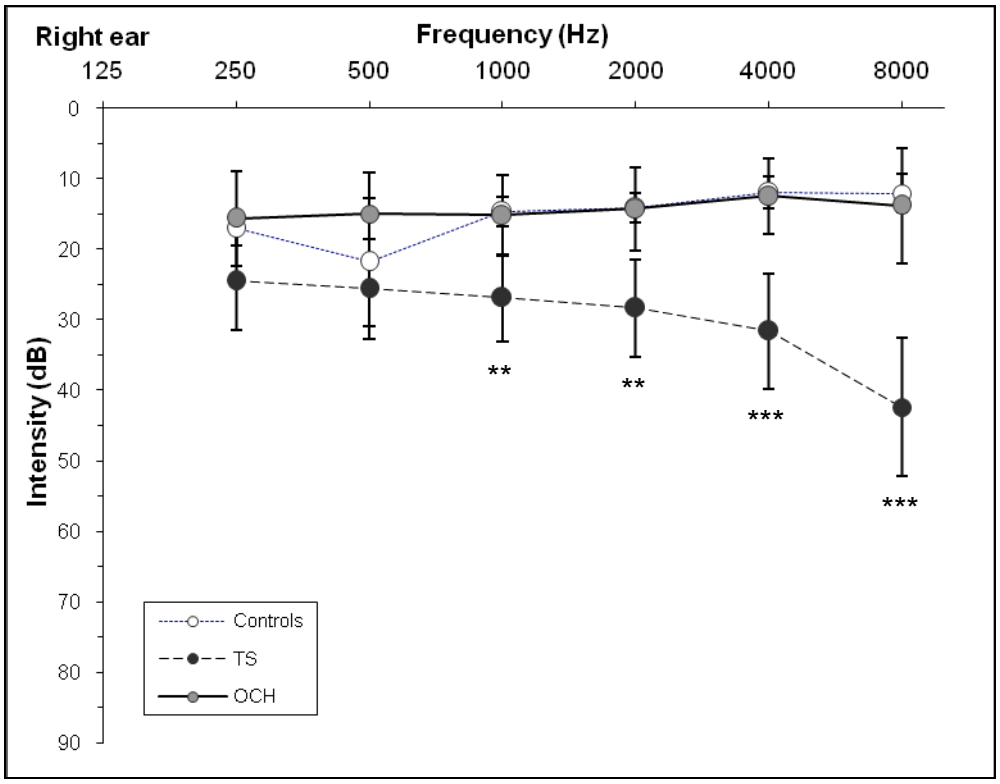


* TS bear a significant hearing loss compared to controls (p = 0.001) and compared to OCH (p=0.015) in a Mann-Whitney test

+ TS bear a significant hearing loss compared to controls (p < 0.001) and compared to OCH (p=0.02) in a Mann-Whitney test

† TS bear a significant hearin loss compared to controls (p <0.001) and compared to OCH (p=0.009) in a Mann-Whitney test

Figure 2. Pure-tone audiometry results of the three study groups. Air conduction hearing thresholds across the frequency range from 250 to 8000 Hz. Average and confidence interval 95% are depicted. (**) indicates p<0.01 between TS and control group and (***) indicates p<0.001 between TS and control group.



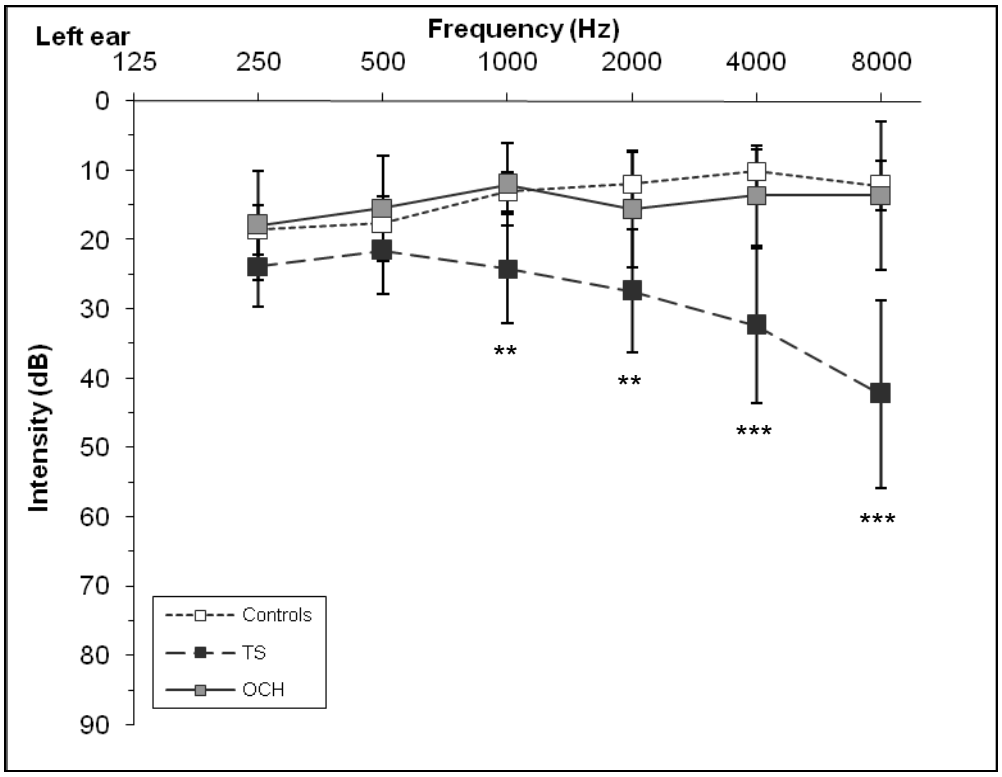


Figure 3. Number of patients of the three study groups and degrees of hypoacusia. TS: Turner's syndrome; OCH: other congenital hypogonadims

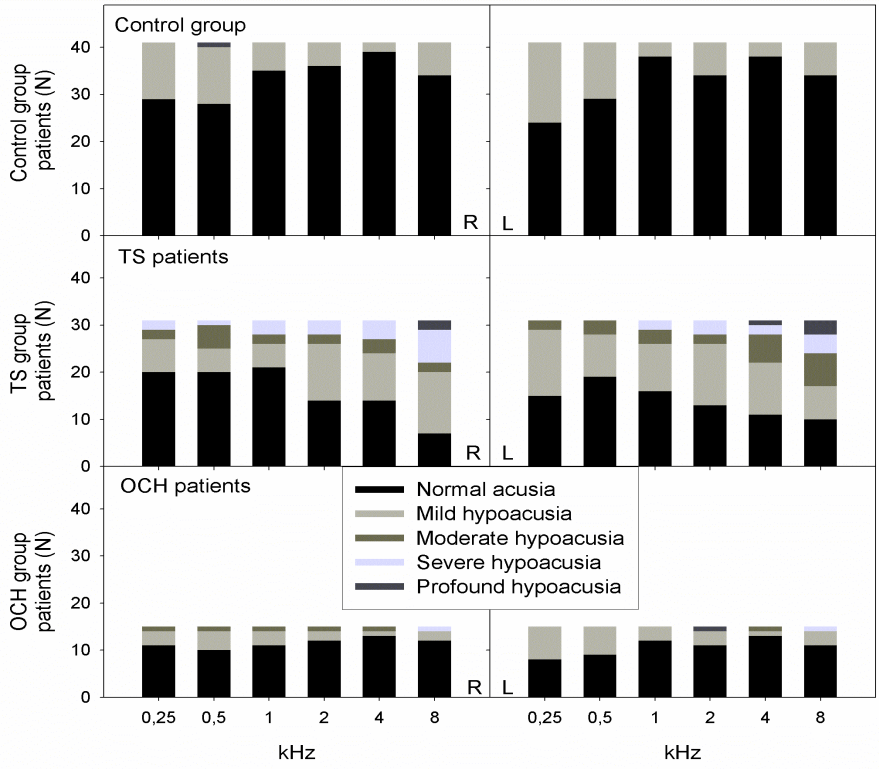
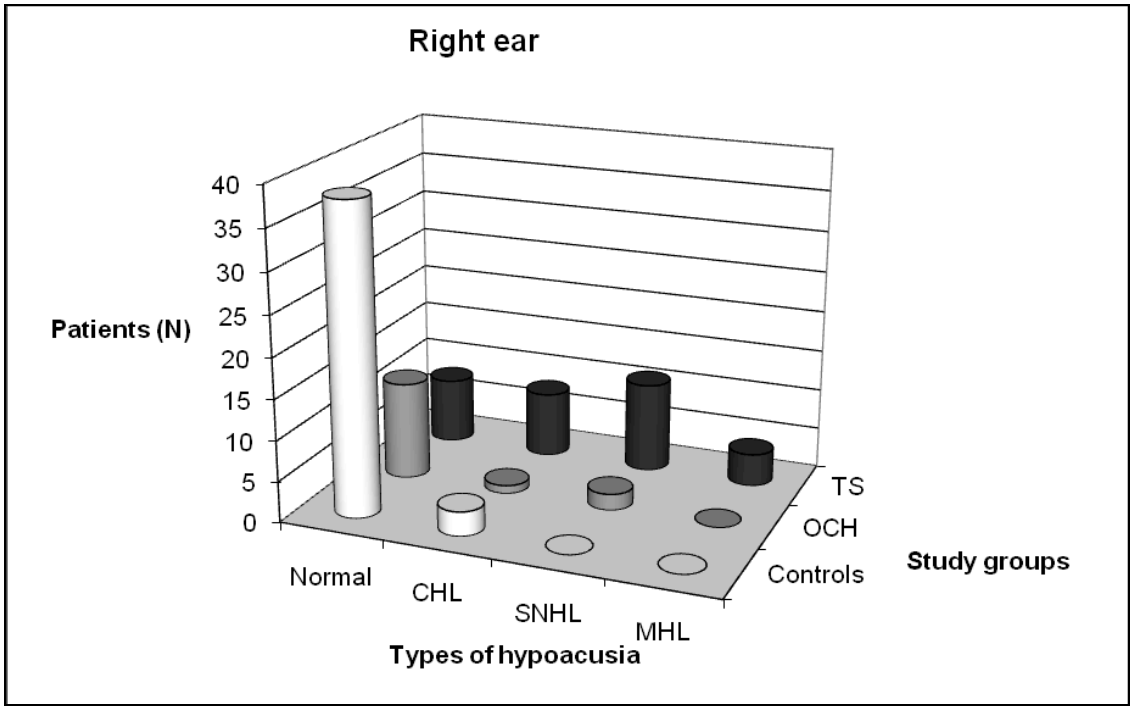
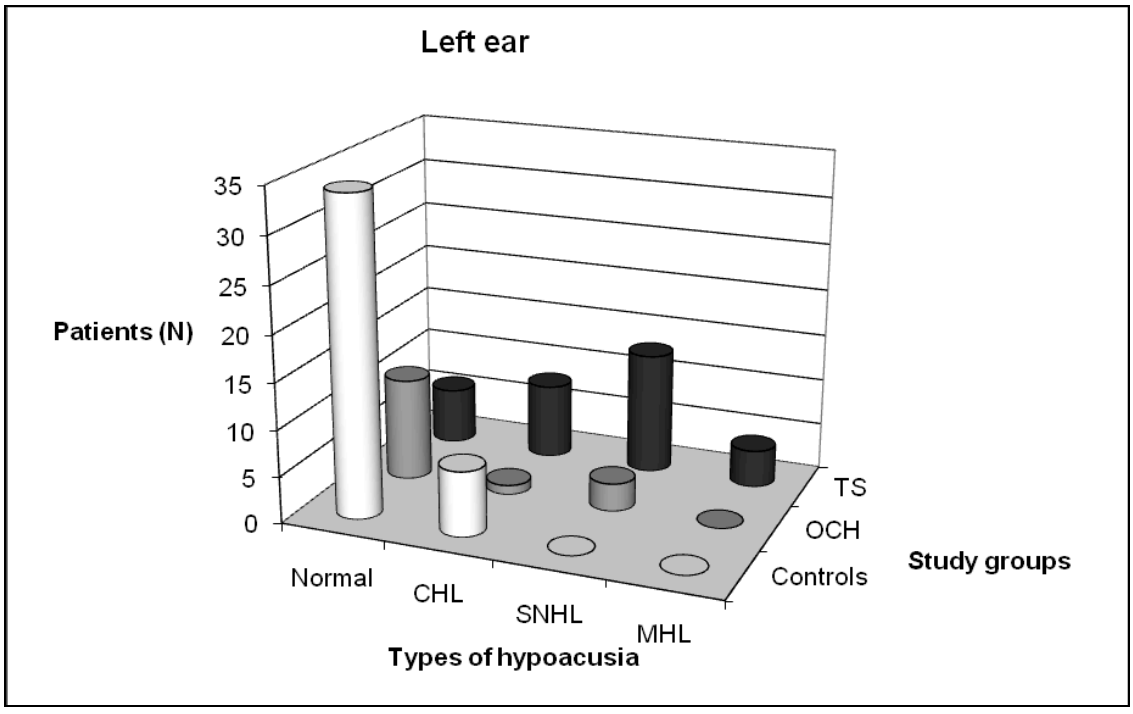


Figure 4. Number of patients of the three study groups and types of hypoacusia. CHL: conductive hearing loss; SNHL: sensorineural hearing loss; MHL: mixed hearing loss; TS: Turner's syndrome; OCH: other congenital hypogonadims.





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