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Review

Hearing Loss and Turner Syndrome: A Scoping Review

Andrea Migliorelli[1], Andrea Ciorba[1], Marianna Manuelli[1], Virginia Corazzi[1], Francesco Stomeo[1], Chiara Bianchini[1], Stefano Pelucchi[1], Daniele Monzani[2], Elisabetta Genovese[3], Silvia Palma[3]

[1]Department of Neurosciences, ENT and Audiology Unit, University Hospital of Ferrara, Ferrara, Italy
[2]Department of ENT and Audiology, University of Verona, Verona, Italy
[3]Department of ENT and Audiology, University of Modena and Reggio Emilia, Modena, Italy

ORCID iDs of the authors: A.M. 0009-0004-8980-3877, A.C. 0000-0003-3455-2295, C.B. 0000-0002-5115-6107.

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Hearing loss (HL) is one of the most frequent disorders in Turner syndrome (TS); HL can be present with a wide spectrum of manifestations and also evolve with age. The aim of this paper is to perform a review of the literature on the prevalence of HL in TS patients also analyzing the possible genetic alterations underlying the auditory features. A review of the literature was performed using PubMed/MEDLINE, EMBASE, and Cochrane Library databases, according to the preferred reporting items for systematic reviews and meta-analyses criteria for scoping reviews (from 2000 to December 2023). A total of 17 articles and 2129 patients with TS have been included; the majority of studies focused on young women/girls, with a mean age range from 2 to 43.6 years. External and middle ear problems, inducing conductive and mixed HL, have been reported to be more frequent in childhood, while sensorineural HL has been described since adolescence. Monosomy 45,X and loss of the X chromosome short arm (p) are the alterations most frequently associated with HL. To date, the pathophysiological mechanisms related to HL in TS are still not fully understood; further studies are necessary to clarify these features and to offer therapies or prevention strategies to avoid the progression of HL in TS subjects.

KEYWORDS: Turner syndrome, hearing loss, sensorineural hearing loss, etiology

INTRODUCTION

Turner syndrome (TS) is a chromosomal disease that affects 1 in 2000 live births females.[1] It is caused by a complete or partial deletion of an X chromosome. The most common karyotype is monosomy 45,X, in which only 1 X chromosome is present in all cells. Mosaicisms (e.g., 45,X/46,XY; 45,X/47,XXX or 45,X/46,XX) may also occur.[2,3] Furthermore, patients may lack the short arm (p) of the X chromosome. Patients with monosomy 45,X usually have more severe manifestations of the disease than those with mosaicism.[4] Short stature and ovarian dysgenesis are the main clinical features of TS.[1,2] A varied spectrum of somatic changes has been described in these patients, including coarctation of the aorta, pulmonary deformities, pterygium colli, autoimmune disorders, renal abnormalities, cubitus valgus, lymphedema, broad chest with wide-spaced nipples, and a low posterior hairline.[1-3,5]

Concerning audiological features, TS patients often present with a variety of disorders. Ear defects, hearing loss (HL), and middle ear disorders are now considered common in TS. Middle ear changes leading to conductive hearing loss/mixed hearing loss (CHL/MHL) have been reported to be more common in childhood/adolescence, while sensorineural hearing loss (SNHL) is reported to be more frequent in adults.[4,6-8] Mid-frequency SNHL is typically described in TS patients and may occur since adolescence.[9]

Numerous studies in the literature have attempted to search for chromosomal alterations as a possible cause of HL, although there is still no consensus in the literature.

The purpose of this paper is to perform a review of the incidence of HL in TS patients, also analyzing the possible genetic alterations underlying the auditory features.

Corresponding author: Andrea Migliorelli, e-mail: mglndr1@unife.it
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METHODS

A detailed review of the English-language literature on TS and HL was performed using PubMed/MEDLINE, EMBASE, and Cochrane Library databases. The search period was from 2000 to December 2023, with the aim of selecting the most recent studies. The MeSH terms used were "Turner syndrome," "Monosomy X," "X Chromosome Monosomy," or "45,X" and "hearing loss," "hearing impairment," or "deafness." The search yielded 1008 candidate articles. The search was performed according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) for scoping review guidelines (Figure 1).[10] The inclusion criteria applied were: i) original studies of cohorts >50 patients (to identify studies with adequate sample sizes; see the article by Dworkin et al for details);[11] ii) publication date after 2000; iii) clear reporting of otologic disease definition; iv) TS patients; and v) English language. Conference abstracts, case reports, publications written in a language different from English, articles with fewer than 50 patients, and articles in which the otologic disease was not clearly defined have been excluded. Two authors (A.M. and M.M.) have independently evaluated all titles, and relevant articles have been identified according to inclusion/exclusion criteria; a senior author (A.C.) resolved any disagreements. At the end of the full-text review, only 17 articles met the inclusion criteria.[4,8,9,12-25]

RESULTS

In this review, 17 articles were included for a total of 2129 patients with TS. The year of publication ranges from 2000 to late 2020.

The result of this review is summarized in Table 1. The majority of studies focus on young women/girls with TS, with a mean age range from 2 to 43.6 years. With the exception of 1 study conducted in Latin America, all studies have been conducted in North America or Europe.

External and Middle Ear

The most common ear anomalies found in the literature are cupped or low-set ears. The incidence of these malformations is quite variable, ranging from 30% to 68%.[4,12,18,25]

MAIN POINTS

- The present review shows that HL is a common and disabling aspect of TS. The otological changes include both morphological (i.e., outer ear defects) and functional features, resulting in conductive, mixed and/or sensorineural HL.
- The complexity of HL in TS subjects seems to be related to its possible evolution within the same patient. While in the pediatric age, a conductive impairment is mostly predominant, neurosensory disorders can occur in adulthood.
- Patients with TS often have a specific mid-frequency sensorineural HL, which is a prognostic factor for the progression of SNHL. Therefore, although high-frequency SNHL is more common in TS, mid-frequency loss is a characteristic of this disorder.
- The association between specific chromosomal abnormalities (monosomy 45,X and short arm (p) loss of the X chromosome) and HL was not found in all the studies included in this review.

Myringosclerosis, endotympanic effusion, and retraction or perforation of the tympanic membrane are the otomicroscopic abnormalities most commonly described in TS patients (20%-49%).[16,17,20,23]

The presence of recurrent otitis media is also common in the case series reviewed (10%-76%).[18-21,23,25]

In addition, patients with TS are more likely to develop cholesteatoma than the general population (5%-8% vs. 0.01%).[16,20,21,23,24]

Given the higher incidence of middle ear disease, patients often undergo ear surgery, the most common of which is the insertion of a ventilation tube (literature range 24%-65%).

Hearing Loss

Hearing loss is a frequent impairment in TS. The prevalence ranges from 21% to 84% in selected studies.[8,13-17,19-25] Especially in the young population, CHL/MHL is frequently described with a prevalence of 6%-51%.[8,12-17,20-25] Recurrent persistent otitis media with effusion, chronic otitis media, ossicular degeneration, and cholesteatoma are the main causes of CHL/MHL in TS. These changes, according to the literature, seem to result from improper ventilation of the middle ear due to Eustachian tube dysfunction.[17,24] In addition, TS is also associated with stapes abnormalities, which could also lead to CHL/MHL.[18] Bergamaschi et al[16] correlated CHL/MHL with craniofacial anomalies such as pterygium, micrognathia, high-arched palate, and low ears. Finally, otologic symptoms resulting in CHL/MHL have been correlated with low serum levels of insulin-like growth factor 1 (IGF-1), so its supplementation could improve the clinical picture, according to some authors.[12]

However, the most common type of HL associated with TS is SNHL (3%-83%).[4,8,13-25] This disorder is less common in children and more common in young adults. It can be further subdivided into i) high-frequency HL (the most common) and ii) mid-frequency HL. The latter specific hearing disorder consists of HL around 1.5-2 kHz. This area corresponds to the superior end of the cochlear basal gyrus. The incidence of this dip in mid-frequency ranges from 8% to 67% in selected studies.[9,13-18,20]

Interestingly, 14 of the 17 studies analyzed investigated the possible genetic cause of the HL.[4,8,9,12,14-18,20-23,25] In 2000, Barrenäs et al[12] presented an analysis of 119 patients and concluded that the severity of SNHL and the occurrence of auricular abnormalities increased with the proportion of 45,X cells. Similar findings were reported 8 years later by Gawron and colleagues.[17] Furthermore, another study of a cohort of 325 patients found that subjects with a 45,X karyotype and isochromosome almost always had a 2 kHz neurosensory dip.[4] Conversely, other studies have associated 45,X monosomy with conductive but not sensorineural HL.[8,14,16] The loss of the X chromosome short arm (p) has also been linked to HL.[15,20] Remarkably, a Swedish study showed that both monosomy 45,X and isochromosome 46,X,i(Xq) (complete Xp monosomy) have significantly lower hearing thresholds than patients with mosaicism or other structural X chromosome abnormalities.[21]

In conclusion, HL is one of the most frequent disorders in TS, with an extremely variable spectrum of manifestation that also evolves with

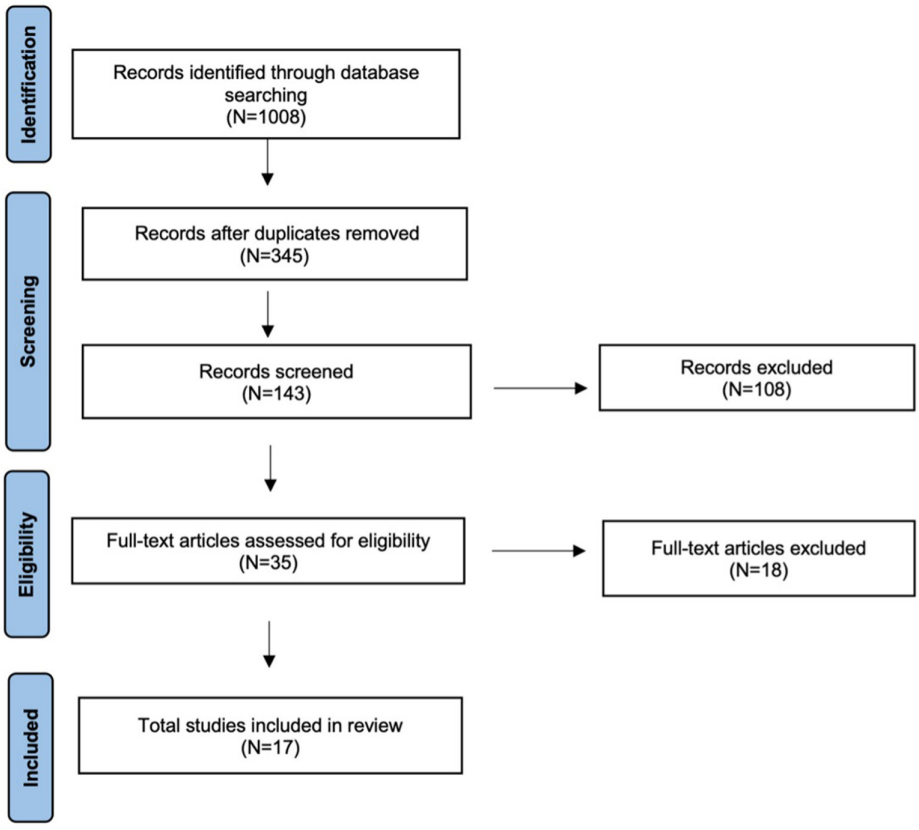

Figure 1. PRISMA flow-chart for a scoping review.

age. Most of the studies included in the present review have suggested that 45,X monosomy and loss of the short arm (p) can cause HL (Table 2).

DISCUSSION

Turner syndrome was first described in 1938 by Henry Turner, after whom it is named.[26] Initially, the HL was not clearly evidenced, whereas nowadays it is among the well-known features of TS patients.

The present review shows that HL is a common and disabling aspect of this disorder. Otologic changes include both morphologic features, with abnormalities of the external ear, and functional features, resulting in conductive, mixed and/or sensorineural HL. The incidence of HL has been reported to range from 21% to 84%.[8,13-17,19-25]

The features of HL in TS subjects appear to be complex and can change throughout the life of the same patient. While in the pediatric age a conductive impairment seems to be predominant, neurosensorial disorders can also occur more frequently in adulthood. Table 1 shows that CHL and MHL are more common in studies where the mean age is low, whereas SNHL is more common in studies where the mean age is higher. In addition, these patients often have a peculiar mid-frequency neurosensory HL. This is a prognostic factor for the progression of SNHL.[9] Therefore, although high-frequency SNHL is more common in TS, the dip in mid-frequency is characteristic of this disorder. First described by Anderson et al[27] in 1969, it consists of a 1.5-2 kHz drop, anatomically corresponding to the superior end of the basal gyrus of the cochlea. Typically, because this loss does not exceed 20 dB HL (hearing level) in most women and does not involve the upper and lower frequency thresholds, it typically does not induce hearing impairment in early life. Eight of the 17 selected studies describe this deficit as ranging from 8% to 67% of the TS population.[9,13-18,20]

To date, it has been assumed that high-frequency HL is progressive with age, although it has been shown that this deterioration is significantly faster than in the general population. Hedersteima et al[9] showed that the HL in TS patients is approximately 0.5-2.2 dB/year compared to 0.2-0.4 dB/year in the general population. As a result of this premature aging, Turner women would have average hearing thresholds similar to those of reference women 20-25 years older.[22]

Interestingly, the majority of TS children are born with a normal hearing threshold. Early in life, these children are more likely to suffer from middle ear disorders leading to CHL.[21,28]

As reported, middle ear problems develop into chronic disorders that require surgical procedures, the most common of which is the insertion of a ventilation tube. With aging, recurrent acute problems decrease, but there is a higher incidence of chronic otitis media and cholesteatoma with associated variable degrees of CHL.[29] In early adulthood, SNHL can occur, initially with a mid-frequency dip as described above, then progressing over the years, thereby affecting the high frequencies and also impairing speech understanding.[28,30]

In their study, Hulcaratz et al[4] observed that CHL was predominantly present in patients under the age of 16, whereas CHL and SNHL were equally prevalent in patients aged 16 and above.

Table 1. Literature Review

Author (year)	Country	n	Mean Age, yrs (range)	EEA	OA	RAOM	Cholesteatoma	HL	CHL/ MHL	SNHL	Mid-Frequency Dip
Barrenäs et al (2000)[12]	Sweden	119	24 (4-73)	41%	NR	NR	NR	NR	26%	NR	NR
Hultcrantz (2003)[4]	Sweden	325	(4-68)	30%-50%	NR	NR	NR	NR	NR	83%	NR
Ostberg et al (2004)[8]	UK	138	29 (16-67)	NR	NR	NR	NR	80%	19%	57%	NR
Beckman et al (2004)[13]	UK	113	27.1 (15-52)	NR	NR	NR	NR	83%	19%	31%	16%
Han et al (2006)[14]	UK	177	32.9 (19-60)	NR	NR	NR	NR	84%	18%	67%	23%
King et al (2007)[15]	USA	200	27.9 (7-61)	NR	NR	NR	NR	49%	6%	34%	8%
Bergamaschi et al (2008)[16]	Italy	173	12 (3-24)	NR	39%	NR	6%	54%	39%	16%	9%
Gawron et al (2008)[17]	Poland	51	14.3 (2-30)	NR	20%	NR	NR	36%	9%	20%	25%
Hederstierna et al (2009)[9]	Sweden	69	43.6 (28-62)	NR	NR	NR	NR	NR	NR	NR	29%
Makishima et al (2009)[18]	USA	91	28.7 (7-61)	53%	NR	76%	NR	NR	NR	63%	67%
Davenport et al (2010)[19]	USA	88	1.98	NR	NR	57%	NR	27%	NR	4.5%	NR
Verver et al (2011)[21]	Netherlands	60	11.2 (1-21)	NR	49%	68%	5%	71%	47%	4%	17%
Verver et al (2014)[20]	Netherlands	65	24.3 (18-32)	NR	NR	66%	8%	66%	34%	32%	NR
Bonnard et al (2017)[22]	Sweden	64	32.6 (25-38)	NR	NR	NR	NR	52%	7%	45%	NR
Bois et al (2018)[23]	France	90	11.9 (1-19)	NR	29%	24%	4%	21%	18%	3%	NR
Hamberis et al (2019)[24]	USA	213	8.7*	NR	NR	NR	7%	59%	51%	8%	NR
Alvarez Nava et al (2020)[25]	Ecuador–Venezuela	93	29.4 (20-49)	68%	NR	10%	NR	75%	25%	50%	NR

CHL/MHL, conductive hearing loss/mixed hearing loss; EEA, external ear anomalies, HL, hearing loss; n, number; NR, not reported; OA, otomicroscopic anomalies; RAOM, recurrent acute otitis media; SNHL, sensorineural hearing loss; yrs., years.
*Expressed as median.

Additionally, King et al[15] reported that SNHL occurs predominantly after the age of 30 and increases its incidence rapidly, affecting more than 50% of TS subjects after the age of 50. Furthermore, as age increases, the severity of HL also increases in a gradual manner.

In contrast, in the adult TS population, SNHL worsens more rapidly than in the healthy adult population, particularly at high frequencies. Additionally, a decline in mid-frequencies has been identified as a negative prognostic factor, indicating a possible rapid deterioration of all the frequencies.[9]

Considering the results of this review, it is possible to consider that in childhood, TS patients are predominantly affected by CHL disorders, with otitis media occurring in up to 60% of cases.[22] Conversely, in adolescence, the frequency of CHL problems decreases, while SNHL can occur in some cases. Therefore, a proportion of patients experience a rapid progression of SNHL in adulthood, which can lead to severe and debilitating consequences.

Therefore, to avoid speech delays, it is extremely important that TS patients undergo complete audiologic evaluation from early childhood, following hearing screening. This includes objective examination, audiometric testing, timely antibiotic therapy, and surgical treatment if indicated.[31] In addition, it is important to follow TS patients, as timely use of hearing aids can be critical for ensuring normal daily activities and interactions.[32] In cases of profound HL, cochlear implants are also a viable treatment option, as reported.[33]

Currently, there are insufficient scientific data to evaluate the effect of growth hormone (GH) or estrogen therapy on the progression of HL,[15,19] as the precise pathophysiology of otologic diseases is still not fully clarified.

Several studies have evaluated the relationship between karyotype and HL in TS patients.[4,8,9,12,14-18,20-23,25] The results analyzed show that in most studies, monosomy 45,X and loss of the X chromosome short arm (p) are the alterations most frequently associated with HL. In 2000, Barrenäs et al[12] first hypothesized a relationship between SNHL and the proportion of 45,X cells, body height, and serum concentration of IGF-1. Four findings from previous literature supported the hypothesis: i) trisomic cells have a longer cell cycle and therefore result in growth retardation;[34] ii) a decrease in 45,X cells with age is determined by a selection disadvantage for monosomal cells in favor of diploid cells;[35] iii) growth retardation of the skull base due to the absence of the SHOX gene (Xp22.33);[36] and iv) IGF-1 deficiency, which is essential for the development of the optic capsule during fetal life.[37] In their paper, the authors proposed that these features may lead to a growth disorder within the mastoid, the skull base, and the Eustachian tube, thus altering the normal function of the middle ear. It would also result in dysregulated inner ear hair cell development in the Corti organ, leading to SNHL.[12] Further research has suggested an association between a 45,X karyotype or loss of the X chromosome short arm (p) and SNHL,[15,20] but a definitive link of the *SHOX* gene to SNHL remains to be demonstrated.[19] It has also been hypothesized that SHOX results in a delayed cell cycle and a

Table 2. Literature Results of Correlation Between Hearing Loss and Karyotype

Author (year)	Results
Barrenäs et al (2000)[12]	The severity of the SNHL and the occurrence of auricular anomalies increased the higher proportion of 45,X cells.
Hultcrantz (2003)[4]	Patients with the karyotypes 45,X and 45,X/46,X,(i),X(q) (isochromosome) almost always had a 2 kHz neurosensory dip.
Ostberg et al (2004)[8]	An association was found between CHL and monosomy 45,X karyotype. In contrast, SNHL was not associated with any karyotype.
Han et al (2006)[14]	Compared with women with other karyotypes, those with monosomy 45,X had significantly higher rates of CHL, with no differences in the incidence of SNHL.
King et al (2007)[15]	In the 46, XiXq, and 46, XdelXp cohorts, the average air conduction threshold was worse than in the 46, XdelqX cohorts. This difference was not confirmed for SNHL. The results supported the assumption that air conduction hearing may be compromised by a short arm (p) loss of the X chromosome.
Bergamaschi et al (2008)[16]	Conductive hearing loss was statistically associated with karyotype (45,X), in contrast to SNHL.
Gawron et al (2008)[17]	Sensorineural hearing loss appeared to be prevalent in patients with genotype 45,X.
Hederstierna (2009)[9]	The presence of a mid-frequency dip was a particularly strong predictor of future high rates of HL and social consequences. Of 20 women with a u-shaped mid-frequency HL (dip): 11 had karyotype 45,X, 5 had 46,XiXq, and the remaining 4 were mosaic: 45,X/46,XX.
Makishima et al (2009)[18]	Neither CHL nor SNHL correlated with karyotype. Low-set ears were more frequent in patients 45,X.
Verver et al (2011)[21]	The different karyotypes did not significantly differ in the incidence of each hearing defect. However, a significant difference was found in air conduction at 0.5 and 4 kHz frequencies, which was better in patients with structural mosaicism/anomaly than in those with monosomy/isochromosome. Similar results were found for bone conduction. These results supported the theory that hearing may be compromised by deletion of the X chromosome p arm.
Verver et al (2014)[20]	Hearing thresholds were significantly worse in patients with complete monosomy Xp compared to those with partial monosomy Xp.
Bonnard (2017)[22]	No correlation was found between karyotype and susceptibility to otitis media in childhood, ear surgery, hearing aid use, or family history of HL. The most common audiogram configuration of SNHL was the sloping pattern with a high representation of karyotypes 46,X,i(Xq) and 45,X. The mid-frequency dip was the second most frequent audiogram configuration and was mainly observed in karyotypes 45,X and 46,X,i(Xq). In the mosaic karyotype, it was also the most frequent pattern after the normal one.
Bois et al (2018)[23]	The most frequent karyotype was 45,X; in this subgroup, otological disorders were most common. Comparing the 45,X subgroup versus the other subgroups together, no audiological differences were found.
Alvarez Nava et al (2020)[25]	There was no statistically significant difference for CHL and SNHL between the complete short arm deletion group (45,X and 46,Xi(Xq)) and the other anomaly group.

CHL, conductive hearing loss; HL, hearing loss; SNHL, sensorineural hearing loss.

reduced number of sensory cells in the cochlea at birth, leading to early cochlear dysfunction.[38] Recently, there has also been scientific interest in the KDM6A (UTX) gene (Xp11.3), which has been found to be downregulated in individuals with TS. This gene may explain the immune deficiency, recurrent otitis media, and subsequent CHL in patients with TS.[39,40]

In conclusion, a positive association between these chromosomal changes and HL is not found in all studies reviewed. Even in studies confirming the association, the results are ambiguous, as it is not clear whether these changes lead to SNHL or CHL. Therefore, further studies should be performed to determine the genetic origin of the HL.

Main drawbacks of this manuscript are: (i) the extreme variability of HL features within different age groups; (ii) the retrospective nature of most studies; and (iii) the fact that audiological data have not been clearly defined in all selected studies, with different clinical tools.

CONCLUSIONS

Hearing loss is one of the most frequent disorders in TS. This impairment presents with an extremely variable spectrum of manifestation that also evolve with age. It is of utmost importance to provide continuous audiological follow-up to TS subjects to ensure proper development of the affected individuals with TS and to ensure proper hearing rehabilitation when necessary. Further studies are necessary in order to fully understand the pathophysiological mechanisms underlying HL in TS and the eventual effectiveness of hormonal therapy in preventing its progression.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.The data that support the findings of this study are available on request from the corresponding author.

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