OTOLARYNGOLOGY

Openventio PUBLISHERS

ISSN 2470-4059 Open Journal http://dx.doi.org/10.17140/OTLOJ-2-126

Mini Review

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Volume 2 : Issue 4
Article Ref. #: 1000OTLOJ2126

Article History
Received: August 26th, 2016
Accepted: September 12th, 2016
Published: September 12th, 2016

Citation
Ralli M, Turchetta R, Cianfrone G. Hearing disorders in Turner's syndrome. *Otolaryngol Open J*. 2016; 2(4): 115-119. doi: 10.17140/OTLOJ-2-126

Hearing Disorders in Turner's Syndrome

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ABSTRACT

Introduction: Turner's Syndrome (TS) is associated with hearing disorders in about 20 to 50% of affected individuals. The most common hearing disorders include congenital auricular malformations, recurrent otitis media and sensorineural hearing loss, although altered vestibular function and tinnitus have also been reported.
Objectives: The aim of this paper is to provide an up-to-date overview of the principal findings and research perspectives about the association between TS and hearing disorders.
Review: Middle ear disorders, found in a range between 21 and 91% of subjects, are a consequence of morphological cranio-facial alterations resulting in middle ear ventilation dysfunction. Sensorineural hearing loss follows 2 main audiological profiles: a bilateral symmetrical mid-frequency dip and a high frequency down-sloping curve. Although the pathophysiologic basis of sensorineural hearing loss in TS patients are still unclear, several hypothesis have been made so far and are reviewed in this paper.
Conclusion: Literature confirms that hearing disorders, although not the most relevant clinical problem in these patients, have a high incidence in patients with TS and should therefore undergo early evaluation and monitoring over time.

KEYWORDS: Turner's Syndrome (TS); Hearing disorders; Hearing loss; Tinnitus.

ABBREVIATIONS: TS: Turner's Syndrome; SNHL: Sensorineural hearing loss; ABR: Auditory Brainstem Responses.

INTRODUCTION

Turner's Syndrome (TS), a common chromosomal condition with an estimated incidence of 1 per 2,000 women,[1] is associated with hearing disorders in about 20 to 40% of affected individuals. TS, also known as 45,X, is caused by a complete or partial deletion of one of X chromosomes; affected subjects are characterized by short stature, typical dysmorphic features, cardiac abnormalities, gonadal dysgenesis, congenital lymphoedema, renal malformations, obesity, diabetes and other minor somatic anomalies described by the Turner's Syndrome Association.[2] Intelligence is usually within normal range, minor problems with non-verbal, social and psychomotor skills may be present.[3]

The most common hearing disorders found in patients with TS include congenital auricular malformations, recurrent otitis media and sensorineural hearing loss.[4] Current studies available in the literature report an incidence of hearing loss in about 50% of patients with TS: 60% for sensorineural hearing loss, 25% for conductive hearing loss, and 15% for mixed hearing loss.[4-7] Asymptomatic vestibular dysfunction and tinnitus have also been reported, but only in the form of case reports; the first could be due to the impact of estrogen on the vestibule, while the second could be a consequence of hearing deafferentation (Table 1).[8]

Conductive hearing loss may be a consequence of lymphatic hypoplasia, common in TS, with lymphatic effusion in the middle ear predisposing to adhesions and impaired aeration and drainage, as well as of morphological alterations of the eustachian tube and middle ear following cranio-facial alterations in TS patients, probably the shortening of longitudinal skull

ISSN 2470-4059 Open Journal http://dx.doi.org/10.17140/OTLOJ-2-126

Conductive/mixed hearing loss	Frequency
Acute otitis media	Common
Recurrent acute otitis media	Common
Otitis media with effusion	Uncommon
Cholesteatoma	Rare
Retraction pocket	Common
Perforation of the tympanic membrane	Uncommon
Sensorineural hearing loss	
Bilateral high frequencies hearing loss	Common
Bilateral mid frequencies hearing loss	Common
Profound hearing loss (>85 dBHL)	Very Rare
Other	
Tinnitus	Case Report
Asymptomatic vestibular dysfunction	Case Report

Table 1: Audiological findings reported in patients with Turner's Syndrome with related frequency.

dimension, and causing inadequate ventilation of the middle ear. The most common alterations include cylindrical shape of the tympanic ostium of the tube, hypotonia of tensor veli palatini muscle and mastoid hypocellularity. This results in chronic ventilation dysfunction often followed by chronic otitis media sometimes associated to cholesteatoma.[9]

Sensorineural hearing loss (SNHL) in TS represents a relatively recent finding and seems to be independent from middle ear diseases; several hypothesis about the pathophysiologic basis have been made so far, but still remain unclear. The most common sensorineural audiological finding in TS patients consists in a bilateral symmetrical mid-frequency dip, mainly at 2 kHz, probably correlated to karyotype.[10] In some patients, high frequency down-sloping SNHL can also be present. SNHL in TS patients can have an early onset, starting during the first decade of life or, most commonly, during the second and third decades, with a tendency to worsen over time. Studies have attributed the mid-frequency dip to cell cycle delay that is more evident in the middle turn of the cochlea where hair cells have the highest concentration per millimeter length of the organ of Corti.[11,12] The early onset of the high-frequency hearing loss may instead be a consequence of a faster apoptotic process of hair cells in the basal turn. Estrogen deficiency could play an important role in these processes through its action on estrogen receptors in the inner ear.[10,13] It is also important to mention that different alterations of auditory brainstem responses (ABR) have been reported in TS, revealing possibly impaired cochlear nerve function to the level of brainstem.

OBJECTIVES

Although several papers have been published about the association between Turner's Syndrome and hearing disorders, some aspects, especially for patients with sensorineural hearing loss, are still debated and certainly need more clinical and basic research studies.[14] The purpose of this review paper is to provide an up-to-date overview of the principal findings and research perspectives about such association.

REVIEW OF THE LITERATURE

Several studies have focused on the hearing function in patients with TS. From a literature research, 26 studies that focused on hearing disorders in patients with TS have been found (Table 2). Studies have been published between 1988 and 2015, with an average of 0.89/year (Figure 1). The most relevant are reported in the following paragraph.

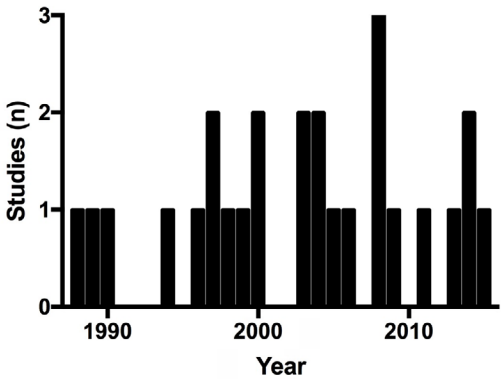

Figure 1: Frequency of studies reporting audiological findings in patients with Turner's Syndrome from 1988 to 2016.

ISSN 2470-4059 Open Journal http://dx.doi.org/10.17140/OTLOJ-2-126

Authors	No. of patients	Year of Publication
Leheupet al[15]	60	1988
Watkin et al[16]	24	1989
Sculerati et al[9]	22	1990
Hultcrantz et al[17]	44	1994
Sculerati et al[18]	24	1996
Hultcrantz et al[19]	40	1997
Benazzo et al[6]	62	1997
Stenberg et al[7]	56	1998
Barrenas et al[20]	115	1999
Barrenas et al[21]	119	2000
Gungo R et al[12]	38	2000
Serra et al[4]	21	2003
Hultcrantz[10]	325	2003
Beckam et al[5]	113	2004
Ostberg et al[22]	138	2004
Dhooge et al[23]	41	2005
Morimoto et al[24]	33	2006
Gawron et al[25]	51	2008
Bergamaschi et al[26]	153	2008
Parkin et al[27]	23	2008
Hederstierna et al[28]	69	2009
Verver et al[29]	60	2011
Oliveira et al[30]	52	2013
Ros et al[31]	31	2014
Verver et al[32]	65	2014
Bakhshaee et al[33]	24	2015

Table 2: Previous studies reporting audiological findings in patients with Turner's Syndrome (literature review).

In 2003, Hultcrantz[10] performed audiometric and karyotype exams in 325 women with TS, finding otitis media in 61% and SNHL in 80% of the individuals studied, most of them having the 45XO or 45XO/46Xi(Xq) karyotype. In 2005, Dhooge[23] published a prospective study with a questionnaire and audiologic evaluation in 41 patients with TS (median age: 24 years), finding pure sensorineural hearing loss in one-third of the patients (38.8%) and pure conductive losses in one-fifth (21.3%). The remaining 60.1% had normal hearing. One year later, Morimoto[24] studied 33 TS patients with age ranging between 8 and 40 years; 20 subjects showed high-frequency SNHL (60.1%) with a statistically significant correlation between hearing loss, age and body height ($p<.001$). Also, age-dependent hearing loss was more apparent in patients with monosomic 45,X kariotype than in those with the mosaic type. This was confirmed in a later study published in 2013 by Oliveira[30] who reported a large prevalence of high frequency hearing loss in TS patients; those with a 45,X karyotype and isochromosomes with loss of the p-arm of the X chromosome had a greater risk of developing hearing loss than patients with mosaicism. Furthermore, the authors described a linear association between hearing loss and age in these patients. In 2008, Gawron[25] studied 51 TS patients (median age: 14.3 years), reporting recurrent acute otitis media in 19.6% of subjects, conductive hearing loss in 11.7%, mixed hearing loss in 5.9% and a moderate sensorineural hearing loss in 18.6%. The authors also reported altered ABR in 52% of the patients revealing a possible retrocochlear involvement. In the same year, a large study by Bergamaschi and colleagues[26] was performed in 173 TS patients (median age: 12 years). Conductive hearing loss was found in 38.7% of patients: persistent secretory otitis media in 55.2%, chronic otitis media in 10.4%, pars flaccida retraction pocket in 19.4%, chronic otitis media with cholesteatoma in 15% of the subjects. Sensorineural hearing loss occurred in 15.6% of the subjects, mostly bilateral (93%) for both high (42%) and mid (58%) frequencies. In a different paper, Parkin and Walker[27] focused on 23 children with TS (median age: 10.4 years), finding middle ear disease in 91% of subjects and SNHL in 9%. In 2009, Hederstierna[28] conducted a longitudinal study of hearing decline in women with Turner syndrome, confirming that young and middle-aged women with TS have a progressive type of hearing impairment, deteriorating rapidly in adult age. The group of Verver of the Radboud University Nijmegen Medical Centre, Netherlands, published 2 studies on hearing function and TS. In the first, the authors studied a group of 60 children with TS and correlated their findings to karyotype, supporting the hypothesis that hearing can be affected by loss of the p-arm of the X-chromosome.[29] In the second paper, published in 2014, the authors studied 65 TS patients finding a higher prevalence of

ISSN 2470-4059 Open Journal http://dx.doi.org/10.17140/OTLOJ-2-126

hearing disorders in patients with monosomy 45,X or isochromosome 46,X,i(Xq), thus confirming the results of their previous study.[32] In the same year, Ros compared 31 adult patients with TS to 15 women with other congenital hypogonadims and 41 healthy age-matched women. Their findings confirmed that more than a half of TS females presented HL; SNHL was the most frequent pattern among middle-aged women with TS and old age, karyotype and recurrent otitis were predisposing factors to induce HL.[31]

CONCLUSION

In conclusion, literature confirms that hearing disorders, although not the most relevant clinical problem in these patients, have a high incidence in individuals with TS. They can be both conductive due to morphological alterations common to other conditions with similar cranio-facial alterations, and sensorineural with a chronic worsening trend over time. Also, sensorineural hearing loss may not be clinically noticeable in most cases, especially at its onset and during the first decades of life. Therefore, it is always recommended investigating the hearing function in TS patients with subjective and objective techniques including audiometry, otoacoustic emissions and auditory brainstem responses; both early hearing evaluation and monitoring over time are necessary. Because patients with TS can present with different manifestations affecting multiple systems, the otolaryngologist should be aware of TS and its association with hearing disorders. Further studies are required to better understand the pathophysiologic basis of SNHL in patients with TS, while an increased clinical attention to conductive hearing loss in the recent years has contributed to a substantial decrease in chronicization of hearing loss and its consequences.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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