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Characteristics of auditory evaluation in Williams syndrome: a systematic review

Características da avaliação auditiva na síndrome de Williams: revisão sistemática

Keywords

Williams Syndrome
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Cochlea
Audiology
Hearing

Descritores

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ABSTRACT

Purpose: Identify the characteristics of the clinical audiological evaluation of individuals with Williams syndrome by means of a systematic literature review. **Research strategies:** The following research question was initially determined: “What are the characteristics of clinical auditory assessment in individuals with Williams syndrome?”. From this, a bibliographic search was conducted in four databases using the descriptors: Williams syndrome, Hearing loss, and Audiology. **Selection criteria:** Only full articles with evidence levels 1 or 2, published in Brazilian Portuguese or English, were selected. **Data analysis:** Results obtained in the auditory tests used in the clinical routine, namely: immittance test, pure-tone audiometry, otoacoustic emissions, and brainstem auditory evoked potential were analyzed. **Results:** Two hundred nine studies were found, but only 12 met the inclusion criteria for the study. It was possible to observe prevalence of type A tympanometry curve, which may occur with absence of acoustic reflexes, mild to moderate sensorineural hearing loss, affecting mainly the high frequencies, absent or less amplified otoacoustic emissions, and brainstem auditory evoked potential without retrocochlear alteration. **Conclusion:** Cochlear impairment is common in individuals with Williams syndrome and the main disorders found in the hearing assessment in this population are absence of otoacoustic emissions and acoustic reflexes, as well as presence of mild to moderate sensorineural hearing loss, mainly in the high-frequency range, observed by audiometry.

RESUMO

Objetivo: Identificar por meio de uma revisão sistemática da literatura quais são as características da avaliação audiológica clínica de indivíduos com síndrome de Williams. **Estratégia de pesquisa:** Inicialmente foi determinada a seguinte pergunta de pesquisa: “Quais são as características da avaliação auditiva clínica em indivíduos com síndrome de Williams?”. A partir desta, foi realizado um levantamento bibliográfico em 4 bases de dados, utilizando-se dos seguintes descritores: síndrome de Williams (*Williams syndrome*), perda auditiva (*hearing loss*) e audiológica (*audiology*). **Critérios de seleção:** Foram selecionados artigos com nível de evidência 1 ou 2, publicados na íntegra nos idiomas português brasileiro ou inglês. **Análise dos dados:** Foram analisados os resultados obtidos nos testes auditivos utilizados na rotina clínica, incluindo: imitanciometria, audiometria tonal, emissões otoacústicas e potencial evocado auditivo de tronco encefálico. **Resultados:** 209 estudos foram encontrados, porém apenas 12 contemplaram os critérios de inclusão para o estudo. Foi possível observar prevalência de curva timpanométrica do tipo A, que pode ocorrer juntamente com ausência de reflexos acústicos, perda auditiva neurosensorial de grau leve a moderado acometendo principalmente as frequências altas, emissões otoacústicas ausentes ou de menor amplitude e potencial evocado auditivo de tronco encefálico sem alteração retrocochlear. **Conclusão:** O comprometimento coclear é comum em indivíduos com síndrome de Williams e as principais alterações na avaliação auditiva nesta população são a ausência das emissões otoacústicas e dos reflexos acústicos bem como a presença de perda auditiva neurosensorial de grau leve a moderado principalmente nas frequências altas na audiometria tonal.

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INTRODUCTION

Williams Syndrome (WS) is a neurodevelopmental disorder resulting from a hemizygous microdeletion of approximately 20 to 28 genes belonging to the long arm of chromosome 7q11.23⁽¹⁻⁴⁾.

The WS phenotype is characterized by several physical⁽⁴⁻⁶⁾ and neurological⁽⁷⁾ disabilities that manifest concomitantly in a very peculiar behavioral and cognitive framework. On the one hand, individuals with WS have a high level of sociability, with preserved linguistic and face recognition skills; on the other hand, they present a global cognitive deficit, including extreme visuospatial processing impairment⁽⁸⁻¹²⁾. In addition, the characteristic of the auditory phenotype has also been a subject of significant scientific investigation: hypersensitivity to sounds, manifested as phonophobia and hyperacusis, is a very common feature in WS⁽¹³⁻¹⁵⁾, which contrasts with the fascination with sounds and musical interest also frequently observed in this population⁽¹⁶⁻¹⁸⁾.

Recent studies have investigated the action of some genes localized in some positions of chromosome 7q11.23, namely, Elastin (ELN), General Transcription Factor 21 (GTF21), and Lim Domain Kinase 1 (LIMK1), which may cause anatomical and physiological changes when absent and thus compromise the structural functioning of the auditory system as a whole^(14,15).

It is believed that deletion of the ELN gene may be responsible for compromising the hearing function, because it is capable of altering the perfusion of the cochlea by vascular stenosis, stiffening the basilar membrane, and deregulating cell proliferation, and it is also able to impair the signal transduction of the hair cells⁽¹⁹⁾. In addition, a deficiency in this gene may be able to hinder the synchrony of the stereocilia, delaying activation of the cochlear nerve⁽²⁰⁾.

Moreover, studies conducted with mice with deletion of genes of the GTF21 family have reported that they were hypersensitive to sounds, as individuals with WS^(21,22). Research has describe that this gene is highly expressed in the neurosensory tissues of the cochlea, serving as a receptor for hair cells in neurons of the spiral ganglion, which are responsible for triggering the action potential to conduct the auditory stimulus to the central auditory pathways, in the Reissner's membrane, and several other cell types within the organ of Corti. Therefore, it is possible that dysfunction of these cells contribute to impairment in cochlear amplification by means of a disturbance in the ionic gradient, thus resulting in hypoacusis⁽²³⁾.

Furthermore, the LIMK1 gene has been reported as important for synaptic transmission, functioning of the central nervous system⁽²⁴⁻²⁷⁾, and regulation of hair cell mobility in the cochlea. Thus deletion of this gene may also be associated with the auditory phenotype observed in WS⁽²⁸⁾.

In addition to the aforementioned genes, other genes localized in regions typically deleted in individuals with WS may also contribute to the hearing impairments observed in this syndrome. Studies have described expression of the FZD9 and STX1A genes in spiral ganglion neurons in the cochlea^(29,30).

Moreover, the STX1A gene seems to be associated with the synaptic activity of the organ of Corti⁽²⁹⁾ and with serotonin level, which can lead to enhancement of specific cognitive functions, such as musical abilities⁽³¹⁾.

In addition, there is the hypothesis of an exclusive genetic model for the processing of sounds in individuals with WS that extends beyond the peripheral system⁽³²⁾. Studies assessing anatomopathological changes in the brain of individuals with WS, using magnetic resonance imaging, have reported increased volume of the auditory cortex in the left hemisphere⁽³²⁻³⁴⁾, or in both hemispheres⁽³⁵⁾.

Considering that changes in the auditory system due to genetic alterations may compromise the functionality of hearing, it is important to learn more about the most common impairments found in patients with WS with the objective of guiding the choice of the main tests to be used in the clinical routine of auditory assessment of these individuals.

PURPOSE

The present study aimed to identify the characteristics of the clinical audiological evaluation of individuals with WS by means of a systematic review of the specific scientific literature.

SEARCH STRATEGY

The following study question was prepared to begin the literature search: "What are the characteristics of clinical auditory assessment in individuals with WS?"

After that, a search in the Descriptors in Health Sciences (DeCS) system was conducted to define the keywords to start the bibliographic survey. Three keywords were selected in English and Brazilian Portuguese: Williams syndrome (*síndrome de Williams*), hearing loss (*perda auditiva*), and audiology (*audiologia*). Next, four searches were performed in each database between May and July 2017 with the following keyword combinations:

- "Williams syndrome" and "hearing loss";
- "Williams syndrome" and "audiology";
- "*síndrome de Williams*" and "*perda auditiva*";
- "*síndrome de Williams*" and "*audiologia*".

The following databases were selected for the search: SciELO, ScienceDirect, *Biblioteca Virtual em Saúde* (BVS), and PubMed.

SELECTION CRITERIA

In order to answer the research question, the present review included articles that addressed the population of individuals with WS written in Brazilian Portuguese and English, and that presented results of the auditory evaluation tests that are routinely used in clinical practice, namely, Immittance Test, Pure-tone audiometry, Otoacoustic emissions (OAE), and Brainstem auditory evoked potential (BAEP).

Considering the small number of articles found with the topic of interest, articles published in any year were included for analysis and those with levels of evidence 1 or 2 were accepted, according to the criteria of the Oxford Centre for Evidence-based Medicine⁽³⁶⁾. Clinical-case studies, book chapters, conference summaries, letters to the editor, and expert opinions were excluded from the study.

DATA ANALYSIS

A table was filled with the reference of each study searched to enable calculation of the total number of articles found. At the end of the bibliographic survey with each combination of keywords in each database, a search was conducted to identify and exclude repeated titles. Sequentially, two independent reviewers read the titles of all studies found. When it was not possible to exclude the article only by reading the title, its abstract was also read. When the reading of the abstract placed the article within the inclusion criteria, it was selected to be read in full.

After completing this stage, the studies selected for the present review were analyzed with regards to the important aspects to answer the research question within the scope of objective, methodology, results obtained, and conclusion. Divergences in the analysis of the studies were resolved through discussion between the reviewers.

RESULTS

Results of the electronic databases

A total of 209 articles were found in each search, with the largest number of articles found in the ScienceDirect database. A larger number of articles were also found using keywords in

English. After exclusion of repeated titles, a total of 156 published articles were obtained (Table 1).

Considering the inclusion criteria, as well as the research question, the titles of the 156 articles found were read. From this stage, 119 articles were excluded and the abstracts of the remaining 37 articles were read. After reading of the abstracts, 18 articles were selected to be read in full, and a total of 12 articles covered all the inclusion criteria and were considered for analysis in the present review (Figure 1).

Considering that each study used different types of procedures, for greater clarity of the selected studies, a choice was made for an initial description of the main methodological criteria of each study (Table 2). The results of each study are described ahead, with analysis of each procedure of interest of the present study (Immittance test, Pure-tone audiometry, OAE, and BAEP).

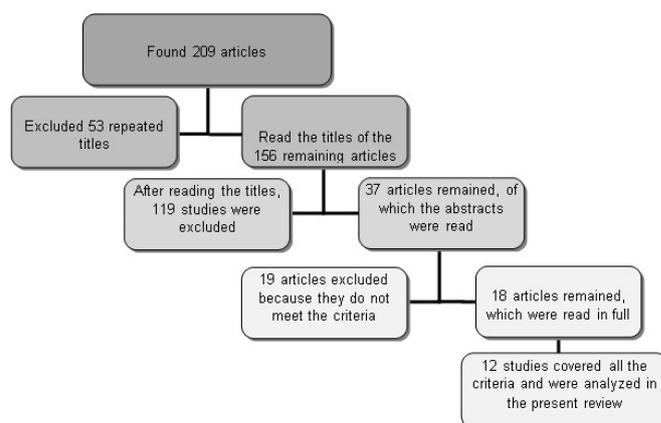


Figure 1. Flowchart of the selection of articles for analysis

Table 1. Results from the literature data collection

Data base	Keyword combination used	Number of articles found	Number of articles in each database after exclusion of repeated articles	Final number of articles after exclusion of repeated articles
ScienceDirect	"Williams syndrome" and "hearing loss"	123	136	156
	"Williams syndrome" and "audiology"	14		
	"síndrome de Williams" and "perda auditiva"	0		
	"síndrome de Williams" and "audiologia"	9		
BVS	"Williams syndrome" and "hearing loss"	23	22	
	"Williams syndrome" and "audiology"	1		
	"síndrome de Williams" and "perda auditiva"	11		
	"síndrome de Williams" and "audiologia"	1		
PubMed	"Williams syndrome" and "hearing loss"	19	22	
	"Williams syndrome" and "audiology"	6		
	"síndrome de Williams" and "perda auditiva"	0		
	"síndrome de Williams" and "audiologia"	0		
SciELO	"Williams syndrome" and "hearing loss"	1	1	
	"Williams syndrome" and "audiology"	0		
	"síndrome de Williams" and "perda auditiva"	1		
	"síndrome de Williams" and "audiologia"	0		
Total		209	181	

Table 2. Detailing of the methodological aspects of each study

Article	Type of study	Sample size	Age group	Age group	Procedures analyzed
Johnson et al. ⁽³⁷⁾	Cohort; Prospective; Cross-sectional	9 individuals with WS	Without information		Pure-tone audiometry; TEOAE
Cherniske et al. ⁽³⁸⁾	Cohort; Prospective; Cross-sectional	20 individuals with WS	Mean of 38 years (30-51 years)		Pure-tone audiometry
Marler et al. ⁽¹⁹⁾	Cohort; Prospective; Cross-sectional	27 individuals with WS	Mean of 15 years (6-48 years)		Pure-tone audiometry; DPOAE
Gothelf et al. ⁽²⁰⁾	Cohort; Prospective; Cross-sectional	49 individuals with WS; Individuals with DT (without information about sample size)	WS: age group of 1-35 years; TD: paired by chronological age		Ipsilateral acoustic reflexes; Pure-tone audiometry; DPOAE; BAEP
Attias et al. ⁽³⁹⁾	Cohort; Prospective; Cross-sectional	21 individuals with WS; 21 individuals with DT	WS: age group of 6-26 years; TD: paired by chronological age		Ipsi- and contra-lateral acoustic reflexes; TEOAE with suppression
Marler et al. ⁽⁴⁰⁾	Cohort; Prospective; Cross-sectional	81 individuals with WS; 14 individuals with DT	WS 1 (43 individuals): mean of 12 years (5-17 years); WS 2 (38 individuals): mean of 31 years (18-59 years); TD: mean of 13 years (7-32 years)		Tympanometry; Pure-tone audiometry; DPOAE
Bedeschi et al. ⁽⁴¹⁾	Cohort; Retrospective; Cross-sectional	13 individuals with WS	Age group of 17-44 years		Pure-tone audiometry;
Paglialonga et al. ⁽⁴²⁾	Cohort; Prospective; Cross-sectional	13 individuals with WS; 14 individuals with DT	WS: age group of 7-23 years; DT: age group of 5-20 years		TEOAE; (Tympanometry, acoustic reflex search, and pure-tone audiometry should be normal because they were used as inclusion criteria)
Zarchi et al. ⁽⁴³⁾	Cohort; Prospective; Cross-sectional	44 individuals with WS; 23 individuals with DT	WS: mean of 16 years (5-35 years); TD: mean of 17 years (6-38 years)		Tympanometry; Ipsilateral acoustic reflexes; Pure-tone audiometry
Barozzi et al. ⁽⁴⁴⁾	Cohort; Prospective; Cross-sectional	69 individuals with WS	Mean of 11 years (2-30 years)		Tympanometry; Contralateral acoustic reflexes; Pure-tone audiometry with visual or conventional reinforcement; TEOAE; BAEP
Barozzi et al. ⁽⁴⁵⁾	Cohort; Prospective; Longitudinal (1 st assessment; 2 nd assessment after 5 years and 3 rd assessment after 10 years)	24 individuals with WS participated in the 1 st and 2 nd assessments, but only 10 of them participated in the 3 rd assessment	Mean of 8 years in the 1 st assessment (5-14 years)		Tympanometry; Contralateral acoustic reflexes; Pure-tone audiometry; TEOAE
Paglialonga et al. ⁽⁴⁶⁾	Cohort; Prospective; Cross-sectional	21 ears of 13 individuals with WS; 13 individuals with DT	WS: age group of 9-31 years; TD: paired by chronological age		DPOAE; (Tympanometry, acoustic reflexes, and pure-tone audiometry should be normal because they were used as inclusion criteria)

Caption: WS-Williams syndrome; TD-Typical development; TEOAE-Transient Evoked Otoacoustic Emissions; DPOAE-Distortion Product Otoacoustic Emissions; BAEP-Brainstem Auditory Evoked Potential

Analysis of the selected studies

Results of this literature review demonstrated that, although there was no restriction with respect to year of publication, studies on hearing assessment conducted with patients with

WS are recent (published in the past 20 years), suggesting that this area of study is relatively new. It was possible to observe that most of the studies used samples composed of an extensive age group, and that some of them presented a large sample size. However, not all participants underwent all procedures, that

is, the sample size for each procedure was different within the same study, which requires caution in the analysis of the results.

Immittance test

Among the 12 selected articles, six presented immittance measurements, four described findings of the tympanometry curve⁽³⁷⁻⁴⁰⁾, and two presented only findings of acoustic reflexes^(20,41).

Of the four studies that analyzed the tympanometry curve, the type A curve was predominant⁽³⁷⁻⁴⁰⁾, and presence of the type B tympanometry curve was not observed in two of them^(37,40). In the first study, normal results were observed in 100% of the children evaluated (34 cases), and seven of the 32 adults assessed presented other types of tympanometry curve other than the type A curve: type Ad and type C curves were observed in five and two cases, respectively⁽³⁷⁾. In the second survey, type A tympanometry curve was found in more than 65% of all evaluations. Type C tympanometry curve was recorded only in the first two assessments, and was observed in 20% of the cases in the first assessment and in 8-12% of the cases in the second assessment. In the aforementioned study, contralateral acoustic reflexes were present in all individuals with type A tympanometry curve⁽⁴⁰⁾.

In contrast, two of these four studies reported type B tympanometry curve in 23% of the cases^(38,39). Type C curve was also observed in 8.1% of the cases and acoustic reflexes were absent in more than 50% of the cases that presented normal middle ear conditions (type A tympanometry curve)⁽³⁸⁾. In the other study, type A tympanometry curve was observed in 76.5% of the patients and, contrary to the previous study, contralateral acoustic reflexes were present in all individuals who presented type A tympanometry curve⁽³⁹⁾.

Both studies that analyzed only the characteristic of acoustic reflexes obtained a higher percentage of absence of reflexes in individuals with WS. In the first study, a higher percentage of absence of acoustic reflexes was found in individuals with WS compared with that of individuals with typical development (TD)⁽²⁰⁾. In the second study, absence of reflexes was observed in 62-86% of the individuals evaluated, and in the patients who presented reflexes, the threshold was higher than that in individuals with TD⁽⁴¹⁾. In both studies, the authors associated this finding with the complaint of hyperacusis frequently observed in this population, considering that one of the functions of the stapedial muscle reflex is to protect the auditory system from intense sounds.

In general, it has been reported that type A curve is predominant in this population, suggesting that middle ear changes do not seem to be a specific feature in this syndrome.

Concerning acoustic reflexes, although two studies did not confirm this observation^(39,40), three other surveys reported absence of acoustic reflexes as a feature commonly found even in patients with no middle ear involvement^(20,38,41). It is worth

noting that in two of these studies the authors agreed that this possible impairment in the stapedius muscle function seems to justify the hyperacusis reported by these patients^(20,41).

Pure-tone audiometry

With respect to auditory threshold data in individuals with WS, nine studies reporting this finding were identified.

In a preliminary study, 16 out of the 20 assessed patients were diagnosed with hearing loss, eight of them presented bilateral mild-to-moderate sensorineural hearing loss, one had unilateral mild sensorineural hearing loss at the high-frequency range, and three individuals presented sensorineural hearing loss at the high- and low-frequency ranges or conductive hearing loss⁽⁴²⁾. In contrast, another survey described a much lower hearing loss prevalence, presenting six patients with normal auditory thresholds and three patients with hearing loss at high frequencies⁽⁴³⁾.

One research observed higher auditory thresholds in individuals with WS compared with those of individuals with TD for frequencies as of 3 kHz, with predominantly mild-to-moderate sensorineural hearing loss. Conductive hearing loss at frequencies below 2 kHz was found in 10% of the individuals, whereas 60% of them presented cochlear hearing loss at higher frequencies (3-8 kHz), with 75% of the cases showing bilateral hearing loss. The degree of hearing loss at the high-frequency range varied from 25 to 55 dB in the right ear and from 25 to 110 dB in the left ear⁽²⁰⁾.

Another survey also reported presence of mild hearing loss in most cases, with only 11.3% of the cases showing moderate to profound hearing loss (threshold >40 dB), with high frequencies (6-8 kHz) as the most affected. Regarding the type of hearing loss, 26.1% of the cases were sensorineural, 21.6% were mixed, and 9.1% were conductive⁽³⁸⁾.

In another study, mild to moderately severe hearing loss was also observed in 63% of the schoolchildren and 92% of the adults evaluated, and sensorineural hearing loss was detected in at least 50% of cases. Another study conducted with 13 patients with WS that used a very similar methodology observed bilateral mild hearing loss in eight individuals (61.6%), with one conductive, two mixed, and five sensorineural cases⁽⁴⁴⁾.

A survey that performed hearing screening in 19 individuals observed that 16 of them failed the test. In addition, the authors reported that six out of the eight individuals who underwent conventional audiometry presented sensorineural hearing loss⁽⁹⁾.

Based on these findings, prevalence of hearing loss was remarkable, found in over 60% of the cases of individuals with WS assessed; only one article described hearing loss in only approximately 33% of the cases, but its small sample size may have influenced the results⁽⁴³⁾. In addition to this article, another survey that evaluated young children also found a lower percentage of hearing loss⁽³⁹⁾. Among the 16 children assessed by means of pure tone audiometry with visual reinforcement, only two presented hearing loss, conductive in both cases, of mild and moderate degrees. Among the patients assessed by conventional audiometry (53 cases), hearing loss was observed at frequencies of up to 2 kHz in 22.6% of the cases (9.4% conductive and

13.2% sensorineural) and at higher frequencies (mean of the thresholds obtained at 4, 6, and 8 kHz) in 30% of the cases⁽³⁹⁾.

Some studies have associated hearing loss with age, and this seems to be progressive in individuals with WS^(39,40,43,44), beginning in early adolescence⁽³⁹⁾ or early adulthood⁽⁴⁴⁾. A research found higher incidence of hearing loss in individuals aged >15 years (46%) than in younger individuals (23%)⁽³⁹⁾, whereas another study showed appearance of hearing loss in these individuals at the age of approximately 25 years⁽⁴⁴⁾.

Considering also the progressive profile of hearing loss, a study performed a longitudinal auditory assessment of patients (three evaluations over a 10-year follow-up). The authors observed hearing loss at the lower frequencies (mean of the thresholds obtained at 0.5, 1, and 2 kHz) in 12.5%, 12.5%, and 30% of the cases, respectively, for the first, second, and third assessments, with predominance of sensorineural hearing loss (only 4% of conductive hearing loss observed in the first two evaluations). For the high-frequency range (mean of the thresholds obtained at 4, 6, and 8 kHz), hearing loss was predominant in 25%, 50%, and 80% of the cases, respectively, in the three assessments⁽⁴⁰⁾.

Sensorineural was the most commonly observed type of hearing loss. Six studies observed presence of conductive hearing loss^(20,38-40,42,44); however, the survey that found the highest percentage of this type of hearing loss reported a value of 10%⁽²⁰⁾. With respect to hearing losses of the mixed type, they were described in only two articles, in which they were observed in approximately 15%⁽⁴⁴⁾ and 21%⁽³⁸⁾ of the cases. Therefore, it is possible to observe that middle ear impairment is not a dominant feature in individuals with WS.

Data concerning the degree and configuration of hearing loss are also worth noting. Prevalence of mild-to-moderate hearing loss was observed in all articles that described this variable^(20,38,39,42,44). The description of hearing loss configuration was also very similar between the articles; descending configuration was predominant in all studies that described this variable, with greater impact on the high-frequency range^(20,38-40,42,43): as of 3 kHz for some authors^(20,39,40) and between 6 and 8 kHz for others⁽³⁸⁾.

Otoacoustic Emissions (OAE)

Nine articles performed OAE: four assessed Distortion Product Otoacoustic Emissions (DPOAE)^(19,20,45) and five analyzed Transient Evoked Otoacoustic Emissions (TEOAE)^(39-41,43,46).

In the studies that conducted DPOAE, the results were convergent when showing smaller amplitude responses in individuals with WS compared with those of individuals with TD^(19,20,37,45), which could differ between frequencies from 2 to 11 dB⁽⁴⁵⁾. In addition, one of the articles observed absence of DPOAE in 23% of the cases⁽²⁰⁾, whereas another survey reported higher involvement in the high-frequency range⁽³⁷⁾. In these four studies, the authors agreed when they reported cochlear impairment in this population, especially at the medium and high frequencies, and indicated the DPOAE evaluation as an important method to detect subclinical findings in cochlear hair cell damage.

Regarding assessment using TEOAE, one of the surveys observed four patients who presented normal hearing thresholds,

but absent TEOAE⁽⁴³⁾. Moreover, another study found absent TEOAE in 39-48% of the patients with normal hearing and no middle ear impairment⁽³⁹⁾. These results demonstrate loss of the cochlear function of the hair cells and the importance of auditory monitoring by TEOAE, considering that this measure seems to be useful to diagnose auditory impairment, even when auditory thresholds are not yet altered.

Another research verified the TEOAE measurements by means of three analyses: energy extracted from the broad-band TEOAE recordings, energy extracted from each of the narrow-band frequency components of the TEOAE, and latency extracted only from the frequency components. The authors observed lower energy, both in the broad-band TEOAE responses in individuals with WS (23.5 dB NPS) compared with that of individuals with TD (30.8 dB NPS) and for energy extracted from the frequency components (with mean difference between the two groups of 5-9 dB NPS, distributed almost evenly across the frequency range). In the latency analysis in the frequency components, higher latency was observed in individuals with WS compared with that in individuals with TD, with the difference between the two groups varying from 0.6 to 1.5 ms⁽⁴⁶⁾.

Furthermore, one of the studies evaluated TEOAE with suppression. The results showed higher suppression of the effect of TEOAE in patients with WS than in individuals with TD, which, according to the authors, suggests a higher activity of the medial olivocochlear efferent system and that this functional alteration may contribute to the presence of hyperacusis in these patients⁽⁴¹⁾.

One last study that monitored TEOAE responses over time also observed a progressive profile of TEOAE loss. Absence of TEOAE was found in approximately 50, 60 and 70% of the patients that presented means of the threshold values in normal low frequencies, respectively, in the three assessments. According to the authors, these data suggest a cochlear fragility in individuals with WS⁽⁴⁰⁾.

Analysis of the TEOAE responses described in these nine articles showed very similar findings for both acoustic stimuli employed. The results have demonstrated absence or decrease in the amplitude of TEOAE in the WS population, even in individuals with normal hearing thresholds. Overall, the authors reported that this finding demonstrates a cochlear fragility or impairment in these individuals, and suggested that TEOAE is a measure of paramount importance for this population.

Brainstem Auditory Evoked Potential (BAEP)

Regarding analysis of the BAEP, only two studies considered and described these findings. In the first study, despite the observation an increased latency values (in individuals with WS compared with those in individuals with TD) of wave I in 61.9% of the cases (means of 1.78 and 1.63 ms for both groups, respectively), of wave III in 42.9% of the cases (means of 3.98 and 3.7 ms for both groups, respectively), and of wave V in 23.8% of the evaluated cases (means of 5.9 and 5.52 ms for both groups, respectively), the interpeak intervals were preserved and no difference between groups was observed. Thus, the authors highlighted that changes in the latencies of

waves III and V were due to a delay in the latency of wave I, and discarded neural conduction impairment⁽²⁰⁾.

In the second study, BAEP was performed in 14 patients. The latency values observed in individuals with WS were as follows: between 1.38 and 1.94 ms for wave I, 3.44 and 4.16 ms for wave III, and 5.08 and 6.02 ms for wave V. As for the interpeak intervals, the following values were observed: between 1.92 and 2.58 ms for interpeak I-III, 1.52 and 1.88 ms for interpeak III-V, and 3.6 and 4.32 ms for interpeak I-V. The authors considered these results as normal and suggested no retrocochlear involvement in this population⁽³⁹⁾.

Although both studies have discarded retrocochlear involvement in these individuals, one of them⁽²⁰⁾ observed increased latency values for all waves, which is an important finding to be considered in the clinical routine. Thus, the results of only two articles seem to be insufficient to determine a conclusion about expected latency values in individuals with WS.

Therefore, further studies addressing BAEP in larger samples of this population would be useful to confirm the results regarding the functionality and integrity of the central auditory brainstem pathways in individuals with WS. Although the WS phenotype is not so thought-provoking, a general convergence in the results of the studies was observed, evidencing a remarkable cochlear impairment in this population. Data from all of these assessments jointly analyzed reinforce the need for routine otolaryngology follow-up with complete auditory monitoring, including multiple auditory tests, in the WS population. Such monitoring should begin on the first days of life, seeking early diagnosis and, consequently, intervention and improvement of the quality of life of these individuals.

CONCLUSION

Based on the articles analyzed in the present literature review, we conclude that the main alterations in auditory assessment in individuals with WS are due to absence of OAE and acoustic reflex and presence of mild-to-moderate sensorineural hearing loss, mainly in the high-frequency range in pure-tone audiometry, and these results show a cochlear impairment in this population.

Regarding the immittance test, it was possible to observe a type A tympanometry curve, demonstrating absence of middle ear impairment. As for the brainstem auditory-evoked potentials, no retrocochlear alteration was observed in individuals with WS.

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Author contributions

LAFS was responsible for collection, classification and analysis of the data and writing of the manuscript; CAK and CGM were responsible for the study design and general orientation of its execution stages and writing of the manuscript.