Peripheral and central auditory findings in individuals with Williams syndrome

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ABSTRACT

Introduction: Williams syndrome (WS) is a rare neurodevelopment genetic condition. The syndrome may present manifestations associated with the central nervous system, hearing, and language. It is possible, as well, to observe an alteration in the central auditory system, which can be diagnosed through long latency auditory evoked potential (LLAEP).

Objective: The aim of this study was to describe and analyze the results obtained by peripheral and central auditory evaluation on individuals with WS, verifying if there is a relationship between audiological findings and gender, age and ear side.

Methods: This is a cross-sectional study in which 14 individuals with WS were evaluated. The exams performed consisted of pure tone audiometry, vocal audiometry, acoustic immittance measures, LLAEP, and cognitive potential.

Results: The sample was composed of patients from 4 to 18 years old, with a mean age of 11.6 years old (±5.3), being 9 males (64.3%) and 5 females (35.7%). We mainly verified mild to moderate degree (40-44%) of sensorineural auditory loss (35.7-42.9%), type A tympanometric curve (57.1-64.3%), and absent acoustic reflexes (57.1%). As for central auditory evaluation, the subjects showed latency delay in all of the LLAEP components. Moreover, it was evidenced
a statistically significant difference when comparing ears for amplitude on cognitive potential evaluation \( (p = 0.032) \), observing higher values at the left ear. It was also observed an inverse association between age and P1 wave latency both on the right \( (p = 0.006) \) and on the left ear \( (p = 0.022) \), and this result can be related to the nervous system maturational process of the WS individuals.

**Conclusion:** There are few studies investigating the central auditory pathway on WS in literature. The present study contributes to the extension of the knowledge about the central involvement of the auditory phenotype in the syndrome. However, considering the sample size, more studies are suggested to confirm these findings.

**KEY WORDS:** Williams syndrome; hearing; central auditory evaluation; event-related potentials; evoked potentials

**<H1>INTRODUCTION**

Williams syndrome (WS) is a rare neurodevelopment genetic condition caused by a deletion on the 7q11-23 region, where is situated the elastin gene. WS is considered an autosomal dominant condition but, in most cases, the syndrome occurs sporadically, with low risk of recurrence. Its frequency is approximately 1:7,500 individuals born alive (1). Further, the
syndrome is clinically characterized by intellectual disability, cardiac defects, central nervous system disorders, and language-related losses, such as stereotypies and semantic comprehension difficulty (1-3). Auditory alterations, such as auditory hypersensitivity, hearing loss, and alteration in the middle ear, are frequently observed in individuals with SW (3).

As for central nervous system alterations, there may be central auditory system alterations, which can be diagnosed through electrophysiological evaluation of hearing, using long latency auditory evoked potential (LLAEP). LLAEPs are bioelectrical responses from thalamus and cortex activities that occur on an interval from 80 to 600 ms, after the introduction of auditory stimulation. When researching these potentials, it can be evaluated the P1-N1-P2-N2 complex, the P3 complex (also called P300) and cognitive potential (4). Cortical electrophysiological activity involved in attention, discrimination, memory, auditory integration, and decision-making skills can be seen through the LLAEP (4,5). The LLAEP objectively evaluates the integrity of the auditory pathway of the central auditory system, being useful to evaluate individuals with auditory processing disorders, since it suffers little interference from extrinsic factors.

Individuals with WS frequently present audiological alterations, with great incidence of
sensorineural hearing losses. It can also be found mixed and conductive hearing losses subsequent to recurrent otitis, which are often observed on WS, particularly on young individuals (6,7). Hearing losses on people with the syndrome typically have an early onset, and it is believed to be progressive (7). However, the analysis of the auditory central pathway in patients with WS has been described in a few studies, and the central involvement is still not clear on auditory phenotype. These studies suggest that the auditory processing on these individuals can be characterized by neural hypersensitivity measured by neural circuits, partially different from those activated on regular development subjects (8,9).

The scarcity of knowledge in this area points to the need for further studies aimed to elucidate the electrophysiological findings, in particular, LLAEP and cognitive potential on this population. The study of parameters related to signal latency, amplitude, and morphology on electrophysiological evaluation allows early intervention and minimizes the negative effects of any auditory disorder.

Thus, the aim of the present study was to describe and to analyze the responses obtained by peripheral and central hearing evaluation on individuals with WS, investigating possible relations between audiological findings and sex, age and difference between ears.
<H1> METHODS</H1>

This is a cross-sectional, contemporary, and observational study. The sample consists of 14 individuals, from 4 to 18 years old, with WS, evaluated by the Clinical Genetics Service (UFCSPA and ISCMPA). The audiological evaluation was performed on the Neuroaudiology and Hearing Electrophysiology Study Center in the period from May 2017 to August 2017. The research was approved by the Ethics in Research Committee from university, by the number 25000.089325/2006-58.

It was included patients with WS, diagnosed by fluorescent in situ hybridization and excluded patients who did not conclude the proposed evaluations and who presented any clinical and/or cognitive compromise that imposed difficulty or impeded the performance of the exams. This was confirmed by review of their medical records.

First, medical and developmental history was investigated, approaching data such as medication use, neuropsychomotor development, education level, medical records, history of ear infections, ventilation tubes, and otologic surgeries, among others. Then, it was performed the inspection of the external acoustic meatus, pure-tone audiometry, vocal audiometry, acoustic immittance measures, and electrophysiological evaluation, through LLAEP and
cognitive potential measurements.

The pure-tone and vocal audiometry were performed with the Harp audiometer from Inventis, using the TDH-39 headset and B-71 bone vibrator. The acoustic immittance measures were performed with the AT 235, from Interacoustics, using a TDH-39 contralateral headset and a probe connected to the main equipment. The LLEAP and P3 were performed using the Masbe ATC Plus, from Conronic®, with the Eartone 3A Insert Earphone (10).

To diagnose hearing losses, the Davis and Silverman (11) classification was used. For acoustic immittance measures, tympanometric curves were studied and then characterized, according to Jerger (12) classification.

Regarding the electrophysiological evaluation, the long latency evoked auditory potential (P1, N1, P2, and N2 complex) and cognitive potential (P3) research were performed using the Masbe ATC Plus, from Conronic®, with the Eartone 3A Insert Earphones. The evoked auditory potential data gathering were performed with the individual comfortably seated on a chair.

The parameters used to research P1-N1-P2-N2 complex were monaural auditory stimulation, with the frequency of 1000Hz (50 cycles), intensity of 80 dBHL, averaging 2000 or more
stimuli. On data acquisition, the full scale was of 200 µV, high-pass filter of 01Hz, low-pass filter of 20Hz, Notch – SIM, reading window of 1000 ms, and trace amplitude of 1 µV. During the process, the individuals were conditioned to watch an interesting and silent video on a tablet.

The parameters suggested by Didoné et al. (13) were used to record the cognitive potential (P3) wave. Two traces were executed, at least, for each individual, to obtain greater reliability on the exam, and finally, the traces were added to obtain a resulting wave. The P300 latency was marked at the wave’s max amplitude point.

Before the start of the procedures, orientations have been given to the individuals about the execution of the evaluation, to avoid misunderstanding about the instructions. It is also important to mention that, to assure greater reliability of the analysis, the electrophysiological records were analyzed by two evaluators, at distinct moments, and two tests were performed on each ear to assure reproducibility among waves.

**<H2>Statistical analysis**

The results were analyzed using the Statistical Package for the Social Sciences Windows software, version 21.0, and a significance level of 5% ($p \leq 0.05$) was adopted. The quantitative
variables were described using mean and standard deviation, while the categorical variables were described using absolute and relative frequencies. To compare both ears, t-student tests for paired samples (quantitative variables) or McNemar tests for categorical variables were applied. Associations between the variables and the age of the individuals were evaluated by the Pearson correlation coefficient. For sex analysis, t-student tests for independent samples (quantitative variables) or Pearson’s Chi-squared test (categorical variables) were used.

**RESULTS**

Initially, 20 individuals were invited to be a part of the research. Among them, 14 attended the audiological test. Therefore, the sample was composed of 14 patients from 4 to 18 years old, with a mean age of 11.6 years old (±5.3), being 9 males (64.3%) and 5 females (35.7%).

As for the data collected in the anamnesis, it was observed that 8 patients (57.1%) had a history of otitis media and 3 (21.4%) subjects underwent surgery for placement of ventilation tubes, according to their parents. There was no statistically significant association of ventilation tube insertion and otitis media history when compared to the results of peripheral and central auditory evaluations.

When comparing the results of the peripheral audiological tests between both ears, it was
verified a statistically significant difference only for the speech reception threshold (SRT) \( (p=0.028) \), where it is observed higher values on the left ear (Table 1). Regarding the comparisons between central auditory evaluation, latencies, and amplitudes of the P1, N1, P2, N2, and P3 waves and ears, it was observed a statistically significant difference among the amplitude of the P3 component \( (p = 0.032) \), with higher values on the left ear (Table 2). When comparing the variables between both sexes, we did not verify differences.

However, there is an inverse association between age and P1 wave latency, both on the right ear \( (p = 0.006) \) and on the left ear \( (p = 0.022) \). The age was greater in those patients with lower latency values of the P1 wave, as shown in Figures 1 and 2.

**DISCUSSION**

In the present study, we could observe a male predominance among WS patients. This is a chance finding since it is not expected differences of occurrence of WS related to sex (14).

As for the peripheral audiological evaluation results, sensorineural hearing loss was the main finding. These data are concordant with findings of other authors, who found more sensorineural hearing loss in adults and children with WS than the other types (mixed and conductive) (3,15). Mild and moderate were the predominant degrees of hearing loss verified
in our sample, which is in agreement with the findings described in literature (3,15,16).

The SRT research, performed during pure-tone audiometry, supplies the speech recognition threshold that is the lowest intensity in which the individual is capable of recognizing 50% of speech stimuli. Moreover, it is useful to the confirmation of aerial thresholds obtained on the pure-tone threshold audiometry (17). The SRT results verified on the present study were in agreement with those observed in the pure-tone threshold audiometry, validating the data obtained on the audiometric evaluation. In the analysis between ears, there was a statistically significant difference from SRT, in which the left ear showed higher values. However, when consulting the literature, the same result is not found. Our hypothesis is that the predominance of the left hemisphere, for verbal stimuli, could generate a greater auditory perception on the right ear, considering that the stimuli recognition is processed primarily by the contralateral ear (18). Another hypothesis is that the number of individuals evaluated was too small, and it could have affected the obtained results. A higher number of subjects would ensure greater statistical strength to the study.

As for the tympanometry study, the type A curve was the most frequent, in concordance with the results found by other authors (3,7). The type A curve suggests normal mobility of the
tympanic membrane and middle ear structures. Individuals with normal auditory thresholds or with sensorineural hearing loss can present this curve. As most individuals on the sample presented sensorineural hearing loss, the predominance of type A curve demonstrated consonance with the verified results (7,16).

As for acoustic reflexes, we detected the absence of reflexes in most part of the patients, both ipsilateral as contralateral reflexes. Other authors observed similar results in their studies. They suggest that this reflexes absence is related to the hypersensitivity present in these individuals, because the acoustic reflex has a protective function against high-intensity sounds, and its absence can represent some auditory intolerance due to the inefficient protection of this mechanism. Another possible hypothesis is that the absence of the acoustic reflex happens due to an auditory nerve dysfunction, which alters the perception of intensity in the afferent auditory system (15,19).

McPherson (4) proposes a wave latency value standardization from LLAEP in children from 3 to 12 years, suggesting 54 to 75 ms for P1; 83 to 132 ms for N1; 137 to 194 ms for P2, and 200 to 280 ms for N2. For those over 12 years old, the author suggests a different latency value for P1, being 54-73 ms. In our study, the patients presented a higher average latency in all
components, which shows a latency delay in relation to children and teenagers with typical
development and without an auditory complaint, as other authors suggest as well (5,19).

The obtained results by other authors point out that the P1-N1-P2-N2 complex amplitude on
individuals diagnosed with WS is higher when comparing to the control groups (20). In this
study, we did not use a control group; however, when observing the P1-N1-P2-N2 complex
mean amplitude on children without auditory complaints evidenced by Agostinho-Pesse and
Alvarenga (21), we noticed higher amplitudes. The amplitude can be related to the amount of
neural structure that participates in the response, being proportional to the synaptic activation
magnitude (22,23).

Some neuroimaging studies with neurophysiological indicators suggest that the auditory
processing of WS individuals can be characterized by neural hyperexcitability measured by
partially different neural circuits from those activated in individuals with typical development
(9,20). In accordance with this finding, Bellugi et al. (24) noted that the auditory responses on
WS individuals were more excitable when compared to those subjects on the control group, a
neural pattern that did not extend to the visual modalities, pointing to cortical hyperactivity.

The latency value proposed by McPherson (4), for the P3 wave on children from 5 to 12 years
old is between 241 and 396 ms, and from 17 to 30 years old is between 225 and 365 ms. We verified that the P3 wave average from our sample was higher, as we found 545.9 ms on the right ear and 546.3 ms on the left ear, suggesting a slower cortical response. According to the literature, there are multiple brain areas that generate P3 components, such as the frontal cortex, the central region of the parietal lobe and hippocampus (4). Thus, the P3 evaluation allows to infer about alteration on language skills, memory, attention, and auditory discrimination.

When comparing P3 results among both ears, it was found a higher amplitude on the left ear. This result was not found by other authors, because on the referred literature we did not find research with P3 potential tests on WS individuals; however, in studies with children and teenagers with auditory thresholds within the normal limits, the difference on amplitude among ears have not been observed (18,25).

The P3 wave amplitude is usually variable and generates little reliability during the results interpretation; therefore, many studies disregard it as a parameter on the data analysis. However, we believe that this analysis is relevant because its observation enables a functional comparison between the intra-subject hemispheres (25). It is known that the non-verbal auditory stimuli recognition is processed by the right-side hemisphere, keeping in mind that
the stimuli are processed primarily by the contralateral ear. Thus, we can have non-verbal stimuli producing a right-side hemispheric predominance and a better left-side auditory perception. The difference is not commonly observed in individuals with auditory complaints, being more evident in those with central auditory processing alterations (18). This can be a hypothesis to explain the results found in the present study.

We observed an inverse association between age and P1 wave latency for both ears (when greater the age, lower was the P1 latency). Considering that the average age of the sample was 11.6 years old, it is necessary to take in consideration the maturational period of the central auditory nervous system. The maturational process of the central auditory nervous system occurs primarily during the 1st year of life; however, it is described in the literature that the development of the P1, N1, and P2 components continue during the second decade of life. Some authors believe that can be observed modifications on LLAEP resulted from auditory maturation, and decrease of the P1 component latency and amplitude (23,26). Our findings corroborate with the hypothesis that the latency delay on younger individuals can be related to the maturational process.

In addition to this, the main source of these potentials involves the auditory cortex region,
structures from the thalamic-cortical and cortico-cortical auditory pathways, primary auditory cortex, and cortical regions. The P1-N1-P2 complex indicates the neural processing from the acoustic signal on the auditory cortex level and reflects the neural activities from the dendrites involved on attention, discrimination, memory, and auditory integration skills (6,21). Thus, the alterations observed in this study could be considered markers of neurofunctional deficits on WS.

It is pertinent to point out that the audiological tests used in the clinical routine examine only the peripheral portion of the hearing. At present, evaluations performed to investigate auditory processing are difficult to apply, especially in children with behavioral and cognitive changes. It is suggested that electrophysiological procedures be included in the auditory evaluation protocol to verify the integrity of the central auditory system in an objective way. Thus, an early and accurate clinical diagnosis for this population is possible.

This study presents some limitations. Difficulties in the performance of the electrophysiological test were found: Anxiety from the individuals regarding unknown activities, and lack of attention during the examination and in the counting of the rare stimuli on the cognitive potential research. Another possible limitation is the sample size, which could
potentially influence the results. Therefore, further studies are suggested to confirm the data found in this sample.

**CONCLUSION**

In the studied sample, most of the individuals with WS presented mild to moderate degree of sensorineural hearing loss on both ears, type A tympanometric curve and absence of acoustic reflexes, which is in agreement with other studies that investigated peripheral hearing on patients with WS. Regarding vocal audiometry, we verified a statistically significant difference in the SRT evaluation between both ears, with higher values on the left ear. As for central auditory evaluation, the sample presented a delay in the P1-N1-P2-N2 complex latency and the cognitive potential. Moreover, we verified an inverse association between age and the P1 component, a result that can be related to the central nervous system maturational process of WS individuals. There was no significant difference in any of the studied variables regarding sex. In contrast, there was a statistically significant difference when comparing P3 amplitude among ears, with higher values found on the left ear.

Therefore, there are few studies investigating the central auditory pathway on WS in literature. Thus, the present study contributes to the extension of the knowledge about the central
involvement of the auditory phenotype in the syndrome and demonstrates the importance of
the application of these evaluations in the clinical practice on this population.

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**<H1>CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.

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Table

|                              | Right ear | Left ear | \( p \) value |
|------------------------------|-----------|----------|---------------|
| **Pure-tone audiometry**     |           |          |               |
| Normal                       | 5 (35.7)  | 4 (28.6) |               |
| Conductive loss type         | 2 (14.3)  | 2 (14.3) |               |
| Sensorineural loss type      | 5 (35.7)  | 6 (42.9) |               |
|                             | Group 1 | Group 2 |
|-----------------------------|---------|---------|
| **Mixed loss type**         | 2 (14.3)| 2 (14.3)|
| **Hearing loss degree**     |         |         |
| Light loss                  | 4 (44.4)| 4 (40.0)|
| Moderate loss               | 4 (44.4)| 4 (40.0)|
| **Vocal audiometry**        |         |         |
| SRT                         | 25.7±15.9| 27.9±17.8|
| **Tympanometry**            |         |         |
| Curve A                     | 9 (64.3)| 8 (57.1)|
| Curve B                     | 4 (28.6)| 2 (14.3)|
| Curve C                     | 0 (0.0)| 2 (14.3)|
| Curve Ad                    | 1 (7.1)| 0 (0.0)|
| Curve As                    | 0 (0.0)| 2 (14.3)|
| **Ipsilateral acoustic**    |         |         |
| Reflexes                    |         |         |
| Present                     | 3 (21.4)| 2 (14.3)|
| Absent                      | 8 (57.1)| 8 (57.1)|
|                    | Right ear | Left ear | \(p\) value |
|--------------------|-----------|----------|--------------|
| **Contralateral**  |           |          | 0.564        |
| **Present**        | 2 (14.3)  | 2 (14.3) |              |
| **Absent**         | 8 (57.1)  | 7 (50.0) |              |
| **Partially present** | 4 (28.6) | 5 (35.7) |              |

Shown data as \(n\) (%), except when indicated. **Mean value±standard deviation.**

*Statistically significant value

**TABLE 2.** Mean value, standard deviation, and \(p\)-value of the left and right ears regarding P1, N1, P2, N2, and P3 waves

|                   | Right ear | Left ear | \(p\) value |
|-------------------|-----------|----------|--------------|
| \(\text{Avg.±SD}\) | Avg.±SD   | Avg.±SD  |              |

**P1 wave**

|                   | Right ear | Left ear | \(p\) value |
|-------------------|-----------|----------|--------------|
| Latency           | 101.9±37.6| 105.5±34.6| 0.438        |
| Wave Type | Amplitude | Latency | p-value |
|-----------|-----------|---------|---------|
| N1 wave   | 3.61±1.25 | 168.9±66.8 | 0.297   |
|           | 3.91±1.92 | 170.4±67.3 |         |
| P2 wave   | 6.39±4.21 | 262.7±125.4 | 0.538   |
|           | 6.43±4.90 | 263.2±128.3 |         |
| N2 wave   | 6.06±3.85 | 291.4±91.9  | 0.176   |
|           | 6.04±4.23 | 277.8±77.4  |         |
| P3 wave   | 4.57±2.02 | 545.9±157.9 | 0.032*  |
|           | 4.45±1.86 | 546.3±155.7 |         |

*Statistically significant value. Avg.: Average, mean value, SD: Standard deviation
FIGURE 1. Scatter plot considering age versus latency of P1 wave in the right ear.
FIGURE 2. Scatter plot considering age versus latency of P1 wave in the left ear.