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ELECTROPHYSIOLOGICAL AND ELECTROACOUSTIC ASSESSMENT OF HEARING IN INDIVIDUALS WITH NEUROFIBROMATOSIS TYPE 1

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

Background: Introduction: Type 1 neurofibromatosis occurs in 1 in every 3,000 individuals, representing 90% of cases of neurofibromatosis. Hearing impairments are not commonly described as an alteration resulting from the pathology; however, sensorineural hearing losses with retrocochlear characteristics may occur as a result of the presence of acoustic neurinomas.

Objectives: To assess the electrophysiological and electroacoustic hearing characteristics of individuals with neurofibromatosis type 1.

Material and methods: We assessed 15 patients, 10 females and 5 males, aged between 9 and 31 years, using the following procedures: pure tone audiometry, transient evoked otoacoustic emissions, contralateral suppression of otoacoustic emissions, and brainstem auditory evoked potentials.

Results: All individuals presented auditory thresholds within normal limits. The mean amplitude of the general responses of otoacoustic emissions in the right and left ears were 11.8 and 12.8 dB, respectively; the suppression effect of otoacoustic emissions was present in 73.3% for the right ear and 66.7% for the left. For brainstem auditory evoked potentials, we obtained mean wave latencies for the right and left ears respectively of wave I: 1.83 and 1.80 ms, III: 4.08 and 4.15 ms, and V: 5.96 and 6.09 ms.

Conclusions: Individuals with neurofibromatosis type 1 present auditory thresholds within normal limits, present transient otoacoustic emissions, the nonsystematic presence of the suppression effect of otoacoustic emissions and prolonged latencies in brainstem auditory evoked potentials.

Key words: brain stem • otoacoustic emissions • hearing disorders • auditory pathways • neurofibromatosis type 1 • hearing tests

ELEKTROFIZJOLOGICZNA I ELEKTROAKUSTYCZNA OCENA SŁUCHU U OSÓB Z NEUROFIBROMATOZĄ TYPU 1

Streszczenie

Wprowadzenie: Neurofibromatoza typu 1 występuje u 1 na 3000 osób i stanowi 90% przypadków neurofibromatozy. Niedosłuch jest rzadko opisywany jako zaburzenie związane z tą chorobą, jednakże obecność nerwiaków słuchowych może prowadzić do wystąpienia niedosłuchu odbiorczego o charakterystyce pozaślimakowej.

Cel: Ocena elektrofizjologiczna i elektroakustyczna słuchu osób chorujących na neurofibromatozę typu 1.

Materiał i metody: Zbadaliśmy 15 pacjentów, 10 płci żeńskiej i 5 płci męskiej, w wieku pomiędzy 9 a 31 lat, z zastosowaniem następujących procedur: audiometria tonalna, badanie emisji otoakustycznych wywołanych trzaskiem, supresja kontralateralna emisji otoakustycznych oraz słuchowe potencjały wywołane pnia mózgu.

Wyniki: Wszystkie badane osoby miały progi słuchowe w granicach normy. Średnia amplituda ogólnych odpowiedzi emisji otoakustycznych w uchu prawym i lewym wynosiła odpowiednio 11,8 i 12,8 dB, efekt supresji emisji otoakustycznych występował u 73,3% osób dla prawego ucha i 66,7% dla lewego ucha. W badaniu słuchowych potencjałów wywołanych pnia mózgu zarejestrowaliśmy odpowiednio dla prawego i lewego ucha latencje fali I: 1,83 i 1,80 ms, III: 4,08 i 4,15 ms, oraz V: 5,96 i 6,09 ms.

Wnioski: U osób z neurofibromatozą typu 1 progi słyszenia znajdują się w granicach normy, występują emisje otoakustyczne wywołane trzaskiem, nieregularnie występuje efekt supresji emisji otoakustycznych, oraz występują wydłużone latencje potencjałów wywołanych pnia mózgu.

Słowa kluczowe: pień mózgu • otoemisje akustyczne • zaburzenia słuchu • droga słuchowa • neurofibromatoza typu 1 • badanie słuchu

Introduction

Described by von Recklinghausen in 1882, neurofibromatosis is a hereditary disease transmitted by a dominant gene [1]. The author used the term neurofibroma for nerve tumors and the term neurofibromatosis for the condition of multiple fibromas [2]. Neurofibromatosis type 1 (NF1) is the most common form of the condition and takes place in 1:3,000 individuals, representing 90% of the cases of neurofibromatosis [3]. Systemic and progressive involvement is one of the main characteristics of this illness and may be manifested by impairment of neurological functions and physical deformities [4]. As examples of these manifestations, there are *café-au-lait* spots, ephelides in axillary regions, multiple peripheral neurofibromas, optical gliomas, bone erosions, and Lisch nodules [5].

Friedman and Birch described other important characteristics that should be taken into account for the diagnosis of NF1, one of them being hearing loss, caused by the presence of vestibular Schwannomas or acoustic neurinomas [6] – benign tumors that grow slowly in the VIII cranial nerve, thereby significantly undermining hearing [7,8].

Although hearing loss is more frequent in patients with neurofibromatosis type 2, it can also be observed in individuals with NF1. Hearing losses are often conductive, due to the amount of neurofibromas in the external acoustic canal [9–11]; however, Barcelos-Corse [12] found individuals with sensorineural loss, auditory neuropathy, and retrocochlear dysfunction, which were diagnosed using the brainstem auditory evoked potential (BAEP).

BAEP is a short latency potential that allows one to assess nerve conduction from the cochlea to the brainstem, being represented by a series of waves that reflect the sequential activation of structures along the auditory pathway. The waves begin up to 10 ms after the presentation of a sound stimulus, and are named from I to VII, the numbering corresponding to the generator sites between the auditory nerve and the brainstem [13,14].

Otoacoustic emissions (OAEs) are of great importance for the assessment of the auditory system and one of their clinical applications is the assessment of the efferent auditory system, thereby contributing to the differential diagnosis between peripheral and central hearing loss. In order to assess the efferent system, one measures the suppression of otoacoustic emissions by contralateral noise, which provides information on the efferent medial olivocochlear system. The efferent system is important in protecting the inner ear from intense noise, increasing perception of an auditory signal in the presence of competing noise, and automatically controlling the gain of the outer hair cells, which can be affected by electrical, chemical, or noise stimulation [15].

The relationship between the functioning of the peripheral auditory system, audiological characteristics, and the neurological integrity of the auditory pathway to the brainstem can help in diagnosing auditory alterations in individuals with NF1.

Accordingly, the objective of this study was to use conventional pure tone audiometry and brainstem auditory evoked potentials to characterize the hearing of patients with NF1; we also wanted to investigate the occurrence of the suppression effect of transient evoked otoacoustic emissions.

Material and methods

This project was approved by the Research Ethics Committee of Universidade Federal de São Paulo and by Support Group for Adolescents and Children with Cancer (CAAE: 80666717.6.1001.5505) and all patients and their relatives were briefed on the Free and Informed Consent Form (FICF), which was signed by the volunteers, relatives, and researchers. According to Hochman's classification, this is a primary, observational, cross-sectional, prospective, descriptive, and single-center study [16].

The eligibility criteria for sample composition were: age from 9 to 35 years; medical diagnosis of neurofibromatosis type 1; no cognitive or psychiatric alterations diagnosed and/or evident; submitted to radiotherapy and/or chemotherapy that had not undermined peripheral hearing; NF1 with the presence of epileptic seizures or epilepsy controlled by a medical team; and present transient-evoked otoacoustic emissions (TEOAEs). As for exclusion criteria, these were: medical diagnosis of NF2 and other comorbidities, such as autism, intellectual disability, middle ear alterations due to the presence of fluid, and having undergone otorhinolaryngological surgery.

In order to select the volunteers, we analyzed the databases of patients from the Child Neurology sector of the Support Group for Adolescents and Children with Cancer hospital, and then the patients who met the inclusion and exclusion criteria were referred to the Audiology Clinic of Department of Speech Therapy and Audiology, Universidade Federal de São Paulo for assessment of the auditory system.

Of the 75 patients followed-up at the Children's Neurology Outpatient Clinic, 43 patients were selected, of which 26 met the inclusion and exclusion criteria of the study. Of these, 11 patients did not agree to take part in the study. Accordingly, the sample consisted of 15 individuals with NF1, 10 females and 5 males ($p = 0.371$), aged between 9 and 31 years.

The audiological assessment started with inspection of the external acoustic canal, checking for obstructions that might prevent the assessment procedures being performed. In case of obstruction by earwax or foreign objects, the patient was referred for otorhinolaryngological assessment. Subsequently, pure tone audiometry [17] was performed in an acoustic booth to investigate auditory thresholds using a Grason-Stadler GSI-61 audiometer, following standard techniques. Then TEOAE and measurement of its suppression was done. For these procedures, we used the Otodynamics ILO v.6 equipment, duly calibrated before the assessment, in an acoustic booth and quiet environment. The record was obtained from two probes, adapted to the individual's external acoustic meatus and containing a signal generator, transducer, microphone, amplifier, filters, and response analyzer. Each participant was instructed to remain comfortably seated, avoid sudden movements, and remain in this position until the end of the test.

For TEOAEs, we used short, non-linear clicks presented in a series of 260 samples using a 20 ms window with intensity between 75 and 85 dB SPL. We considered responses that met the following criteria: signal-to-noise ratio response above 3 dB at 1000, 2000, 3000, and 4000 Hz, with overall reproducibility above 50% and probe stability above 70% [18,19].

Contralateral suppression of otoacoustic emissions was done immediately after the TEOAE, in both ears, with the objective of avoiding repositioning of the probe. Accordingly, the sequence of tests involved: TEOAE in the right ear (RE) followed by measurement of suppression using noise in the contralateral ear. This sequence was repeated for the left ear (LE). During suppression testing, the equipment sent alternating linear clicks with 60 dB SPL intensity to probe 1 and contralateral white noise at 65 dB SPL to probe 2, looking for peaks in a 15 ms window without noise and again in a 15 ms window with noise.

The suppression of otoacoustic emissions was measured by comparing the difference of the general response values in each ear in the presence and absence of suppressive noise [20]. If the difference in general response values was 0.5 dB SPL or higher, the efferent olivocochlear medial auditory system was considered functional, i.e., a suppression effect was present [21]. The procedures described above were held in a single assessment session, with a mean duration of 60 min.

For the electrophysiological assessment, the individual was positioned in a comfortable armchair in an electrically and acoustically treated room. After cleaning the skin with Nuprep® abrasive paste to minimize the electrical impedance between the skin and the electrodes, we used Ten20® conductive paste and micropore tape to fix the electrodes in the following positions: active electrode in Cz, reference electrodes in A1 (LE lobe) and A2 (RE lobe), and ground electrode on the forehead. Impedance was less than 5 kΩ with a maximum inter-electrode difference of 2 kΩ. Acoustic stimuli were presented by means of ER-3A insert earphones, adapted to the external acoustic meatus with disposable foam plugs made of PVC material and selected according to the size of the meatus of each individual.

BAEP was elicited by clicks, which were monaurally presented at a rate of 19.1 per second, with averaging of 2048 stimuli at 80 dBHL, recording window of 10.66 ms, high-pass filter of 100 Hz, and low-pass filter of 1500 Hz. A second run was done to ensure reproducibility of the waveform and further averaging performed. Finally, the absolute latencies of waves I, III, and V, and the interpeak intervals I–III; III–V, and I–V were identified and analyzed. The topographic classification was performed according to Matas [22,23] and the latencies were classified according to the biological calibration of the equipment, considering two standard deviations for absolute latencies and one standard deviation for interpeak intervals.

For the statistical analysis, we used parametric tests, which are more powerful in detecting significance, since the data showed a distribution of normality. In addition, we performed a descriptive analysis of the collected data, considering the variables: ear side, frequency, latency, interpeak intervals, amplitude of the suppression effect of otoacoustic emissions, and TEOAE amplitude. The tests used to compare the results were Pearson's Chi-square test, a paired Student *t*-test, and one-way ANOVA to identify gender effects. We set a significance level of 0.05 (5%), and confidence intervals were constructed with 95% statistical confidence.

Results

The results of pure tone audiometry, TEOAE, otoacoustic emission suppression, and BAEP in individuals with NF1 were organized into tables and graphs, which are displayed below.

Table 1. Descriptive measures of pure tone audiometry thresholds, comparing right and left ears

Audiometry		*N*	Mean (dB HL)	Median (dB HL)	Standard deviation (dB HL)	Min (dB HL)	Max (dB HL)	CI	*p*-value
250 Hz	RE	15	11.33	10	5.81	5	20	8.11 – 14.55	0.610
	LE	15	12.00	15	4.93	0	20	9.27 – 14.73	
500 Hz	RE	15	12.00	15	3.68	5	15	9.96 – 14.04	0.136
	LE	15	10.33	10	3.99	0	15	8.12 – 12.54	
1000 Hz	RE	15	8.67	10	4.42	0	15	6.22 – 11.11	0.164
	LE	15	7.33	5	3.72	0	15	5.27 – 9.39	
2000 Hz	RE	15	4.33	5	2.58	0	10	2.90 – 5.76	0.486
	LE	15	5.33	5	4.80	0	15	2.67 – 7.99	
3000 Hz	RE	15	3.33	5	3.62	0	10	1.33 – 5.34	0.072
	LE	15	6.00	5	4.70	0	15	3.39 – 8.60	
4000 Hz	RE	15	5.67	5	3.72	0	10	3.61 – 7.72	0.818
	LE	15	5.33	5	5.16	0	15	2.47 – 8.19	
6000 Hz	RE	15	7.33	5	5.94	0	20	4.05 – 10.62	0.424
	LE	15	8.33	10	4.50	0	15	5.84 – 10.82	
8000 Hz	RE	15	5.66	5	4.58	0	15	3.13 – 8.20	0.405
	LE	15	7.66	5	7.04	0	25	3.77 – 11.56	

Key: *N*: number of subjects; RE: right ear; LE: left ear; Min: minimum; Max: maximum; CI: confidence interval for 95%, representing the lower and upper limits; statistical test: paired Student *t*-test

Table 2. Descriptive measures of transient-evoked otoacoustic emissions, comparing right and left ears

TEOAE		*N*	Mean	Median	Standard deviation	Min	Max	CI	*p*-value
General response	RE	15	11.79	10.10	4.81	2.9	20.1	9.12 – 14.45	0.127
	LE	15	12.78	13.70	4.94	4.7	22.8	10.04 – 15.52	
1000 Hz	RE	15	14.06	11.60	6.55	7.7	26.1	10.43 – 17.69	0.916
	LE	15	14.32	17.00	7.72	4.0	25.5	10.05 – 18.60	
2000 Hz	RE	15	16.40	16.20	5.37	10.1	29.5	13.43 – 19.37	0.486
	LE	15	15.37	14.90	5.79	4.3	24.7	12.26 – 18.58	
3000 Hz	RE	15	13.04	12.80	4.41	5.8	21.3	10.59 – 15.48	0.160
	LE	15	14.88	15.90	6.92	4.03	27.8	11.05 – 18.71	
4000 Hz	RE	15	11.31	12.90	7.17	NR	23.6	7.34 – 15.28	0.659
	LE	15	11.76	11.50	7.09	2.5	23.9	7.83 – 15.69	
Stability (%)	RE	15	99.27	99.00	0.45	99	100	99.01 – 99.52	0.228
	LE	15	98.67	99.00	1.87	92	100	97.63 – 99.71	
Reproducibility (%)	RE	15	90.75	95.00	9.40	65	99	85.54 – 95.95	0.288
	LE	15	88.40	94.00	10.68	69	99	82.48 – 94.32	

Key: TEOAE: transient-evoked otoacoustic emission; RE: right ear; LE: left ear; NR: no response; *N*: number of subjects; Min: minimum; Max: maximum; CI: confidence interval for 95%, representing the lower and upper limits; statistical test: paired Student *t*-test

Table 3. Descriptive measures of the suppression effect comparing the right and left ears

Suppression		*N*	Mean	Median	Standard deviation	Min	Max	CI	*p*-value
With noise	RE	15	6.63	5.90	7.10	–5.4	16.6	2.70 – 10.56	0.788
	LE	15	6.39	5.20	6.09	–0.8	20	3.02 – 9.76	
Without noise	RE	15	7.62	5.90	6.64	–2.2	17.2	3.94 – 11.30	0.305
	LE	15	6.88	6.60	6.49	–0.4	20.5	3.28 – 10.47	
Suppression	RE	15	0.77	0.70	1.58	–3.5	3.2	–0.10 – 1.65	0.566
	LE	15	0.49	0.80	1.39	–0.4	1.80	–0.29 – 1.26	

Key: *N*: number of subjects; RE: right ear; LE: left ear; Min: minimum; Max: maximum; CI: confidence interval for 95%, representing the lower and upper limits; statistical test: paired Student *t*-test

Table 4. Qualitative analysis of suppression effect of otoacoustic emissions

Suppression effect	RE		LE		*p*-value
	N	Frequency (%)	*N*	Frequency (%)	
Normal	11	73.3	10	66.7	0.077
Altered	4	26.7	5	33.3	

Key: RE: right ear; LE: left ear; *N*: number of subjects; statistical test: Fisher's exact test

Table 1 shows the results of pure tone threshold audiometry in both right and left ears, as well as a comparison between the ears.

We found that, at all audiometry frequencies, there was no statistically significant mean difference between the ears. In addition, no tonal auditory threshold exceeding the normal limit (25 dBHL) was obtained. For all thresholds between 250 and 8000 Hz, the correlations between threshold and gender were not significant for the right ear or the left ear.

In Table 2, the descriptive results and comparisons between the right and left ears in the TEOAE register are presented. All individuals presented TEOAEs with amplitude better than 3 dB in each frequency band, and the measures of reproducibility and stability confirmed that the test was performed under ideal conditions. In the comparative analysis between the ears, no significant differences were observed, revealing similar results when considering right and left ears. The correlation between gender and TEOAE was not significant for the right or left ear for general response, stability, or reproducibility.

Table 3 presents the descriptive measures of TEOAE registers with and without noise and its difference (suppression), for right and left ears.

Table 5. Descriptive measures of the brainstem auditory evoked potential, comparing right and left ears

BAEP		*N*	Mean	Median	Standard deviation	Min	Max	CI	*p*-value
Wave I	RE	15	1.83	1.85	0.07	1.68	1.93	1.79 – 1.87	0.105
	LE	15	1.80	1.80	0.07	1.68	1.93	1.76 – 1.84	
Wave III	RE	15	4.08	4.08	0.10	3.90	4.30	4.01 – 4.13	0.143
	LE	15	4.15	4.18	0.20	3.83	4.60	4.04 – 4.26	
Wave V	RE	15	5.96	5.93	0.20	5.70	6.55	5.85 – 6.07	0.215
	LE	15	6.09	5.98	0.46	5.65	7.43	5.84 – 6.35	
Interpeak I – III	RE	15	2.24	2.25	0.13	2.00	2.45	2.17 – 2.31	**0.032***
	LE	15	2.35	2.38	0.22	2.00	2.90	2.23 – 2.34	
Interpeak III – V	RE	15	1.88	1.85	0.19	1.60	2.40	1.77 – 1.99	0.370
	LE	15	1.94	1.90	0.32	1.63	2.83	1.76 – 2.12	
Interpeak I – V	RE	15	4.12	4.05	0.23	3.85	4.80	3.99 – 4.25	0.122
	LE	15	4.29	4.13	0.50	3.85	5.72	4.01 – 4.57	

Key: BAEP: brainstem auditory evoked potential; RE: right ear; LE: left ear; NR: no response; *N*: number of subjects; Min: minimum; Max: maximum; CI: confidence interval for 95%, representing the lower and upper limits; statistical test: paired Student *t*-test; *: significant *p*-value

Table 6. Qualitative analysis of the results of brainstem auditory evoked potential

BAEP *N*		RE		LE		*p*-value
		Frequency (%)	*N*	Frequency (%)		
Wave I	Normal	2	13.3	6	40.0	0.143
	Altered	13	86.7	9	60.0	
Wave III	Normal	10	66.7	6	40.0	0.580
	Altered	5	33.3	9	60.0	
Wave V	Normal	11	73.3	9	60.0	0.235
	Altered	4	26.7	6	40.0	
Interpeaks I – III	Normal	15	100.0	12	80.0	– x –
	Altered	0	0.0	3	20.0	
Interpeaks III – V	Normal	14	93.3	12	80.0	0.200
	Altered	1	6.7	3	20.0	
Interpeaks I – V	Normal	14	93.3	13	86.7	0.133
	Altered	1	6.7	2	13.3	

Key: BAEP: brainstem auditory evoked potential; RE: right ear; LE: left ear; *N*: number of subjects; statistical test: Fisher's exact test; x: there was zero variability in the sample, so no statistics possible

In both ears, a reduction in otoacoustic emission amplitude could be observed in the presence of noise (evidencing the presence of suppression effect) but without a significant difference between them. The correlation between gender and suppression effect was not significant either for the right ear (with noise, $p = 0.082$; without noise, $p = 0.120$; suppression, $p = 0.660$) or the left ear (with noise, $p = 0.441$; without noise, $p = 0.405$; suppression, $p = 0.590$).

Table 4 reveals the percentage variance regarding the responses to the suppression effect of otoacoustic emissions.

Comparison as to the presence of the suppression effect showed no statistically significant differences between the ears, evidencing the greater occurrence of present responses for both ears.

Table 5 describes the results for the BAEP considering absolute latencies of waves I, III, and V and the interpeak intervals I–III, III–V, and I–V, comparing the ears.

These results demonstrate the presence of responses from generator sites of waves I, III, and V. For interpeak I–III latency, the difference between the ears was statistically significant, with higher latency for the left ear. The correlation between gender and other BAEP measures for the right ear was not significant.

Table 6 presents the number and percentage of responses regarding the qualitative analysis of BAEP considering absolute latencies and interpeak intervals, with statistical correlations.

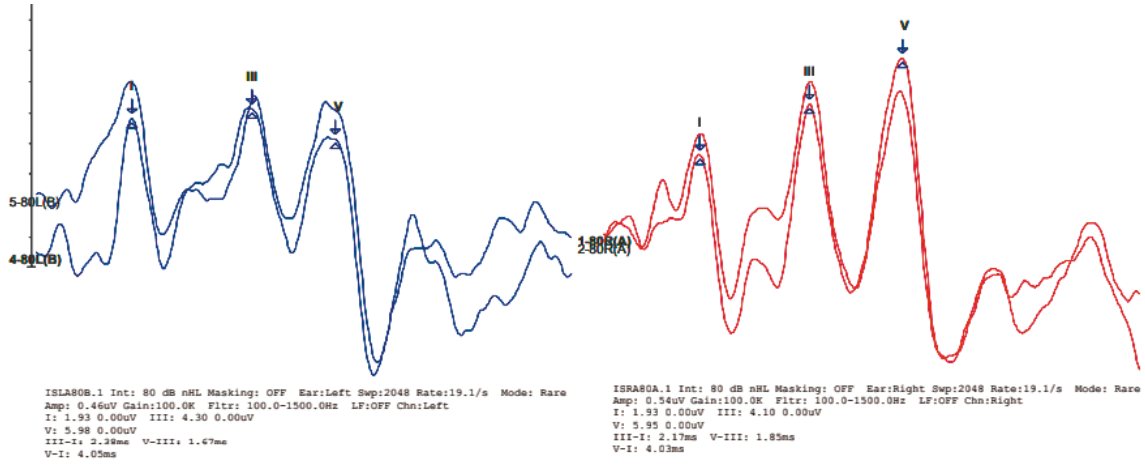

Figure 1. Example of brainstem auditory evoked potentials for patient 6

The results in Table 6 show the frequency of alteration in wave latencies revealing greater commitment in wave I in frequency of occurrence, without difference between the ears. This table shows the frequency of alteration for both ears, when 86.6% were seen in the right ear and 60% in the left ear, with no significant differences between the ears. The percentage of change is also high for wave III in the left ear (60%). Normal values were higher than altered ones for the other waves and interpeak intervals.

The record of the BAEP of one of the patients in the study (patient 6) is shown in Figure 1, to represent the record format.

Discussion

NF1 carriers present several dysplasias, since it is a multisystemic pathology of variable expressiveness and extreme pliotropy, with highly variable phenotypic expression, where it can highlight alterations in the entire central nervous system, with cognitive alterations, brain hyperintensiveness, macrocephaly, neuropsychological and learning damage. Similarly, at the peripheral level, there are tumors of neural origin – optical, ophthalmologic, osteomuscular, cardiovascular, endocrine, skin (spots and ephelides), and bone (dysplasias, osteopenia) gliomas [3,24–30].

In this study, the sample was mostly composed of female adolescents, although studies show that NF1 affects the genders in a similar manner [31]. This gender imbalance showed no statistically significant correlation.

Individuals with NF1 presented pure tone thresholds within normal limits bilaterally without any difference between the ears (Table 1), thereby showing consistency with the study by Corse [12], where the auditory thresholds found in patients with NF1 did not exceed 15 dBHL.

Some authors [11,32,33] describe that audiological findings in NF1 are not characteristic; however, mechanical alterations are more commonly observed, with the presence of conductive hearing loss by neurofibromas involving the external acoustic meatus, such as stenosis of the external auditory canal, deconfiguration of the auditory canal, ear infections, and hearing loss. However, the sample of this study did not include patients with external and/or middle ear alterations, which was corroborated by the results of tonal audiometry.

As for TEOAEs (Table 2), we observed the presence of otoacoustic emissions with adequate responses in the surveyed frequency bands, under ideal test conditions. These results corroborate the pertinent literature, where, according to Probst [34], OAEs can be recorded in 98% of the individuals with hearing ability within normal standards, regardless of age or gender. OAEs are sounds emitted after a short acoustic stimulus which occur over a wide range of frequencies, thus allowing wide stimulation of the cochlea; they can be detected in individuals with normal function or in individuals with hearing thresholds below 30 dBHL [18,19,34]. Studies with type 1 neurofibromatosis and otoacoustic emissions are scarce. Nevertheless, Sone and colleagues [35], when studying a case of neurofibromatosis type 2 that received chemotherapy for 1 year, observed that otoacoustic emissions in both ears were present at all frequencies bands below 2.5 kHz.

When analyzing Table 3, we can see that, on average, the assessed individuals showed a reduction in the amplitude of OAE in the presence of contralateral noise, thereby indicating the presence of the suppression effect of otoacoustic emissions and the proper functioning of the efferent olivocochlear medial system. Nonetheless, negative minimum response values (i.e., the responses with noise were higher than those without noise) occurred in two patients, indicating no suppression effect. Rabinovich [36], when assessing individuals with multiple sclerosis, observed less occurrence of statistically significant suppression effects in these patients. Liang and colleagues [37] also reported absence of suppression effect in individuals with retrocochlear hearing loss. In turn, Pialarissi [38] showed that, in the studied group with retrocochlear injuries, sometimes suppression effect was present, but sometimes it was absent. Therefore, the results of this study agree with that of Pialarissi [38], since the majority of the studied sample of individuals with NF1 showed a suppression effect on TEOAE. The assessment of the olivocochlear complex, through the suppression of OAE, contributes to the identification of auditory

processing alterations, since this complex plays an important role in the cases of hearing in noise [36,38,39]. Some authors have pointed out that in NF1 patients with normal peripheral hearing there are neural or central injuries that commonly impair the central auditory system [9,40–43].

The absence of an OAE suppression effect (Table 4), observed in 26.7% of right ears and 33.3% of left ears, had a tendency towards statistical difference ($p = 0.077$) with the suppression effect more frequently observed in the right ear (73.3%). The absence of a suppression effect may be related to auditory processing alterations. The predominance of one side of the ear during contralateral stimulation was studied by Khalfa [44], thereby revealing a higher activity of the efferent system on the right side.

The BAEP results (Table 5) highlight the presence of waves I, III, and V in all individuals in the sample, with a statistically significant difference between the ears for the interpeak interval I–III, thereby showing a prolongation of latency for the LE compared to the interpeak interval I–III for the RE. These results partially corroborate the Barcelos-Corse's findings [12], where there were responses from the generator sites of waves I, III, and V in all individuals, emphasizing the integrity of the auditory system in this population. Taking into account the findings in the literature that refer to retrocochlear problems in NF1 [10,12,31,45], in this study it is possible to say that the sound information reaches the cochlea and is transformed into nerve impulses, thereby proving the functioning of the auditory pathway, but there are signs of delays along the pathway – observed in the extension of the BAEP wave latencies.

Analysis of the data found in the BAEP assessment (Table 6) showed the prolongation of latencies of all components (except for the interpeak I–III latency in the right ear). Frequently observed in this study was an increase in the absolute wave I latency (which has the auditory nerve as its generator site), and this was observed in 86.7% of right ears and 60% of left ears (although the difference between the ears was not statistically significant, $p = 0.143$). This finding can be correlated with research from Friedman [6], Ferner [46], and Fortman [5], which showed alterations in the nerve with delayed transmission of waves I and/or V and the absence of wave V [10,47]. Nonetheless, differently to this study, some authors highlight the presence of plexiform neurofibromas and the onset of brainstem gliomas that may present a more benign course in NF1. Some authors [9,12,46–48] state that neural or central injuries in NF1 commonly take place in the ganglia of the basal and internal capsule, but are also found in the mesencephalon, subcortical white substance, optical pathways, brainstem, and cerebellum.

In this study, it was possible to ascertain that individuals with NF1, when diagnosed and adequately treated, may have peripheral hearing within normal limits, despite the neural origin of their illness. It is worth emphasizing that the presence of the suppression effect of otoacoustic emissions is extremely important for the individual to perform some auditory tasks, such as the abilities to detect acoustic signals in the presence of noise, auditory attention, sound location, and protection against acoustic overload. Taking into consideration that the assessment of the efferent medial olivocochlear system allows us to make a differential diagnosis between cochlear and retrocochlear hearing disorders, and that some of the individuals in the current study had no suppression effect, it becomes extremely important to fully assess their hearing systems, both in order to make a differential diagnosis and, especially, to check the need for some intervention that might improve their quality of life.

Further studies with other electrophysiological tests and behavioral assessment of central auditory processing may help in determining other alterations along the auditory pathway and open the possibility of interventions designed specifically for improving auditory skills in this population.

Conclusion

From the results of this study, it is possible to conclude that individuals with neurofibromatosis type 1 show auditory thresholds within normal limits and have transient evoked otoacoustic emissions, even though they show the unsystematic suppression effects with otoacoustic emissions and prolonged latencies in their brainstem auditory evoked potential.

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