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IMPROVEMENT IN PERFORMANCE OF THE CENTRAL AUDITORY SYSTEM IN TYPE 1 NEUROFIBROMATOSIS AFTER FORMAL AUDITORY TRAINING

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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: The aim was to electrophysiologically evaluate changes in the peripheral and central auditory systems in individuals with neurofibromatosis type 1 who underwent formal auditory training.

Material and methods: The sample consisted of 6 individuals aged between 9 and 15 years. The procedures involved anamnesis, meatoscopy, brainstem auditory potentials and long-latency evoked potentials, and behavioral tests of central auditory processing. All individuals were given 9 weekly sessions of formal auditory training.

Results: After therapeutic intervention we observed improved performance in auditory closure ($p = 0.014$) and figure–background discrimination for verbal sounds ($p = 0.025$). There were no significant changes in brainstem auditory evoked potentials. However, the P300 of the long-latency auditory evoked potential showed significant differences for the left ear in terms of latencies of waves N2 ($p = 0.05$) and P3 ($p = 0.05$) and the amplitude of N2–P3 ($p = 0.05$).

Conclusions: Therapeutic intervention by means of formal auditory training is effective in rehabilitating central auditory processing disorder. There were improved responses in both behavioral and electrophysiological assessments, which were maintained for at least 4 months.

Keywords: neurofibromatosis 1 • auditory perceptual disorders • acoustic stimulation

WYNIKI OBSERWACJI PACJENTÓW Z NEUROFIBROMATOZĄ TYPU 1 PO FORMALNYM TRENINGU SŁUCHOWYM

Streszczenie

Wprowadzenie: Celem badania była ocena zmian od obwodowego do ośrodkowego układu słuchowego za pomocą pomiarów elektrofizjologicznych związanych z wynikami oceny behawioralnej ośrodkowego przetwarzania słuchowego, a także ocena trwałości uzyskanych wyników w czasie u pacjentów z neurofibromatozą typu 1.

Materiał i metoda: Grupa badana składała się z 6 pacjentów, niezależnie od płci, w wieku od 9 do 15 lat. Wykonane badania obejmowały: badanie podmiotowe, endoskopię kanału słuchowego, badania potencjałów pnia mózgu i późnych potencjałów wywołanych oraz ocenę behawioralną ośrodkowego przetwarzania słuchowego.

Wyniki: Po interwencji terapeutycznej zaobserwowaliśmy poprawę funkcjonowania w zakresie zdolności łączenia dźwięków w słowa ($p = 0{,}014$), umiejętności wyławiania dźwięków mowy z tła ($p = 0{,}025$), z tendencją do czasowego porządkowania dźwięków mowy ($p = 0{,}083$) i słuchania obuusznego ($p = 0{,}083$). Badania elektrofizjologiczne: zapis słuchowych potencjałów wywołanych z pnia mózgu był stabilny, a późne słuchowe potencjały wywołane P300 wykazywały istotnie statystyczne różnice dla lewego ucha w zakresie latencji fali N2 ($p = 0.050$) i P3 ($p = 0{,}050$) oraz amplitudy N2-P3 ($p = 0{,}050$).

Wnioski: Interwencja terapeutyczna w postaci formalnego treningu słuchowego jest skuteczna w zakresie rehabilitacji ośrodkowych zaburzeń przetwarzania słuchowego w przypadkach patologicznych i skutkuje lepszymi wynikami zarówno w badaniach behawioralnych, jak i elektrofizjologicznych, które były stabilne w dłuższym czasie.

Słowa kluczowe: zaburzenia percepcji słuchowej • neurofibromatoza 1 • stymulacja akustyczna • zaburzenia słuchu

Introduction

Neurofibromatosis, formerly known as Von Recklinghausen's disease [1], was described by Von Recklinghausen in 1882 and is an autosomal dominant disease resulting in a lack of control of cell growth and division [2]. It is characterized by multiple benign tumors of the peripheral nervous system, caused by heterozygotic inactivation of the tumor suppressor gene *Neurofibromatosis Type 1* in 17q11.2 [2,3], which acts to suppress cell growth [4], resulting in the loss of the neurofibromin protein.

Individuals with neurofibromatosis type 1 (NF1) can develop a variety of benign and malignant tumors, the most frequent of which are peripheral sheath tumors, the so-called neoplasms resulting from Schwann cells [3,5]. Among the effects on the neural pathways, involvement of the VIII cranial nerve is frequently described in neurofibromatosis type 2 (NF2) with hearing loss. However, there are complications along the entire auditory pathway, even in individuals with NF1, among which the following have been described: alterations in neural conduction [6–8], conductive hearing loss related to the presence of neurofibromas in the external auditory canal [9,10], and alterations in central auditory processing (CAP) [11–15].

According to Batista et al. [11], the multisystemic involvement of central auditory processing disorder (CAPD) may be associated with the clinical polymorphic characteristics and varied phenotypes resulting from a neurofibromine production deficiency in the nervous system. The authors demonstrated a high frequency of CAPD in this population, with about 84% of them presenting some abnormality [11–18].

Auditory training is a therapeutic proposal to improve auditory skills in patients presenting NF1 [15]; there is evidence of improvement in hearing skills after auditory training in other etiologies with CAPD [19].

Neurophysiological changes resulting from plasticity of the central auditory nervous system (CANS) can be monitored by means of electrophysiological tests, such as the long-latency auditory evoked potential (LLAEP), specifically the P300 wave. These tests measure electrical changes that occur in the peripheral and central auditory systems in response to an acoustic or electrical stimulus [20–23]; they depend on the functional use that the subject makes of a stimulus during a specific task, such as discriminating two sound stimuli. Using this paradigm, it is possible to measure electrical activity at each site of the auditory pathway and thereby observe how auditory information is processed [22]. In this way, important information can be gained about the neurophysiological processes occurring in the cerebral cortex that relate to cognition (memory and auditory attention) and which underlie the CAP [20,23]. By recording evoked potentials (P1, N1, N2, P3, and N450 components) during a task involving problem solving, it can be shown that individuals with NF1 have significantly longer latencies than their peers without the disorder. However, in behavioral terms, conflict resolution can generally be successful, being achievable in both groups [24].

In individuals with NF1, intervention in cases of CAPD by using auditory training is not widely addressed, since the pathology is multisystemic with variable expressiveness and extreme pleiotropy. There are some studies involving therapeutic intervention in individuals with NF1 [13,15], but despite describing improvements in hearing skills they did not use electrophysiological measures to objectively assess the benefits obtained. In addition, the auditory training implemented did not strictly control the auditory stimulation, especially the signal-to-noise ratio and use of an acoustically treated environment.

Therefore, our aim was to evaluate changes in the CANS of individuals with NF1 by recording the Brainstem Auditory Evoked Potential (BAEP) and the P300 of the LLAEP, looking at the results of the CAP behavioral assessment before and after formal auditory training. We also wished to investigate whether the results of the training were maintained over time.

Material and methods

This project was approved by the research ethics committee of Federal University of São Paulo and Support Group for Adolescents and Children with Cancer (CAAE 80666717.6.1001.5505). All patients and family members gave written informed consent, which was signed by the volunteer, family member, and researcher. This was a clinical trial (protocol number: RBR-8wmvbnw) classed as a primary, observational, cross-sectional, prospective, descriptive, single-center study [25].

To select volunteers, we analyzed the patient databases of the Child Neurology sector at Support Group for Adolescents and Children with Cancer; we referred those who met the inclusion and exclusion criteria to our Clinical Audiology outpatient clinic for auditory evaluation. The inclusion criteria were: age from 9 to 59 years old; medical diagnosis of type 1 neurofibromatosis; bilateral hearing thresholds less than or equal to 15 dB HL between 0.25 and 4 kHz; bilateral type A tympanometric curves; presenting CAPD; and absence of diagnosed and/or evident cognitive or psychiatric disorders. The exclusion criteria were: presenting NF2 or other medical diagnosis of comorbidities such as autism, intellectual disability, attention deficit disorder with or without hyperactivity, any alteration of the middle ear; having undergone otorhinolaryngological surgery; NF1 undergoing radiotherapy and/or chemotherapy; NF1 with epileptic seizures or uncontrolled epilepsy, and having previously undergone any format of rehabilitation of the CAP.

We evaluated 43 out of the 75 patients of the child neurology outpatient clinic regarding the audiological criteria for inclusion and exclusion in the study. A total of 26 subjects met the inclusion and exclusion criteria described above. We invited all to participate in the study, but 20 declined. Therefore, the sample consisted of 6 individuals with NF1, without distinction as to gender, between 9 and 15 years old. The subjects voluntarily agreed to participate and perform the evaluation procedures and formal auditory training.

We used the following equipment in the evaluations: Grason-Stadler audiometer GSI-61, TDH-39 supra-aural

earphones, and recording of behavioral tests to evaluate central auditory processing [26–29]. For the electrophysiological evaluation, we used a two-channel I.H.S.-Systems model Smart EP equipment.

The following procedures were followed: clinical history questionnaire; electrophysiological evaluation of hearing, comprised of BAEP and LLAEP-P300; behavioral evaluation of CAP; and 9 formal auditory training (FAT) sessions. After the FAT sessions, the individuals underwent two sessions of behavioral and electrophysiological reevaluation, in order to assess changes in the CANS – one performed right after the FAT and the other 4 months later aiming at verifying the maintenance of performance over time after the therapeutic intervention. Thus, we carried out the assessments three times: initial assessment, reassessment 2 months later, and a third assessment 6 months after the initial assessment.

For the electrophysiological evaluation, we positioned the individuals in a comfortable armchair in an electrically and acoustically treated room. The impedance of the electrodes was kept below 5 Ω, with an inter-electrode difference of less than 2 Ω. The responses were collected by four surface electrodes, fixed according to the international 10–20 system. Thus, the ground electrode was positioned in Fz, the active electrode in Cz, with the right (A2) and left (A1) lobe and reference electrodes on the forehead. The acoustic stimuli were presented by ER-3A insert earphones. The BAEP [30] test protocol consisted of rarefaction stimuli presented separately to the right and left ears at a rate of 19.1 stimuli per second, using 2048 stimuli at 80 dB HL, recording window of 10.66 ms, with high-pass filters of 100 Hz and low-pass filters of 1500 Hz. We performed a second stimulation in order to reproduce and confirm the waveform and the absolute latencies of waves I, III, and V, as well as the interpeak intervals I–III; III–V, and I–V.

The LLAEP-P300 was registered with monaural tone bursts [31], presenting 300 stimuli (255 for the frequent and 45 for the rare), in an oddball paradigm. The polarity was rarefaction, presentation speed 1.1 stimuli per second, filters 1 to 30 Hz and pre-stimulus –100 ms and post-stimulus 510 ms. To obtain auditory evoked potentials, tone bursts were presented at 75 dB HL at frequencies of 1000 Hz for the frequent stimulus and 2000 Hz for the rare stimulus. During the test, each individual was asked to mentally count or write down on paper the number of times the rare stimulus appeared, and at the end tell the experimenter how many rare stimuli had been perceived. For analysis, we considered the latency normality values proposed by McPherson [32].

The behavioral evaluation of the CAP included the following procedures: sound localization test (SLT): investigates the source of sound in five directions: right, left, above, in front and behind, with the head as reference. Memory for verbal sounds in sequence (MVS): evaluates the memory for the presentation of four syllables (pa, ta, ca, fa) in three different sequences presented without visual cue. Memory for nonverbal sounds in sequence (MNVS): presentation of four instrumental sounds in three different sequences without visual cue. Speech in noise test (SNT): a list of monosyllables presented in noise in a monotic task. Staggered Spondaic Word (SSW): sequences of four disyllables partially overlapped two by two, two in each ear, alternating the competitive condition and the ear that initiated the test. Synthetic sentence identification with ipsilateral competitive message test (SSI-ICM): sentences presented in speech to the same ear (monotic task) at an SNR of –15 dB. Duration pattern test (DPT): stimuli in a sequence of three items with two sounds of different durations (long = 500 ms; short = 250 ms). Dichotic consonant–vowel test (DCV) (free recall): simultaneous presentation of two syllables (pa, ta, ca, ba, da, or ga), one in each ear. Random gap detection test (RGDT): variation of silent intervals from 0 to 40 ms in a random manner, at frequencies 0.5, 1, 2, and 4 kHz; the threshold is the shortest time interval for which the individual is able to detect two tones. Masking Level Difference (MLD): determination of the threshold by a pulsed pure tone of 0.5 kHz in the presence of a narrowband masking noise in single-phase and anti-phase conditions; the difference in responses between conditions was considered the MLD. The normality criteria used for each test were those proposed by Pereira & Schochat [33].

Formal Auditory Training (FAT)

We conducted the FAT with the objective of stimulating auditory skills and improving communication abilities, especially in noisy environments. There were 9 individual sessions once a week, lasting 50 minutes each. During the sessions we applied different auditory activities focusing on figure–ground for sentences, words, syllables, and non-verbal sounds; binaural integration for verbal and non-verbal sounds; auditory closure, and temporal aspects (intensity, frequency, duration). The FAT procedures took place in an acoustic booth, as part of formal training [34,35], under earphones. Activities were presented under progressively adverse listening conditions, i.e., increasing the degree of difficulty by modifying the signal-to-noise ratio. The task progressed according to the subject's performance, so the relationship between main message/next competitive message (more difficult) was modified according to the achievement of 70% correct answers.

Table 1 lists the schedule of 9 weekly FAT sessions. The sessions encompassed different forms of auditory stimulation and to promote inter-hemispheric integration, the individual was instructed to perform the presentation of responses with different motor activities.

FAT started with figure–ground work for verbal sounds (phrases) in a dichotic listening task [27,29], where the main message was superimposed on the competitive message, in this way, signal and noise relationships varied between +40 to 0 dB in the contralateral competitive message and +10 to –20 dB in the ipsilateral competitive message. In this way, the correctness of sentences was modified by making more difficult the relation the main message and the next competitive message.

Similarly, training in figure–ground skill was carried out with verbal sounds (digits and syllables) [27,29], with S/N ratios of +10 to –30 dB. Figure–background tests used nonverbal sounds, with S/N ratios of 0 to –40 dB. For binaural integration (digits), in a dichotic listening condition, four stimuli were presented (digits and non-verbal) and

Table 1. Schedule of weekly formal auditory training sessions over 9 weeks

1st session	Figure–background for sentences
2nd session	Figure–background for words: directed listening (dichotic digits RE) + figure–background for non-verbal sounds (dichotic non-verbal LE)
3rd session	Figure–background for words: directed listening (dichotic digits LE) + figure–background for non-verbal sounds (dichotic non-verbal RE)
4th session	Binaural integration (dichotic digit + non-verbal dichotic) + speech in noise with phrases
5th session	Auditory closure (speech with noise: figures and words) + temporal aspects (intensity pattern)
6th session	Temporal aspects (duration pattern: audiometer, flute, and pure tone)
7th session	Temporal aspects (duration pattern) + figure–background for syllables (consonant vowel: directed listening RE)
8th session	Temporal aspects (frequency pattern: audiometer, flute, and pure tone) + figure–background for syllables (vowel consonant: directed listening LE)
9th session	Temporal aspects (frequency pattern) + figure–background for words (dichotic disyllables: binaural integration)

the individual was asked to recognize and repeat them, identifying the ear in which they heard them. For auditory closure skill [28], the S/N ratios were +10 to –5 dB for sentences, +5 to –5 dB for words, and +10 to –10 dB for figures, using white noise.

Temporal ordering involves being made aware of differences in the acoustic aspects of intensity, duration, and frequency [26]. These aspects were addressed using different combinations of intensities, presented binaurally, with pure tone stimuli at frequencies of 0.5, 1, 2, and 4 kHz, with different combinations of intensity ranging from 20 to 10 dB.

The duration pattern test was done using the audiometer. The stimuli were presented binaurally at 1 kHz with variable duration; there were brief and long stimululi within a sequence of two or three sounds. For frequency pattern training, the audiometer presented combinations of 2 or 3 different frequencies (0.5 and 4 kHz, 1 and 4 kHz, 2 and 4 kHz, and 0.75 and 1 kHz). Then, the recorded frequencies centered at 880 and 1430 Hz, 880 and 1122 Hz, and 440 and 493 Hz were proposed.

Analysis

To analyse the results we collected numerical and categorical data, presented as normal or altered (delayed and absent for electrophysiological measures). We obtained the data in three different instants: first, second, and third evaluation. For statistical analysis we used the asymmetry and kurtosis tests, and descriptive measures (mean, median, minimum, maximum, and standard deviation). To compare categorical data, we used non-parametric statistical techniques: Pearson's chi-square association test or Fisher's exact test extension for contingency tables; and significance test for correlation between the continuous variables obtained in the follow-ups. Finally, in order to verify the variability between the evaluations with the Cochran test (homogeneity of variance), we considered the statistical significance to be $p \leq 0.05$. For values of p between 0.05 and 0.10) we accepted an indication of a non-significant tendency. We used SPSS version 19; Statistica version 13.5.0.17; and Excel 2013.

Results

The sample consisted of 6 individuals with neurofibromatosis type 1 who underwent formal auditory training: five (83%) were female and one (17%) male, aged between 9 and 15 years, with a mean of 11.8 years and standard deviation of 2.2. Four subjects were right-handed and two left-handed ($p = 0.162$). All had school difficulties as described by parents and teachers. Despite such difficulties, students were taking their courses without school delays, ranging from 3rd year of elementary school to 1st year of high school.

The tests provided SLT, MVS, MNVS, SNT, SSI, DCV, SSW, DPT, RGDT, MLD measures (involving mean, median, minimum, maximum, and standard deviation) at the three moments of the evaluation, allowing qualitative analysis and statistical analysis as a function of time (**Table 2**).

Table 2 indicated that the analysis of the three moments of SNT, SSI, DCV, SSW, and RGDT reflected statistically significant differences between assessments, with improved performance throughout. As for the binaural interaction (MLD) and temporal ordering (MVS), there was a tendency to improve the response across the three moments of the CAP evaluation.

When we checked the performance of the CAP behavioral assessment tests with differences for the three moments of the assessment, we correlated each moment of assessment for auditory closure skills, SSI and DCV, and SSW reversals and temporal resolution. **Table 3** shows the statistical correlation between the three evaluation moments: first and second, second and third, and last, first and third evaluations.

Table 3 shows the improved performance in auditory closure soon after the therapeutic intervention ($p = 0.014$) between the second and third evaluations: there were no changes, which shows that performance in this ability remained stable as with comparing the first and third evaluations ($p = 0.014$). As for the figure–ground for verbal sounds ($p = 0.083$), there were stable responses between

Table 2. Descriptive measures of central auditory processing behavioral tests at three moments of assessment and statistical correlation as a function of time

	Evaluation	Auditory skills	Qualitative analysis		*N*	Mean	Min	Max	SD	*p*-value
			Normal (%)	Altered (%)						
SLT	1st	Localization	100	0	6	4.67	4.00	5.00	0.52	–
	2nd		100	0	6	4.50	4.00	5.00	0.55	
	3rd		100	0	6	4.50	4.00	5.00	0.55	
MVS	1st	Temporal ordering	33	67	6	1.50	1.00	3.00	0.84	0.097
	2nd		67	33	6	1.83	0.00	3.00	1.17	
	3rd		83	17	6	2.17	1.00	3.00	0.75	
MNVS	1st	Temporal ordering	67	33	6	2.17	1.00	3.00	0.98	0.135
	2nd		100	0	6	2.50	2.00	3.00	0.55	
	3rd		100	0	6	2.83	2.00	3.00	0.41	
SNT RE	1st	Auditory closure (%)	0	100	6	71	56	80	9	**0.002**
	2nd		100	0	6	86	76	96	7	
	3rd		100	0	6	87	84	92	3	
SNT LE	1st		0	100	6	61	28	88	21	
	2nd		100	0	6	88	80	96	7	
	3rd		100	0	6	87	80	96	5	
SSI RE	1st	Figure–background for phrases (%)	0	100	5	54	30	100	30	**0.018**
	2nd		50	50	5	64	60	70	5	
	3rd		83	17	5	70	60	80	7	
SSI LE	1st		0	100	5	46	40	70	13	
	2nd		50	50	5	70	60	90	14	
	3rd		83	17	5	78	60	100	14	
SSW RE	1st	Figure–background for words (%)	0	100	6	85	73	98	11	**0.022**
	2nd		50	50	6	95	88	100	5	
	3rd		83	17	6	96	93	98	2	
SSW LE	1st		0	100	6	74	50	90	15	
	2nd		50	50	6	88	70	95	10	
	3rd		83	17	6	90	78	95	7	
DPT	1st	Temporal aspects (%)	0	100	6	40	33	50	6	0.368
	2nd		0	100	6	52	30	73	17	
	3rd		17	83	6	67	57	77	8	
DCV RE	1st	Figure–background for syllables	0	100	6	14.0	7.0	19.0	4.47	**0.022**
	2nd		50	50	6	16.7	14.0	20.0	2.50	
	3rd		83	17	6	15.2	12.0	18.0	2.32	
DCV LE	1st		0	100	6	3.0	0.00	6.0	2.00	
	2nd		50	50	6	3.0	0.00	6.0	2.37	
	3rd		83	17	6	4.7	2.0	7.0	2.07	
DCV errors	1st		0	100	6	7.0	3.0	11.0	2.90	
	2nd		50	50	6	4.3	4.0	5.0	0.52	
	3rd		83	17	6	4.2	3.0	5.0	0.98	

Table 2 continued. Descriptive measures of central auditory processing behavioral tests at three moments of assessment and statistical correlation as a function of time

	Evaluation	Auditory skills	Qualitative analysis		*N*	Mean	Min	Max	SD	*p*-value
			Normal (%)	Altered (%)						
SSW Inversion	1st	Temporal ordering	0	100	6	1.67	0.00	6.00	2.16	**0.015**
	2nd		0	100	6	0.17	0.00	1.00	0.41	
	3rd		17	83	6	0.67	0.00	1.00	0.52	
RGDT	1st	Temporal resolution (ms)	17	83	6	19.17	7.50	32.50	9.99	**0.015**
	2nd		83	17	6	7.33	2.00	12.50	3.35	
	3rd		100	0	6	5.08	2.00	8.00	2.48	
MLD	1st	Binaural interaction (dB)	50	50	6	8.33	6	10	1.97	0.097
	2nd		67	33	6	9.67	6	14	2.94	
	3rd		100	0	6	10.67	8	14	2.07	

Key: SLT, sound localization test; MVS, memory for verbal sounds in sequence; MNVS, memory for nonverbal sounds in sequence; SNT, Speech in noise test; SSI, synthetic sentence identification; SSW, staggered spondaic word; DPT, duration pattern test; DCV, dichotic consonant-vowel test; RGDT, random gap detection test; MLD, masking level difference; RE, right ear; LE, left ear; *N*, number of subjects; Min, minimum; Max, maximum; ms, millisecond; dB, decibel; SD, standard deviation.

Table 3. Statistical correlation between the moments of CAP evaluation and auditory skills

Auditory skills	1st and 2nd evaluation	2nd and 3rd evaluation	1st and 3rd evaluation
Localization	–	–	–
Temporal ordering for verbal sounds	0.157	0.317	0.083
Temporal ordering for non-verbal sounds	0.157	–	0.157
Auditory closure	**0.014**	–	**0.014**
Figure–ground for verbal sounds	0.083	0.157	**0.025**
Temporal processing	–	0.317	0.317
Binaural interaction	0.317	0.157	0.083

the second and third evaluations right after the end of the auditory training, but with significant changes regarding the first and third evaluations ($p = 0.025$), which indicates that even after the end of the auditory training the CANS continued to improve its performance.

Table 4 lists the mean, median, minimum, maximum, and standard deviation for the latency of BAEP components for the three assessment moments and the statistical correlation for performance over time. It shows that there were no differences in BAEP over time for the right and left ears.

Table 5 shows the mean, median, minimum, maximum, and standard deviation of the latency and amplitude parameters of the LLAEP-P300 components for the three different evaluation moments, and the statistical correlation regarding performance over time.

Table 5 demonstrates improved results over time for the long latency potentials, showing statistically significant differences for the N2 latencies on the left ear ($p = 0.05$), with reduced latency right after the FAT and a latency increase at the third evaluation. For wave P3 there was an increase in latency when comparing the first and the following evaluations ($p = 0.05$). Finally, considering N2–P3 amplitude, there was a reduction in the second and an increase in the third evaluation ($p = 0.05$).

Discussion

NF1 is a rare genetic disorder with an incidence ranging from 1 in 2700 to 1 in 7800 [18,36,37], and a prevalence varying from 1 in 3000 to 7800 live births [7,38,39]. It has a highly variable phenotypic expression [40] and its carriers may present several dysplasias, since it is a multisystemic pathology of variable expressivity and extreme pleiotropy. This highlights changes in the central and peripheral nervous systems, including ophthalmologic, osteomuscular, cardiovascular, endocrine, skin, and bone involvement [14,37,41–43]; all which show the heterogeneity of NF1 [40]. Due to the incidence and prevalence the sample calculation was performed, with a confidence level of 95%, resulting in 5 subjects to be evaluated for an adequate population representation, so the number of evaluated subjects adequately represents the NF1 population. Therefore, the number of individuals evaluated in this study allows the evaluation and monitoring of changes in the peripheral and central auditory system in the pathology.

Table 4. Descriptive measures of the latency (ms) of the components of the BAEP, per ear, in the three moments of assessment and statistical correlation as a function of time

Component	Evaluation		*N*	Mean (ms)	Median (ms)	Min (ms)	Max (ms)	SD (ms)	*p*-value
Wave I	1st	RE	6	1.80	1.82	1.68	1.88	0.07	–
	2nd		6	1.77	1.79	1.63	1.85	0.09	
	3rd		6	1.79	1.80	1.68	1.88	0.08	
	1st	LE	6	1.78	1.78	1.70	1.85	0.06	–
	2nd		6	1.78	1.75	1.73	1.88	0.06	
	3rd		6	1.77	1.78	1.68	1.85	0.06	
Wave III	1st	RE	6	4.06	4.04	3.88	4.30	0.14	0.223
	2nd		6	3.99	3.99	3.90	4.10	0.08	
	3rd		6	4.04	4.04	3.90	4.18	0.11	
	1st	LE	6	4.15	4.08	3.90	4.60	0.27	0.368
	2nd		6	4.06	4.06	3.88	4.22	0.15	
	3rd		6	4.11	4.08	3.90	4.40	0.17	
Wave V	1st	RE	6	5.87	5.90	5.58	6.03	0.15	0.368
	2nd		6	5.80	5.83	5.55	5.98	0.19	
	3rd		6	5.86	5.86	5.75	5.98	0.10	
	1st	LE	6	6.11	5.88	5.75	7.43	0.65	> 0.999
	2nd		6	5.81	5.74	5.65	6.10	0.18	
	3rd		6	6.12	5.88	5.68	7.53	0.71	
Interpeak I–III	1st	RE	6	2.26	2.24	2.13	2.45	0.11	–
	2nd		6	2.23	2.22	2.17	2.30	0.04	
	3rd		6	2.24	2.25	2.15	2.32	0.06	
	1st	LE	6	2.37	2.29	2.13	2.90	0.29	0.368
	2nd		6	2.28	2.24	2.15	2.47	0.13	
	3rd		6	2.34	2.28	2.20	2.65	0.17	
Interpeak III–V	1st	RE	6	1.81	1.88	1.58	1.97	0.17	–
	2nd		6	1.81	1.83	1.60	2.05	0.18	
	3rd		6	1.83	1.90	1.60	2.00	0.17	
	1st	LE	6	1.97	1.88	1.60	2.83	0.45	–
	2nd		6	1.75	1.78	1.58	1.88	0.10	
	3rd		6	2.01	1.83	1.63	3.13	0.57	
Interpeak I–V	1st	RE	6	4.07	4.10	3.78	4.23	0.15	0.368
	2nd		6	4.04	4.04	3.80	4.35	0.20	
	3rd		6	4.07	4.08	3.88	4.25	0.15	
	1st	LE	6	4.33	4.05	4.00	5.72	0.68	–
	2nd		6	4.03	4.00	3.78	4.35	0.19	
	3rd		6	4.35	4.14	3.83	5.78	0.72	

Table 5. Descriptive measures of latency (ms) and amplitude (μV) of the components of the LLAEP (P300), per ear, in the three moments of assessment and statistical correlation as a function of time

Components	Evaluation		*N*	Mean	Median	Min	Max	SD	*p*-value
Latency N2 (ms)	1st	RE	5	183.0	149.0	100.0	316.0	84.6	0.135
	2nd		6	152.2	157.5	107.0	173.0	23.4	
	3rd		6	170.7	153.5	118.0	262.0	50.5	
	1st	LE	3	151.7	150.0	133.0	172.0	19.6	**0.050**
	2nd		6	132.0	137.5	115.0	146.0	13.5	
	3rd		6	169.5	160.5	136.0	208.0	29.4	
Latency P3 (ms)	1st	RE	5	267.6	231.0	228.0	377.0	63.9	0.368
	2nd		6	244.5	230.0	210.0	317.0	39.7	
	3rd		6	259.8	240.0	221.0	338.0	45.5	
	1st	LE	3	231.3	219.0	208.0	267.0	31.4	**0.050**
	2nd		6	244.0	243.0	204.0	289.0	29.9	
	3rd		6	242.0	242.0	209.0	272.0	27.9	
Amplitude N2–P3 (μV)	1st	RE	5	4.82	5.24	2.56	6.98	1.81	0.368
	2nd		6	5.96	6.49	2.95	8.55	2.24	
	3rd		6	5.28	4.76	3.97	7.64	1.53	
	1st	LE	3	4.41	4.31	3.74	5.17	0.72	**0.050**
	2nd		6	3.97	3.24	2.54	7.62	1.89	
	3rd		6	4.17	4.15	2.94	5.56	1.10	

NF1 affects both sexes equally and is inherited from one parent in 30–50% of cases [37,44]; the remaining cases have no family history, i.e., they appear spontaneously by gene mutation. This suggests a high incidence of new mutations, with autosomal transmission dominant with complete penetrance. Neuropsychological profiles, as well as physical symptoms, vary from one patient to another, and include a reduction in some intellectual abilities associated with difficulties in certain cognitive domains, such as oral and written language, visuospatial understanding, arithmetic, executive function, and attention [45]. In this study, we observed that despite any such difficulties our students undertook schooling without delays.

CAPD has been observed in patients with normal peripheral hearing [11–13], raising the suspicion that in such cases it is the language and learning part of the auditory system that has been affected [17,46]. This study corroborated previous work showing that with CAPD peripheral hearing was within normal standards (**Table 2**).

Formal auditory training seeks to rehabilitate features that handicap subjects with NF1. It seeks to exercise central auditory processes, teaching improved resource allocation strategies to overcome residual deficits in auditory processing [47–49]. **Table 3** shows statistically significant differences in auditory closure, figure–ground for sentences and syllables, and temporal ordering and resolution, all of which show that FAT has been effective in improving these skills.

Regarding sound localization, temporal ordering, temporal processing, and binaural interaction, there was a tendency for improvement in the MLD test, and all other tests showed better mean outcomes. Thus, although there were no statistical differences, the behavior after FAT was generally better than initially. Thus, similar to the literature [15], this study corroborated work that has shown improvements in auditory closure, figure–background discrimination, and temporal resolution, with the results maintained over time.

Some researchers [15,50], concerned about the comorbid conditions of neurofibromatosis, have investigated the improvements that auditory training can bring to such patients. They have verified improvements in listening skills, as well as stable benefits over time, but without overcoming the diagnosis of CAPD. In this study, changes in CAP performance over time related to a range of auditory skills (**Table 3**). We saw improvement in performance immediately after therapy for auditory closure ($p = 0.014$), showing that FAT was effective in rehabilitation. The change in auditory closure remained stable after training, as when performance between the first and third assessments is compared ($p = 0.014$). Benefits were also observed for other auditory skills, such as figure–background discrimination for verbal sounds (with a tendency, $p = 0.083$) after the end

of the FAT. Indeed, they improved over time, with stabilization of responses between the second and third assessments and significant changes between the first and third assessments ($p = 0.025$). This indicates that even after the end of auditory training, CANS abilities continued to improve, despite the pathological process. This result corroborates the literature on the effect of brain plasticity under stimulation and demonstrates the effectiveness of auditory training [15,51–54].

The BAEP results before and after therapeutic intervention (**Table 4**) did not show statistically significant correlations between assessments for the right and left ears, i.e., the training did not produce changes in the short latency potentials. BAEP has neural generating sites and early modulators of acoustic signals [55] that may not change between pre and post training [56] because neural plasticity occurs largely at the cortical level where CANS can activate neurons and induce new neural connections [57]. Thus, although training might produce behavioral changes, as shown with special tests such as MLD, we found that changes in the short latency potentials were not observable.

For the LLAEP-P300, however, there were statistically significant differences between pre- and post-FAT evaluations (for the left ear) in terms of the N2 ($p = 0.05$) and P3 latencies ($p = 0.05$) and N2–P3 amplitude ($p = 0.05$), showing a decrease in N2 latency soon after the end of the FAT and an increase in the third evaluation (**Table 5**). Thus, although there was no stability in these measures, the P3 latency did finally increase compared to its initial value ($p = 0.05$).

Although some authors [51,58,59] see that auditory training leads to changes in auditory evoked potentials, such changes appear only in the left ear [31,32,60–62], probably due to the way acoustic signals are transmitted in the auditory system [58]. Thus, the neurophysiological responses may still be normal in cases of CAPD, but diffuse and not able to alter electrophysiological parameters, even though there are still functional difficulties observed in behavioral tests and reported by interviewees [62–65].

Due to the multiplicity of NF1 comorbidities, studies involving electrophysiological evaluation through LLAEP research are scarce. Nevertheless, some researchers [65–67] have investigated electrophysiological aspects of the pathology, looking at characteristics of the mismatch negativity (MMN) potential [66,67]. Bluschke et al. [68] studied the components in patients with NF1 who had longer latencies and slightly reduced amplitudes compared to a control group.

Among other impairments, NF1 presents non-specific cognitive deficits, language and learning disorders, motor impairment, scoliosis, and the appearance of cancer [39]. The severity of the pathology can vary between minimal and severe [37,69] involving the control abilities of these individuals [37]. Remigereau et al. [45] pointed out that neuropsychological profiles, as well as physical symptoms, vary from one patient to another, but reductions in intellectual performance – associated with difficulties in several cognitive domains, including oral and written language, visual and spatial abilities, mathematics, executive function, and attention – are common. Thus, stimulation of certain cognitive functions can promote rehabilitation, and allow better social performances and quality of life to be achieved.

Although NF1 gives rise to a high incidence of alteration in the CANS, with repercussions on the academic and social life of the patients [69], in our study FAT therapy promoted the reorganization of neural pathways, generating better responses in objective electrophysiological tests and better behavioral changes, although they did not overcome the CAPD diagnosis. Our results are similar to those of other pediatric studies [11–13,15]. Therapy tended to normalise many aspects of the behavioral assessment, resulting in improved quality of life for these NF1 patients. Therapy also tended to normalise long latency electrophysiological responses, although short latency potentials remained unchanged.

Further studies in this area would benefit from investigating other objective measures, such as otoacoustic emissions and suppression effects, as ways identifying changes in the auditory pathway at an early stage. Different therapeutic strategies aimed at rehabilitating CAP deficits in NF1 may also be effective.

Conclusions

After therapeutic intervention by means of formal auditory training, the performance of the central auditory nervous system improved, with better behavioral and electrophysiological responses which remained stable over at least 4 months. This demonstrates that in cases of neurofibromatosis type 1, rehabilitation efforts can prove effective.

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