Longitudinal Analysis of the Absence of Intraoperative Neural Response Telemetry in Children using Cochlear Implants

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Int Arch Otorhinolaryngol 2014;18:362–368.

Abstract

Introduction Currently the cochlear implant allows access to sounds in individuals with profound hearing loss. The objective methods used to verify the integrity of the cochlear device and the electrophysiologic response of users have noted these improvements.

Objective To establish whether the evoked compound action potential of the auditory nerve can appear after electrical stimulation when it is absent intraoperatively.

Methods The clinical records of children implanted with the Nucleus Freedom (Cochlear Ltd., Australia) (CI24RE) cochlear implant between January 2009 and January 2010 with at least 6 months of use were evaluated. The neural response telemetry (NRT) thresholds of electrodes 1, 6, 11, 16, and 22 during surgery and after at least 3 months of implant use were analyzed and correlated with etiology, length of auditory deprivation, and chronological age. These data were compared between a group of children exhibiting responses in all of the tested electrodes and a group of children who had at least one absent response.

Results The sample was composed of clinical records of 51 children. From these, 21% (11) showed no NRT in at least one of the tested electrodes. After an average of 4.9 months of stimulation, the number of individuals exhibiting absent responses decreased from 21 to 11% ($n = 6$).

Conclusion It is feasible that absent responses present after a period of electrical stimulation. In our sample, 45% ($n = 5$) of the patients with intraoperative absence exhibited a positive response after an average of 4.9 months of continued electrical stimulation.

Keywords
- cochlear implants
- neural response telemetry
- children

received January 21, 2014
accepted February 10, 2014
published online July 17, 2014

DOI http://dx.doi.org/10.1055/s-0034-1372510.
ISSN 1809-9777.

Introduction

Severe or profound sensorineural hearing loss causes several deficiencies that are not only sensorial but also social and emotional. Characterized by a lack of perception and speech coding, individuals with this degree of hearing loss might need special resources to minimize the consequences of such a loss.

With the advancement of medicine and technology, the cochlear implant (CI) represents an alternative that allows access to the sounds of speech in individuals with severe to profound hearing loss.[1] Such improvements can also be observed in the objective methods used to verify the integrity of the cochlear device and the electrophysiologic response of users.

Neural response telemetry (NRT), developed from the studies by Abbas et al,[2] is a fast and easily applicable technique that assesses the response of the peripheral segment of the auditory nerve to electrical stimulation. The implant used for NRT elicits stimuli and records the electrically evoked compound action potential (ECAP). Given that this is a fast and easily applicable technique, NRT is also used in the intraoperative setting. The major contribution of NRT is the confirmation of the physiologic integrity of the auditory nerve.[3] It is also useful when establishing the electrodes that might be included in a given map, the best stimulation speeds, the speech coding strategies, and the estimation of the stimulation of T (minimum stimulation) and C (maximum stimulation) levels.[4]

Composed of a negative peak (N1) followed by a positive peak (P2), the ECAP is analyzed with regard to the amplitude of the response. The measurement between N1 and P2 yields the wave amplitude, which varies according to the increased stimulation intensity. The ECAP represents the synchrony of a group of neurons, and the amplitude of response is proportional to the number of neurons activated by a stimulus. Consequently, the presence of the ECAP allows one to predict a satisfactory postoperative performance,[5] which likely corresponds to better synaptic efficiency and synchronization of the neural response.[6]

Knowledge of the physiology and responses of the auditory nerve to electrical stimuli is important in establishing the current level used for stimulation and other programming adjustments.[7] In some cases, the ECAP is not present during surgery, which might suggest a dysfunction of the cochlear nerve and existing neural structures. In some of these cases, continual stimulation predicts the appearance of neural response, which might be related to the synchronization of nerve fibers.[8]

Cafarelli Dees et al[9] and van Dijk et al[10] suggested the rates of postoperative presence of ECAP to be 96 and 90%, respectively, whereas Guedes et al reported a rate of 80%.[3] Guedes et al found that the absence of responses was correlated with limited prognosis.[11] The continued use of CIs has tended to result in the emergence of the action potential after some months of stimulation. Even longitudinal studies on neural responses, however, have failed to mention the possibility of the appearance of a response or the average time required for the onset of such a response.

This study aimed at establishing whether the ECAP of the auditory nerve, when absent intraoperatively, can appear after continual electrical stimulation. When NRT responses were absent during surgery, we analyzed the evolution of these responses after at least 3 months of stimulation.

Materials and Methods

This study was approved by the Ethics Committee of Research Projects (CAPPesq) of the Clinical Board of the Clinical Hospital and the Medicine Faculty of the Universidade de São Paulo, protocol no. 010/11. This was a retrospective study conducted through the survey and analysis of the database of the Cochlear Implant Group of the Clinical Hospital of the Medicine Faculty of the Universidade de São Paulo (HC-FMUSP).

Case Series

We selected the clinical records of children who underwent multichannel CI (Nucleus Freedom, Cochlear Ltd., Australia, model CI24RE) surgery between January 2009 and January 2010 at the Cochlear Implant Group of the HC-FMUSP. Sixty-three children received CIs during that period. The criteria for sample selection included systematic use of the multichannel CI (more than 8 h/d), the use of the CI24RE internal and external units, and NRT records during the intra- and postoperative periods for 6 months after surgery for electrodes 1, 6, 11, 16, and 22. Of the 63 children, 51 met the inclusion criteria, with ages at implantation varying between 11 and 187 months.

Procedures

To record the NRT, the Cochlear Implant Group of the HC-FMUSP used a speech processor, an external magnet antenna, a link wire between the speech processor and the external antenna, a programming interface (Pod), and a computer to send and receive the neural data. All data were analyzed using the NRT software Custom Sound EP 2.0 (Cochlear Ltd., Australia), which controls the parameters of ECAP stimulation and recording.

The NRT results were analyzed according to the protocol described by Abbas et al[2] and van Dijk et al.[10] ECAP comprises a negative peak (N1) with an approximate latency between 0.2 and 0.4 milliseconds, followed by a positive peak (P2) with an approximate latency up to 1 millisecond. The amplitude of the response (measurement between N1 and P2) is proportional to the increase in the intensity of stimulation, which is measured in current units (CU). The presence of a visible N1 peak accompanied by the reproducibility of tracing, lack of artifact, or saturation of the amplifier (►**Figs. 1** and **2**) was considered a valid neural response.[12] The values of positive responses represented the NRT thresholds expressed as CU, which is the smallest amount of current needed to generate an ECAP with an amplitude measurable by the software according to the autotelemetry protocol of van Dijk et al.[10]

Data regarding the etiology, model of electrodes, chronological age, and length of auditory deprivation were collected from the clinical records. It should be emphasized that the length of auditory deprivation is equal to the length of time between the onset of hearing loss and implant surgery. According to the intraoperative response, the children were separated into two groups. One group had positive neural

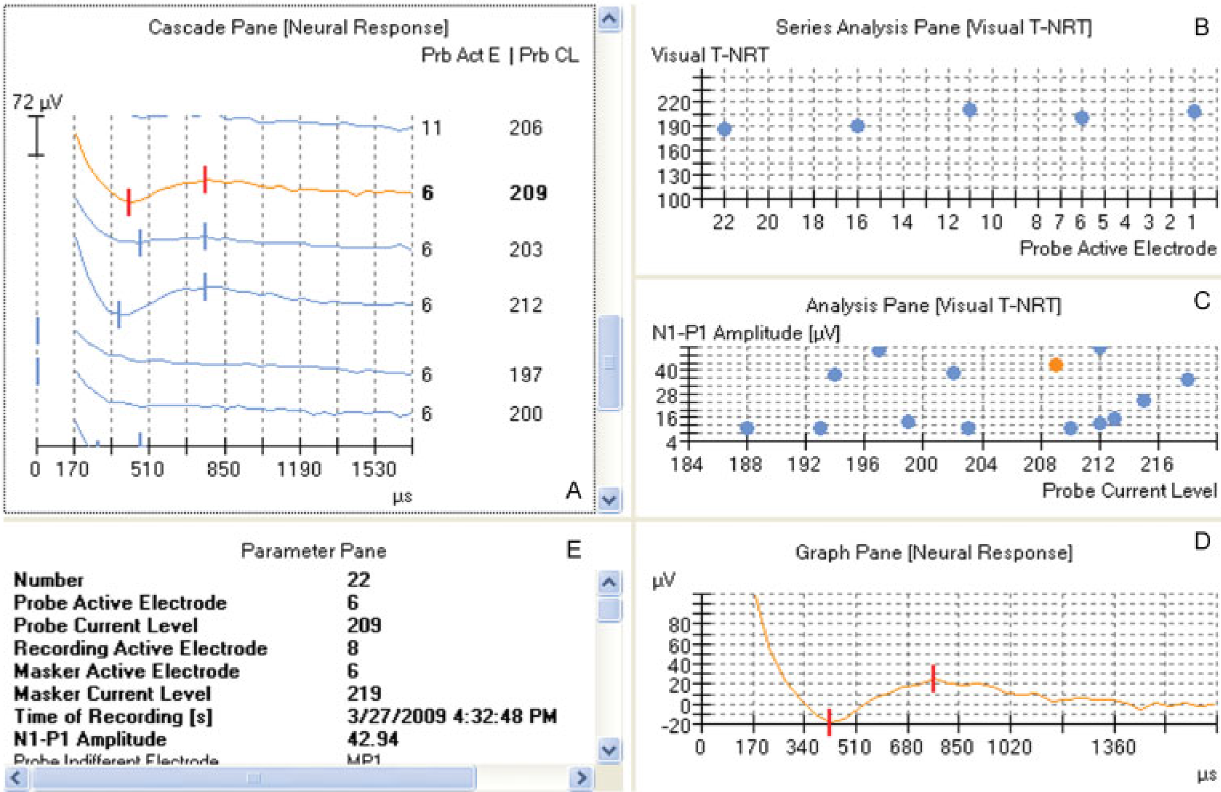

Fig. 1 Present response. (A) Stimulation and recording parameters employed for the measurement of the ECAP on electrode 6 and the stimulation level equal to 209 CU. (B) Different ECAP amplitudes obtained by various stimulation levels. (C) ECAP amplitudes as a function of the stimulation levels. (D) Regression curve supplied by the software. (E) ECAP response present at 209 CU with 42.94 µV of amplitude. Abbreviations: CMV, cytomegalovirus; CU, current units; ECAP, evoked compound action potential; NRT, neural response telemetry.

responses in all electrodes, and the other group exhibited an absence of response in at least one electrode. The NRT records were collected during surgery and at least 3 months after the activation of the CI.

The average length of stimulation was estimated from the record of a postoperative time per individual. Patients returned for follow-up at ~3 and 6 months after activation, and the NRT response at the second or third times was used depending on the availability of records in the database.

Statistical Analysis

The values obtained for the threshold of neural responses per electrode (1, 6, 11, 16, and 22) were initially analyzed in a descriptive manner. The Mann-Whitney test was used to establish the relationships between the absence of response and age and the absence of response and length of deprivation. The Wilcoxon matched pairs test was used to analyze the appearance of postoperative NRT responses per electrode. Values of p less than 0.05 were considered statistically significant.

Results

Of the 51 children, 40 exhibited positive responses during intraoperative NRT in all of the tested electrodes, whereas 11 children exhibited an absence of response in at least one electrode (►**Table 1**). Regarding the implant model CI24RE, all patients received the perimodiolar electrode (Contour Advance), except for one child who received the CI24RE implant with a straight electrode beam. Regarding the causes of hearing loss found in the total sample (►**Fig. 3**), both groups exhibited a heterogeneous distribution in which an unknown etiology predominated.

Although 21% of the children showed an absence of response in at least one electrode, a positive intraoperative neural response was observed in all cases. The absence of an intraoperative NRT was observed in 16% (16) of 255 electrodes tested (►**Table 2**). The absence was most frequent in the basal electrodes, primarily in electrode 1 (18%) compared with electrodes 6, 16, and 22 (4%) and electrode 11 (2%).

After an average of 4.9 months of continual stimulation, the number of individuals in the total sample exhibiting an absence of response decreased from 21% (11) to 11% (6), thus reducing the relative absence/individual ratio by 18%. Within the group exhibiting an intraoperative absence of response, the presence of NRT responses appeared in 45% (5) of the individuals and 14% (8) of the tested electrodes. Among the positive responses, three appeared in patients with hearing loss due to unknown etiology, in one patient with hearing loss due to meningitis, and in one patient with hearing loss due to genetic causes. The results of the Mann-Whitney test indicated that age at implantation ($U = 184.500$, $z \leq 814$, $p < 0.05$ and length of deprivation

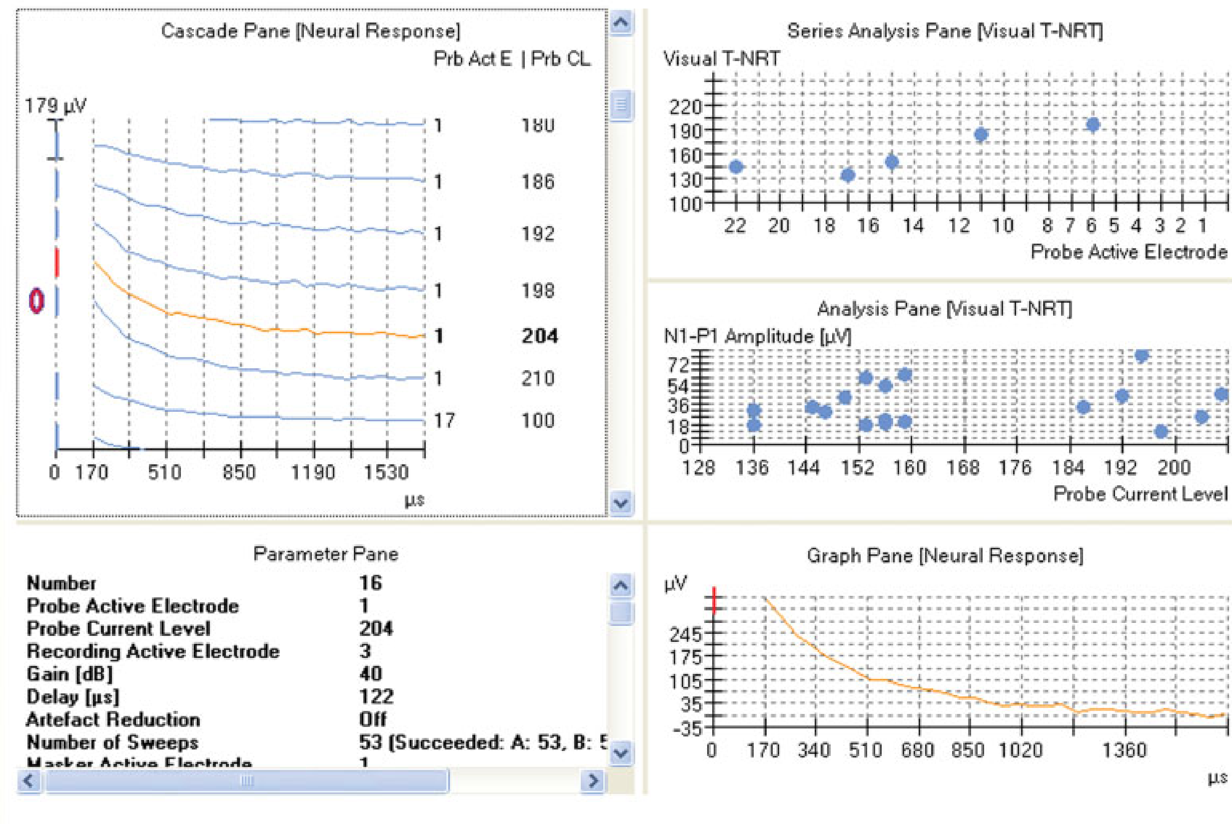

Fig. 2 Patient with hearing loss. Stimulation and recording parameters employed for the measurement of the evoked compound action potential (ECAP) on electrode 1 and stimulation level equal to 204 current units (CU). (B) Different ECAP amplitudes obtained by various stimulation levels. (C) ECAP amplitudes as a function of the stimulation levels. (D) Regression curve supplied by the software. (E) Absent ECAP response at the highest acceptable level within compliance.

($U =$ 177.000, $z \leq 986$, $p < 0.05$ were not statistically significant between the groups.

►**Table 3** shows the comparison between the thresholds of the intra- and postoperative neural response in all of the tested electrodes in the group exhibiting an intraoperative absence of response and the time when the postoperative response was recorded. Electrode 1, which exhibited the highest rate of absence (82%), was excluded from the analysis due to the low number of present responses. A Wilcoxon matched pairs test showed that the postoperative appearance of NRT responses was not statistically significant in any of the tested electrodes. There was, however, a tendency toward significance in electrode 22, which might be confirmed by studying a larger sample.

Discussion

Periodic NRT testing can be a helpful tool in clinical practice for determining the readaptation and recuperation of the cochlear nerve fibers after continued stimulation. In our study, 21% of the children exhibited an intraoperative absence of response to NRT. After an average of 4.9 months of continual stimulation, NRT responses appeared in 45% of individuals who had an absence of response during surgery.

Table 1 Sample distribution according to the presence (group P) or absence (group A) of response to intraoperative NRT according to age at implantation, length of deprivation, and model of electrode array

	Group P	Group A	Total
Age at CI (mo) (±SD)	36.75 (±18.28)	66.91 (±56.60)	43.25 (±32.53)
Time of deprivation (mo) (±SD)	34.85 (±18.18)	64.82 (±56.17)	41.31 (±32.30)
Electrodes (*n*)			
Perimodiolar	39	11	50
Straight	1	0	1
Total	40	11	51

Abbreviations: CI, cochlear implantation; NRT, neural response telemetry; SD, standard deviation.

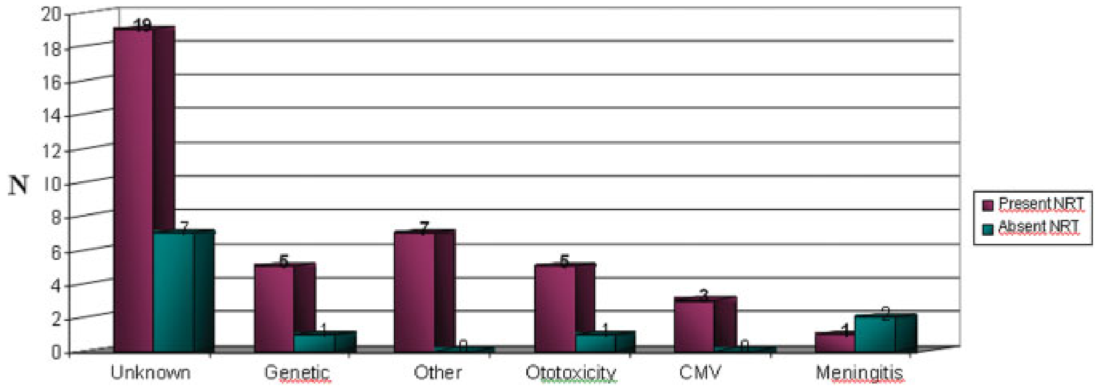

Fig. 3 Distribution of etiology in the total sample between the group with positive intraoperative neural response telemetry (NRT) response in all tested electrodes and the group with absent intraoperative NRT response in at least one tested electrode.

This finding suggests a tendency for the response to appear after continual use of the CI, which might be related to the hypothesis that electrical stimulation causes alterations in the synaptic activity and supplies the auditory nerves with reinforced neurotrophic support.[13,14] As a result of such modifications, it is believed that the synchronization of neural fibers occurs more efficiently due to the manner in which stimulation activates the primary neurons as well as causing a possible reduction in the periods of neuronal firing.[15]

Age at implantation and length of hearing loss, which are variables that often interfere with the determination of resources and the programming of the CI in clinical practice, did not exhibit any significant influence on the absence of

Table 2 Distribution of the presence and absence of intraoperative response in 255 tested electrodes

	Electrode 1, *n* (%)	Electrode 6, *n* (%)	Electrode 11, *n* (%)	Electrode 16, *n* (%)	Electrode 22, *n* (%)	Total, *n* (%)
Present	42 (82)	49 (96)	50 (98)	49 (96)	49 (96)	239 (94)
Absent	9 (18)	2 (4)	1 (2)	2 (4)	2 (4)	16 (6)
Total	51 (100)	51 (100)	51 (100)	51 (100)	51 (100)	255 (100)

Table 3 NRT thresholds in an intra- and postoperative setting in individuals exhibiting at least one absence of response during surgery

ID	Electrode 1		Electrode 6		Electrode 11		Electrode 16		Electrode 22		
	Intraop	Postop	Intraop	Postop	Intraop	Postop	Intraop	Postop	Intraop	Postop	Time postop (mo)
6	198	128	213	146	234	166	245	167	↓	146	6
7	↓	190	↓	152	196	157	↓	170	166	130	4
19	↓	↓	202	187	204	184	203	184	197	166	6
22	↓	214	195	163	218	↓	222	↓	↓	145	5
28	↓	211	181	187	157	154	163	166	193	166	6
29	↓	↓	178	178	183	202	179	205	182	190	6
30	↓	↓	199	207	178	192	186	132	200	159	4
35	↓	↓	214	209	189	184	206	194	185	178	3
36	↓	↓	↓	↓	↓	↓	194	211	197	188	4
37	178	187	187	202	187	202	↓	202	148	175	4
44	↓	↓	211	193	204	199	202	190	176	175	6

Abbreviations: Intraop, intraoperatively; Postop, postoperatively; NRT, neural response telemetry; SD, standard deviation.
Note: All responses are given in current units; ↓ indicates the absence of a response. Analyzing whether the presence (or appearance) of a response is significant in any electrode.

NRTs or in the later appearance of response. In our study, these results can be explained by the fact that the sample was comprised exclusively of children between the ages of 11 and 187 months. Similar studies should be performed with adults to analyze the possible relationship between age at implantation, length of hearing loss, and absence of intra- and postoperative ECAP responses.

In our case series, hearing loss due to unknown causes was the prevailing etiology. Due to the small number of individuals lacking an NRT response, the results reported in prior studies,[3,10] which indicate a prevalence in the absence of response in all electrodes in progressive and ossifying conditions (meningitis and otosclerosis), could not be confirmed. This is likely because in the present study, only children were analyzed, and otosclerosis is known to be predominantly present in the adult population.

Electrodes 1, 6, 11, 16, and 22 were tested using the default settings in the Custom Sound (Cochlear) software, which is programmed to record the NRT responses from the bundle of electrodes allocated in the cochlea. The recorded responses therefore must have originated from every cochlear area to detect possible tonotopic interferences in the ECAP responses. Only individuals with an impedance telemetry within the normal range (above 0.7 kΩ and below 20 kΩ) were analyzed, thus avoiding the integrity of the chain of electrodes from becoming a defining variable in the recording of the NRT responses.

We observed a tendency for the response to be absent at higher current levels in the basal electrodes, which is consistent with previous studies.[3,16–18] This absence is possibly associated with the position of the electrodes on the basal turn, which becomes more distant from the modiolus (due to the position of cochleostomy) and leads to the need for higher levels of energy in this area.[19] In this case, the position of cochleostomy would distance the array of electrodes from the modiolus. It would, however, be interesting to study the influence of electrode position on the threshold of neural responses in implanted patients using the technique of insertion through a cochleostomy and a round window with straight and perimodiolar electrodes. In our case series, only one child had a straight electrode implant, and this child exhibited responses in all of the tested electrodes. Other studies have suggested a relationship between residual hearing and the need of lower levels of current required to elicit a response in these areas, possibly explaining the need for higher levels of energy in the basal electrodes (an area with less auditory residue).[2,20]

►**Table 3** shows that in individual 22, the postoperative record analysis showed the appearance of NRT responses in electrodes that were absent from the intraoperative setting (1 and 22). It was, however, possible to observe that two of the electrodes (11 and 16) began to exhibit absent responses. There are no data in the literature explaining this phenomenon. Further studies are therefore needed to analyze the frequency and causes of these events.

The results of our study highlight the importance of conducting intraoperative NRT examinations, which is a fast and simple procedure that can ensure the physiological integrity of the cochlear nerve and allow for the monitoring of the response over time. In addition, this method can assist in the programming of the speech processor of the CI. Periodic retesting of ECAP responses allows for a deeper understanding of the neural physiology of patients presenting with an absence of response and may assist in the development of better coding strategies for the device and more efficient rehabilitation for each individual.

Conclusion

ECAPs of the auditory nerve appeared in 45% of individuals with intraoperative absence of response after an average of 4.9 months of continual stimulation.

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