INTRODUCTION
The cochlea can be affected by a number of malformations, ranging from absence of a single turn (Mondini syndrome) to complete absence of all turns (common cavity). In patients with cochlear malformation, cochlear implantation is technically possible, but different malformations require specific CI surgical techniques as standard techniques (e.g., posterior tympanotomy, cochleostomy, and electrode insertion by round window) are not viable. Nonetheless, in these patients, clinical outcome of CI surgery is unpredictable and variable, especially in terms of hearing performance. For example, Buchman et al. showed that patients with the constellation of an incompletely partitioned (IP) cochlea, enlarged vestibular aqueduct, and a dilated vestibule (i.e., Mondini’s malformation) achieved relatively good levels of speech perception, while patients with total semicircular canal aplasia, isolated IP, cochlear hypoplasia, or common cavity showed impaired levels. Thus, whether patients with a malformed cochlea should be considered candidates for CI surgery remains controversial.

An outcome of CI surgery is typically assessed using a battery of tests. The speech perception test assesses the patient’s ability to both perceive and discriminate speech information. While widely used, scores are influenced by several factors, including the

OBJECTIVES: This study aims to compare the electrical auditory brainstem response (EABR) following cochlear implant (CI) surgery in pediatric subjects with cochlear malformation and a normal cochlea, in order to assess the sensitivity of EABR and to evaluate the surgery outcome.

MATERIALS and METHODS: A total of 26 pediatric subjects who were deaf and scheduled for CI surgery were enrolled into this case control study. Group A (n=20) included subjects with a normo-conformed cochlea. Group B (n=6) included subjects with cochlear malformation. Subjects were evaluated with EABR immediately (T0) and 6 months (T1) post-CI surgery. The EABR Waves III and V average amplitude and latency were compared across time, separately for each group, and across groups, separately for each time.

RESULTS: Auditory brainstem response (ABR) could only be recorded in Group A. We were able to record EABR from all subjects at T0 and T1, and waves III and V were present in all the recorded signals. There were no statistically significant differences between T0 and T1 in EABR Waves III and V in terms of average amplitude and latency in neither group. When comparing Groups A and B, the only statistically significant difference was the average amplitude of wave V, both at T0 and T1.

CONCLUSION: EABR is a valid tool to measure the auditory nerve integrity after CI surgery in patients with a normal and malformed cochlea, as shown by its ability to measure waves III and V when ABR is absent. The EABR testing should be performed before and after CI surgery, and EABR should be used as a measure of outcome, especially in patients with a malformed cochlea.

KEYWORDS: Cochlear malformation, cochlear implant, EABR, ABR, cochlear nerve conduction
intelligence quotient, ability to focus, and age. These limitations highlight the need for more objective outcome measures. The auditory brainstem response (ABR) test is a tool to determine the patient’s ability to hear and measures the way the hearing nerve responds to different acoustic stimuli. The electrical auditory brainstem response (EABR) testing is similar to ABR testing, but it uses an electrical stimulus delivered directly to the cochlea, which makes EABR more effective than ABR for quantifying the auditory pathways nerve conduction (from spiral ganglia to the auditory cortex). EABR can objectively measure the CI function and responsiveness of the peripheral auditory neurons/nerve up to the level of the brainstem; additionally, these signals can be recorded even when excessive stimulus artifacts preclude successful acquisition of the electrically evoked compound action potentials (ECAPs). In patients with a malformed cochlea, EABR can measure proper transmission of signals from the ear to the brain with high sensitivity and accuracy, as shown by Kim et al.

This study aims to quantitatively compare EABR recorded from CI subjects with a normal cochlea and with cochlear malformation, with the goal to evaluate the EABR sensitivity and the outcome of cochlear implantation. While previous studies have shown that EABR can be used to record the signal from the ear to the brain in CI patients with cochlear malformations, how EABR recorded from these patients compare to EABR recorded from CI patients with a normal cochlea has not been investigated. Such a comparison might help understand to which extent outcome of CI surgery in patients with a malformed and normal cochlea is comparable.

MATERIALS AND METHODS
This study was conducted from January 2017 to August 2018 at the Otology and Cochlear Implant Unit of a tertiary referral center. All the study procedures followed the international ethical guidelines for biomedical research involving human subjects and were approved by the institutional regulatory board. Parents/legal guardians were informed about the study procedures, and they authorized them on their children by signing a written consent.

All pediatric subjects affected by deafness who needed to undergo CI surgery were enrolled into the study. Prior to surgery, all subjects underwent a high-resolution computed tomography examination of the temporal bone and magnetic resonance imaging (MRI) of the cerebellopontine angle (CPA-MRI) with TSE T2 DRIVE sequences or 3D Fast Field Echo (FFE) T2-weighted sequences to assess cochlear abnormalities. Then, subjects were assigned to either Group A (subjects with a normal cochlea) or Group B (subjects with cochlear malformation). The otoacoustic emissions (OTOAE) and ABR tests were performed to assess the retro-cochlear function from spiral ganglia to the superior auditory area. The ABR signals were recorded with a direct communication between the internal auditory canal (IAC) and cochlea basal turn; and 2 subjects presented with a Type II incomplete cochlea partition (Mondini deformity) associated with a direct communication between the internal auditory canal (IAC) and cochlea basal turn; and 2 subjects presented with a Type II incomplete cochlea partition associated with an enlargement of the IAC bulbous. Besides these cochlear malformations, 3 out of the 6 Group B subjects presented with a dysmorphic profile of the vestibule and semicircular canals, and 1 subject presented with a mild dilatation of the temporal bone and mastoid cavity.

CI surgery was performed using a posterior tympanotomy and cochleostomy approach in all subjects by the same team to minimize the inter-operator variability. The surgical approach to the cochlea was the same in all patients, except for the electrode insertion, which was standard (cochleostomy) in subjects with a normal cochlea, and it used as the “releasing method for electrode positioning in subjects with a malformed cochlea.”

EABR was recorded for all subjects immediately (T0) and 6 months (T1) post-CI surgery by the same operator and under the same experimental conditions. EABR was recorded from three CI electrodes stimulating respectively at low, middle, and high frequencies, according to the configuration available for each CI model and manufacturer. The EABR signals were processed with analogical filters (high-pass filter, cut-off frequency 100 Hz, low-pass filter, cut-off frequency 2000 Hz), which define the frequency range visualized in the graph window of Eclipse, and with digital filters, designed by Interacoustics, to smooth the curve removing myogenic, electromagnetic, and stimulus artifacts. A time window of 10 ms was used for the data acquisition synchronized with the stimulus generated by the CI, using a trigger cable connected to the CI programming interface (dub box). Once the EABR graph was obtained, the marker for Waves III and V was manually inserted, and then the software calculated the waves latency and amplitude.

Statistical Analysis
The analysis of EABR focused on Waves III and V. The EABR Wave III amplitudes and latencies at T0 and T1 were compared using a two-tailed t-test separately for each group; a similar analysis was performed on Wave V. Also, EABR Wave III amplitudes and latencies of Groups A and B were compared using a two-tailed t-test, separately for T0 and T1; a similar analysis was performed on Wave V. The level of significance p for all tests was set to 0.05.

RESULTS

Subjects
Group A included 20 subjects (13 females, 7 males; average age 25 months) (standard deviation [SD], 10.9; confidence interval [CI] 95%, 12-48). Group B included 6 subjects (4 females, 2 males; average age 31.6 months old) (SD, 13.7; CI 95%, 20-40).

As shown by the MRI and CT, the cochlear nerve was intact in all subjects. Subjects in Group A had a normal cochlea. Subjects in Group B had cochlear malformation with significant alterations of different severity in the inner ear, but a normal mastoid cavity and middle ear bones (see Figures 1 and 2 for examples of a CT and MRI scan of a malformed cochlea). Specifically, in Group B, 4 subjects presented with a Type II incomplete cochlea partition (Mondini deformity) associated with a direct communication between the internal auditory canal (IAC) and cochlea basal turn; and 2 subjects presented with a Type II incomplete cochlea partition associated with an enlargement of the IAC bulbous. Besides these cochlear malformations, 3 out of the 6 Group B subjects presented with a dysmorphic profile of the vestibule and semicircular canals, and 1 subject presented with a mild dilatation of the temporal bone and mastoid cavity.
Figure 1. a, b. Axial and coronal images of the temporal bone and cerebellopontine angle at a high-resolution CT scan (a) and MRI FFE T2-weighted sequence (b). Bilateral inner ear malformations with incomplete partition (Type III) of the cochlea and lack of separation from the dilated internal auditory canal.

Figure 2. a-c. Magnified axial MRI FFE T2-weighted image (a) and axial CT image (b) of right temporal bone. Volume rendering of the right internal acoustic canal and inner ear (MRI cisternography), superior and anterior view (c). Bulbous dilatation of the bottom of IAC and lack of the cribriform plate (dotted line), with direct communication between IAC and the basal turn of cochlea. The cochlea is dysmorphic (white arrowhead), with the absence of the modiolus. Note the normal cochlear nerve within IAC (black arrowhead). Also note the dysmorphic profile of the vestibule and semicircular canals, with small saccular dilatations of the wall (arrow).
the vestibular aqueduct. Moreover, one of the subjects with the Mondini deformity showed a mild ventricular dilatation and mild macrocephaly associated with bilaterally enlarged jugular bulb. None of the other subjects in Group B had any morphological brain malformation.

**Otoacoustic Emissions and Auditory Brainstem Response**

The OTOAE response was absent in all subjects. Waves III and V could only be recorded from subjects in Group A, where the average amplitude and latency were 0.14 µV (SD, 0.007; CI 95%, 0.13-0.15) and 3.62 msec (SD, 0.12; CI 95%, 3.4-3.7), respectively, for Wave III and 0.28 µV (SD, 0.013; CI 95%, 0.26-0.31) and 5.61 msec (SD, 0.14; CI 95%, 5.3-5.8) respectively for Wave V.

**Electrical Auditory Brainstem Response**

Figure 3 shows examples of typical EABRs recorded from Groups A and B at T1.

In Group A, the EABR recorded at T0 displayed Wave III with an average amplitude and latency of 0.81 µV (SD, 0.09; CI 95%, 0.7-1) and 1.81 msec (SD, 0.08; CI 95%, 1.7-2), respectively, and Wave V with an average amplitude and latency of 0.12 µV (SD, 0.008; CI 95%, 0.11-0.14) and 3.79 msec (SD, 0.09; CI 95%, 3.6-3.9), respectively. The EABR recorded at T1 displayed similar Wave III and Wave V average amplitude and latencies. There was no statistically significant difference between T0 and T1 in the average amplitude (p=1) nor latency (p=0.98) of Wave III. Similarly, there was no statistically significant difference between T0 and T1 in the average amplitude (p=0.97) nor latency (p=0.99) of Wave V.

In Group B, the EABR recorded at T0 displayed Wave III with an average amplitude and latency of 0.20 µV (SD, 0.01; CI 95%, 0.19-0.22) and 4.56 msec (SD, 0.1; CI 95%, 4.5-4.7), respectively, and Wave V with average amplitude and latency of 0.32 µV (SD, 0.007; CI 95%, 0.32-0.33).
0.34) and 6.78 msec (SD, 0.07; CI 95%, 6.7-6.9), respectively. The EABR recorded at T1 displayed Wave III with an average amplitude and latency of 0.13 µV (SD, 0.01; CI 95%, 0.12-0.15) and 3.86 msec (SD, 0.1; CI 95%, 3.7-3.9), respectively, and Wave V with an average amplitude and latency of 0.25 µV (SD, 0.01; CI 95%, 0.23-0.26) and 5.8 msec (SD, 0.06; CI 95%, 5.7-5.9), respectively. There was no statistically significant difference between T0 and T1 in the average amplitude (p=0.75) nor latency (p=0.42) of Wave III. Similarly, there was no statistically significant difference between T0 and T1 in the average amplitude (p=0.51) nor latency (p=0.46) of Wave V.

There was no statistically significant difference between Groups A and B neither in average amplitude nor in latency of Wave III at T0 (p=0.35 and p=0.72, respectively), nor at T1 (p=0.08 and p=0.35, respectively). As for Wave V at T0, there was a statistically significant difference between Groups A and B in the average amplitude (p=0.002), but not in the average latency (p=0.06). Similarly, at T1 there was a statistically significant difference between Groups A and B in the average amplitude (p=0.022), but not in the average latency (p=0.18) (see Table 1). When comparing the ABR and EABR data, we found no changes in amplitude or latencies of Wave III or V in Group A; and a reduction of the amplitude and decrease of latency of Waves III and V in Group B.

**DISCUSSION**

The CI implantation in subjects with cochlear malformation is controversial. In fact, in these patients, the outcome of CI surgery is variable, but previous studies have shown that it can be predicted from the EABR recorded presurgery. The presence of EABR Waves III and V predicts a favorable outcome \[11\] and indicates that the CI proper-

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ly stimulates the auditory pathways [10]. In patients with a malformed cochlea, the EABR testing prior to CI surgery not only is particularly informative, but it can also overcome the limitations of the ABR testing. In fact, in these patients, the absence of the ABR response at 100 dB might be simply due to the low number of spiral ganglion cells [4, 12], to elicit an electrical response, an acoustic stimuli exciting 100 dB would need to be used, which is painful for the patient.

In this study, we could only record ABR from subjects with a normal cochlea, but we were able to record EABR from all subjects. We compared the amplitude and latency of EABRs waves III and V recorded immediately and 6 months post-CI surgery, and we found that there was no statistically significant difference in subjects with a normal cochlea. A similar result was found for subjects with a malformed cochlea. A between-group comparison in the amplitude and latency of the EABR wave III and V showed a statistically significant difference only for the amplitude of Wave V, which in subjects with cochlear malformation was smaller than in subjects with a normal cochlea. Such difference in the amplitude of Wave V may be due to a different brain maturity stage [13], in fact, the subjects with a malformed cochlea were older than those with a normal cochlea for about 4 months, possibly due to the fact that surgery planning periods are typically longer and more complex in the former group (e.g., patients with a malformed cochlea typically undergo a 3D MRI rather than a traditional MRI, as well as genetic, neurological, and nonsymptomatic organ malformation consultation to prevent surgery complications) [14].

Another factor that could explain why the amplitude of the EABR Wave V was smaller in subjects with a malformed cochlea than in subjects with a normal cochlea is the possible reduction of spiral ganglion number in the modiolus [12, 13] in the former group. A malformed cochlea presents less turns and, consequently, less space for spiral ganglion cells, [14] which can lead to a faulty transmission of signals [4, 12]. In fact, the amplitude of an EABR wave is a function of the power with which an impulse is transmitted from the periphery (cochlea) to the other structures of the auditory pathways (cochlear nuclei and brain), [16] and reduction of spiral ganglion number in the modiolus [12, 13] may lead to attenuated waves (Figure 4). Differently from Wave V, we did not see a difference in Wave III between groups. This might be due to the releasing technique used in the CI surgery of subjects with cochlear malformation, which supposedly helped achieve a correct allocation of the electrode and, in turn, possibly yielded to a stimulation power sufficient to generate Waves III, but not high enough to produce Waves V comparable to those from normo-conformed cochlea subjects.

In both Group A and Group B, it was possible to record Waves III and V after CI. The fact that we were able to record the EABR Waves III and V from subjects with a malformed cochlea suggests that nonstandard surgical techniques are necessary to achieve good CI outcomes in these patients [20]. Although we did not find a statistically significant change between T0 and T1 in either group (possibly due to the fact that the follow-up was too short), our data suggest that EABR may be used to evaluate changes in the auditory pathways of children who have undergone CI surgery. Compared to diffusion tensor imaging proposed by other authors, [15] EABR is less expensive, and its efficacy to detect even minimal changes (e.g., due to a demyelination) in signal transmission over the auditory pathways has been widely shown [118].

Limitations of this study include lack of pre-surgery EABR recordings. Furthermore, the age difference (and thus the different stages of brain maturation) between the groups may have partially affected the features of the EABR Waves III and V. Finally, the sample of patients with a malformed cochlea was small, and it displayed different cochlear malformations.

Future studies should focus on analyzing the correlation between the EABR Waves III and V and clinical outcomes such as speech and psychological assessment scores, and on further investigating whether these variables can predict the outcome of CI surgery.

CONCLUSION

Our results show that CI is able to stimulate the hearing pathways correctly, not only in patients with a normal cochlea, but also in patients with cochlear malformation, provided that a suitable CI surgery technique is used. We recommend including EABR as part of the patient examination performed during CI surgery planning, especially in patients with a malformed cochlea. We also recommend using EABR to monitor reconnection of the auditory pathways and development of the brain function after CI.

Ethics Committee Approval: Ethics committee approval was received for this study from Ethics Committee of Santobono-Posilipon Hospital.

Informed Consent: Written informed consent was obtained from the patients’ parents who participated in this study.

Peer-review: Externally peer-reviewed.


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Conflict of Interest: ADS is a consultant for Oticon Medical. The other authors have no conflict of interest to declare.

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