COCHLEAR IMPLANT IN IMMUNE MEDIATED INNER EAR DISEASES: IMPEDANCE VARIATIONS AND CLINICAL OUTCOMES

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ABSTRACT

OBJECTIVE: Immune-mediated inner ear disease (IMIED) is characterized by severe/profound hearing loss. Although IMIED might lead to cochlear disorders with modification of electrode impedance these patients are ideal candidates for cochlear implant (CI). The aim of the study was to evaluate whether impedance values and impedance fluctuations over time were significantly higher in IMIED patients treated with CI compared to the control group.

METHOD: The sample was composed of CI patients with severe/profound hearing loss: a study group (SG) of IMIED patients (31 ears) and a control group (CG) of patients with hearing loss not related to their immune system (31 ears). Audiological performance and impedance values were measured and compared amongst groups at 3, 6, 12 and 18 months following the fitting sessions.

RESULTS: Speech perception was significantly better for SG in word and sentence recognition in quiet. Impedance values were, on average, significantly higher for apical and middle electrode segments in SG compared to CG at the 3 month follow-up and were maintained over a longer time period. Additionally, a subset of SG patients (*active patients*) experienced significantly greater impedance fluctuation corresponding to clinical symptom reactivation.

DISCUSSION AND CONCLUSION: IMIED patients achieved good audiological performance. However, the surgical intervention could change the inner ear environment, causing impedance fluctuations and, consequently, more frequent CI fittings. Additionally, impedance evaluation could be utilised as an early warning sign of IMIED recurrence and as an aid to therapeutic decision-making.

Key words: cochlear implant, impedances, autoimmune hearing loss, inner ear

INTRODUCTION

Cochlear implants (CIs) are the most advanced technological devices available to clinicians for improving hearing function in people with severe/profound hearing loss, functioning by means of an electrode array that stimulates the residual spiral ganglion fibers and cell bodies (Wilson & Dorman, 2008). A critical factor in the sequential process from sound stimulus to auditory comprehension is the cochlea-electrode interface consisting of electrode position, neural health, cochlear geometry, and bone and tissue growth in the cochlea (Duan et al., 2004). In order to better understand the factors involved in electrochemical impedance at this level, animal research suggests that changes in volume and/or composition of perilymphatic fluid and/or tissue modifications adjacent to electrode structures leads to changes in contact impedance, thereby interfering with the efficiency and quality of neural stimulation (Duan et al., 2004).

The introduction of telemetry in 1993 allowed, for the first time, the objective evaluation of the CI electrodes function and stimulation characteristics independent of patient's reporting (Kessler, 1999). Technological improvements since 1999 have led to further implementation of telemetry to measure electrode voltage compliance and impedance and to diagnose implant and electrode function. The assessment of nerve/electrode interfaces is mainly described by reproducible impedance measurements for each electrode in the array (Patrick et al., 2006).

Clinically derived impedance increases in the first few weeks after CI surgery as the fibrotic reaction to the electrode develops (Tykocinski et al., 2005). Conversely, impedance decreases when electrical stimulation begins (Newbold et al., 2014). This reduction has been attributed to current flow, which causes an alteration in the adherence of fibrous tissue and/or protein in the electrodes (Garcia-Berrocal & Ramirez-Camacho, 2000; O'Leary et al., 2013). Impedance remains relatively stable in most CI recipients after the first 3 months following surgery, with the exception of 'stimulation-induced activity-dependent' fluctuations at the beginning (Newbold et al., 2014; Wilk et al., 2016).

Electrical impedance is influenced by a variety of factors; surrounding tissue, the composition of

the intracochlear fluid, and electrode deposits (Swanson et al., 1995; Charlet de Sauvage et al., 1997; Busby et al., 2002; Tykocinski et al., 2005). This should be carefully considered in patients and especially children with meningitis-related deafness (Mancini et al., 2008), or in intra-cochlear inflammatory events such as Relapsing Polychondritis (Mancini et al., 2011; Vos et al., 2016), that induce fibrosis or ossification of the cochlea whether these morphological changes occur pre- or post-operative. Inflammation increases the impedance value, hindering the correct functioning of the implant, and requires frequent adjustments to achieve optimum perception. Lastly, inflammation interferes with nerve stimulation because the level of the current diverges with very high impedances (Mancini et al., 2008; Mancini et al., 2011; Helmstaedter et al, 2018).

In addition, sudden variations in impedance were also observed which, if wide enough, would also affect the sound quality of the implant. (Newbold et al., 2014; Wilk et al., 2016). Studies have shown that impedance peaks coincide with dizziness / vertigo in patients with CI (Neuburger et al., 2009; Shaul et al., 2019) and may also be a biomarker for inner ear pathology. Impedance variations were also associated with a sudden loss of all residual hearing in patients undergoing hearing preservation surgery (Choi et al., 2017; Shaul et al., 2019).

Impedance variations have also been described in Meniere's disease (MD) (McNeill & Eykamp, 2016). Several theories attempt to explain the fluctuation of CI performance in MD. The most commonly postulated theory is that endolymphatic hydrops cause scala media swelling, thereby altering the position of the electrodes relative to target neurons and leading to changes in implant impedances. A second theory hypothesizes that endolymphatic hydrops directly affects the connection between the electrode and afferent spiral ganglion neurons (Brown et al., 2015). However, scarring, fibrosis, and ossification after implantation make this theory less reliable (Samy et al., 2015). Furthermore, animal studies (Brown et al., 2016) have shown no CI impedance changes after endolymph injection in the cochlea of guinea pigs. Finally, Charlet de Sauvage et al (1997) demonstrated a slow decrease in electrical impedance when distilled water was introduced

into the ear, switching to a drastic reduction when distilled water was replaced by saline, suggesting that the changes were not due to a mechanical disturbance caused by the injection, but rather to a change in electrical recording conditions.

In Immune mediated inner ear disease, (IMIED) physiopathological findings are common to MD and Meningitis. Although these patients are ideal candidates for cochlear implantation, having become deaf after years of hearing, the main problem is cochlear fibrosis or ossification, which has been found to affect 50% of the implanted ears in patients with IMIED (Aftab et al., 2010).

Furthermore, as with MD, the fluctuation of systemic and organ-specific diseases may, over time, change intra-cochlear tissues and fluid composition by altering the functioning of the electrodes and which may then require changes to the fitting parameters. Inner ear disease has been divided into immune-mediated "organ-specific" (os-IMIED) and "systemic" (s-IMIED) (Malik et al., 2012) bearing in mind that some organ-specific disorders could only be the initial manifestation of a more systemic disease.

The aim of the present study was to evaluate whether IMIED patients treated with CI exhibited greater and more significant changes in impedance, over time, compared to a control group. To this end, both s-IMIED and os-IMIED patients were analysed and compared with a control group.

MATERIALS AND METHODS

Subjects

The study group (SG) included 26 post-lingually deafened patients: 16 female and 10 male, 21 unilateral and 5 bilateral CI users, for a total of 31 ears. Age at implantation ranged from 22 to 74years (mean 47, SD 15). All patients in SG were diagnosed as being affected by immune mediated inner ear disease (IMIED). According to García-Berrocal et al (2003), the clinical criteria for the clinicopathological diagnosis of IMIED were applied. Three positive major criteria were applied or, alternatively two positive major and two minor criteria, leading to the suspicion of IMIED in the absence of a specific seromarker or a diagnostic test (*Table 1).* Specific tests, such as

the HSP70 antibody test were not performed, considering that clinical utility appears to be limited with respect to the diagnosis of IMIED (Matsuoka & Harris, 2013). In these patients sensorineural hearing loss (SNHL) was bilateral, rapidly progressive (McCabe, 1979) with the involvement of three contiguous frequencies (Lehnhardt, 1958) and showing initial positive response to corticosteroid treatment (Hughes et al., 1984). Sixteen patients (2 bilateral CI users, 18 ears) presented s-IMIED for which they were treated by immunologists: 3 patients (1 bilateral) had Systemic Vasculitis, 2 Psoriasis (1 bilateral), 2 Sarcoidosis, 1 Systemic Lupus Erythematosus (SLE), 2 Autoimmune Thyroiditis, 1 Sjogren's syndrome, 1 Cogan syndrome, 1 Susac syndrome and 3 Relapsing Polychondritis. Ten patients (3 bilateral CI users) did not have any systemic autoimmune disease and therefore were defined as os-IMIED.

Overall, bilateral cochlear implant had been performed in 2 s-IMIED and 3 os-IMIED patients. With regard to the CI type of the SG, 15 ears were implanted with Advanced Bionics (AB) (E1-E15), 12 with Med-El (E16-E27) and 4 with Cochlear devices (E28-E31). Med-EL patients were implanted with the FLEX electrode series which are free-fitting lateral wall arrays. Among patients implanted with AB, 9 had a Hi-Focus 1J, 1 had a perimodiolar C1 Standard, and 5 had a Mid-Scala Hi-Focus. Cochlear arrays were perimodiolar, 3 with CI24 and 1 with CI24RE.

Generally, patients with S-IMIED and os-IMIED were considered as a single group within SG, as there were no significant differences in the audiological outcomes or impedance values and variations.

The control group (CG) included 26 patients: 16 female and 10 male, 21 unilateral and 5 bilateral CI users, for a total of 31 ears. Patients in CG were implanted following hearing loss unrelated to the immune system (e.g. progressive unknown, ototoxic, otosclerosis, and middle ear disease). The distribution by gender, age, hearing deprivation, and characteristics of CI devices was compared between the two groups (*Table 2*). Due to the differing etiologies, the time between the onset of hearing loss and surgery for CI was significantly longer in CG than in SG. All patients in both

groups were implanted in 2 CI centres: the Department of Sense Organs, Sapienza University, Rome and at the Otology and Auditory Implants and Skull Base Surgery Unit of the University Hospital Pitié Salpêtrière, Paris.

Impedance measurements and audiological evaluation

Fitting sessions were routinely scheduled at 3, 6, 12 and 18 months after surgery. During each fitting session, the impedance values (kΩ) were recorded using the different generations of programming software: Maestro for Med-El, Custom Sound for Cochlear, Sclin-2000 and Sound-Wave for AB devices. A subgroup of 7 patients in SG, defined as *active patients* [10 ears, 5 AB (4 subjects) and 5 Med-El (3 subjects); 4 s-IMIED and 3 os-IMIED] showed a higher number of visits to the CI centre due to a change in hearing perception caused by the reactivation of the autoimmune disease: the impedance values of those patients were collected at every visit to the CI centre. Consequently, the analysis of these patients relies on more measurements than with CG. The impedance variations between each visit were recorded and analysed in comparison to the CG.

All patients underwent an audiological assessment before CI surgery, post-surgery and during the last fitting session. Unaided thresholds at octave frequencies 125-8000 Hz were obtained using a warble tone from an Aurical audiometer (Taastrup, Denmark) and using TDH39 headphones in a standard sound-proof booth. Likewise, aided thresholds were measured in sound field through a loudspeaker (Tangent EVO, Denmark) placed at 0° azimuth and at 1 metre distance from the participant's head. Speech perception performance was evaluated in daily listening mode. The stimulus was presented by two separate loudspeakers for signal and noise, placed at 0°. The speech material consisted respectively of Italian in phonetically balanced bi-syllabic words and sentences for an adult population (Cutugno et al., 2000) and MBAA French bi-syllabic words and sentences (Fraysse et al., 1998). Signal was presented at 65 dB in quiet and with a signal/noise ratio (SNR) + 10 and + 5 dB. Italian patients were further evaluated with Speech Reception Threshold in noise leading to 50% correct sentences (SRT) using the Italian Matrix (It-Matrix) sentence test (Puglisi et

al., 2015).

Statistical analysis

Where appropriate, median (min-max) and average (SD) values were calculated for audiological and impedance outcomes. Audiological and impedance comparative analysis between SG and CG was performed using the Mann-Whitney U test.

Impedances from different devices were pooled after having divided electrodes into basal, middle and apical segments based on frequency allocation. Consequently, for Med-El implants the apical electrodes ranged from 1 to 4, middle from 5 to 8 and basal from 9 to 12. For AB devices, apical electrodes ranged from 1 to 4, middle from 5 to 10 and basal from 11 to 16, except for the one patient who had a C1 standard device with 8 active electrodes, which was considered separately. For Cochlear devices, apical electrodes were considered ranging from 22 to 16, middle from 15 to 9 and basal from 8 to 1. Impedance variations were also assessed separately for each different device.

The *active patients* who showed greater impedance variations, were further analysed, exploring the impedance variation (Δ kΩ) between each fitting session.

Impedance fluctuation (Δ kΩ) was calculated as the level of variation for each electrode compared to the previous check which could result in both negative and positive values. *Active patients* Δ kΩ were compared to CG Δ kΩ; for this group (CG) Δ kΩ was considered as the variation between 12-18 months follow-up. Impedance values were considered as significantly varied when there was a variation ≥4 kΩ (Filipo et al, 2008; Garcia-Berrocal & Ramirez-Camacho, 2000), or more than double the equivalent median value for CG electrodes. Data were analysed using the Statistical Package for Social Sciences (SPSS) version 25.0 (Chicago, IL, USA).

RESULTS

Audiological assessment

The analysis of audiological performances within SG showed no significant differences between os-

IMIED and s-IMIED patients ($p>0.05$). Average CI sound field 125-8000 Hz was 35.1 dB HL for s-IMIED and 36.5 dB HL for os-IMIED. Average word and sentence recognition scores in quiet and in noise SNR+10 were respectively: s-IMIED, words in quiet=83,8%, words in noise SNR+10= 47.8%, sentences in quiet=83.8%, sentences in noise SNR+10=53.7%; os-IMIED, words in quiet=71.2%, words in noise SNR+10= 37.6%, sentences in quiet=89.4%, sentences in noise SNR+10=53.1%. Based on these results, IMIED patients were analysed as one group (Study Group, SG).

The average pre-implant 125-8000 PTA of SG and CG were 111.56 and 108.38 dB HL, respectively. The average CI sound field 125-8000 Hz was 35.8 dB HL for SG and 36 dB HL for CG and these differences therefore were not considered significant ($p> 0.05$).

The average word and sentence recognition score in quiet, in noise at SNR +10 and +5 are reported in Table 3. Differences between the two groups were only significant for speech perception in quiet ($p<0.05$). The It-Matrix test showed no significant differences between the two groups, with mean scores of 7.61 dB (Slope 7.36) for SG and 10.15 dB (Slope 5.93) for CG.

Impedance characteristics and variations

The impedance values recorded after 3, 6, 12 and 18 months following surgery were analysed in all patients. Impedance value fluctuations were observed in both os-IMIED and s-IMIED implanted patients but were not significantly different. Therefore, these patients were analysed as one group. At 3, 6 and 12 month follow-ups a statistical significance was found between SG and CG only for apical and middle segment electrodes ($p<0.05$) (Fig.1). At 18 months a statistical significance remained only for the middle segment electrodes ($p<0.05$) although the SG's impedance at basal segment increased to above 10 kΩ.

Analysis by device

The impedance evaluation in SG when compared to CG showed higher values in patients implanted

with AB devices. The average values for SG and CG were respectively: at 3 months 10.1 kΩ and 8.8 kΩ; at 6 months 10.1 kΩ and 7.4 kΩ; at 12 months 8.8 kΩ and 6.0 kΩ; and at 18 months 10.1 kΩ and 6.5 kΩ. Statistical analysis performed for single electrodes showed that 3 months after surgery there were no significant differences between the groups, except for the first apical electrode ($p < 0.05$). After 6 months, significant differences were found, with higher values for SG patients with 3/16 electrodes ($p < 0.05$). At 12 and 18 months respectively, the electrode levels for 11/16 and 8/16 varied significantly from the CG ($p < 0.05$).

For Med-EL patients, the average values for SG and CG were respectively: at 3 months 7.1 kΩ and 6.8 kΩ; at 6 months 8.1 kΩ and 6.7 kΩ; at 12 months 7.5 kΩ and 6.9 kΩ; and at 18 months 6.95 kΩ and 7.4 kΩ. No significant statistical differences were found between SG and CG at 3 months and 18 months after surgery ($p > 0.05$), while significant differences were found for 5/12 and 2/12 electrodes at the 6 and 12 month follow-ups ($p < 0.05$). This variability between follow-ups is compatible with a fluctuation in impedances.

Finally, in patients with Cochlear devices it was not possible to perform a statistical evaluation due to the small sample size (4 patients). In this group, the maximum follow-up was 12 months. The average values for SG and CG were respectively: at 3 months 11.6 kΩ and 10.9 kΩ; at 6 months 9.9 kΩ and 9.4 kΩ; and at 12 months 10.0 kΩ and 9.4 kΩ.

Figure 2 represents the percentage of electrodes with impedance variations (Δ kΩ)> 4 kOhms or double the mean impedance value of the CG. In the histogram all subjects AB and Med-El were represented and the bilateral ones coded for the right (R) and left (L) ear. Single device impedance variations were recorded between 12- and 18-months. No Cochlear device implanted ears have been represented because no patients reached the 18-month follow-up.

Active Patients

The *active patients* Δ kΩ were identified as those showing a variation ≥4 kΩ in impedance values

recorded between 12 and 18-month follow-up assessments (Fig.2). These patients were also those who requested more frequent fitting sessions and were controlled on average 2.7 times more often when compared to the remaining SG cohort and to the CG. No active Cochlear patients were observed in the follow-up period in which data were collected.

For the comparative analysis between *active patients* and CG, the Δ kΩ values collected between 12 and 18 months of follow-up were used. The Δ kΩ for *active patients* and CG were represented respectively with a 'box-and-whisker' plot for basal, middle and apical electrode segments (fig 3a and b). The box represents the interquartile range (25-75th); the whiskers represent the values outside of 1.5 times the interquartile range, excluding outliers, indicating variability outside the box between which lies the median distribution. Δ kΩ was significantly different between *active patients* and CG in all electrodes' segments. (Table 4).

DISCUSSION

The inner ear can be affected by an immune-mediated inflammatory process that is localized in the ear (os-IMIED) or it can involve other organs or apparatus (s-IMIED). Hearing loss might represent the first manifestation of systemic autoimmune disorder in 25% of patients (Hughes et al., 1984; Veldman, 1987; Aftab et al., 2010). Patients affected by IMIED with severe/profound hearing loss represent ideal candidates for cochlear implantation: better audiological outcomes have been described in implanted IMIED patients compared to patients with other causes of deafness (Hughes et al., 1984; Veldman, 1987; Quaranta et al., 2002; Aftab et al., 2010; Mancini et al, 2018). Whilst these patients represent ideal candidates, the associated systemic disease, the specific damage to inner ear structures and the required daily therapies may influence the results of cochlear implantation. The main issue could be cochlear fibrosis or ossification that has been shown to affect up to 50% of implanted ears in patients suffering from autoimmune and immune-mediated SNHL. Hence, in the presence of severe/profound SNHL earlier implantation may be indicated before post-inflammatory obliterative changes to the cochlea occur (Mancini et al., 2018).

In the present study, data from implanted IMIED patients were compared to data from a control group. Impedance value fluctuations were observed in both os and s-IMIED implanted patients and seemed to be comparable in both groups. Similarly, no significant differences were found in the audiological performances. The audiological outcomes were better in IMIED patients compared to CG. Better performance is not unusual in autoimmune patients, who generally have a rapidly progressive hearing loss with shorter hearing deprivation compared to matched controls (Quaranta et al., 2002; Aftab et al., 2010; Malik et al., 2011). Statistically significant differences between groups were found in quiet only. One possible explanation is the small sample undertaken for measurements in noise, in particular for the adaptive It-Matrix test which was performed in a subset of patients. As for the fixed SNR tests, these are widely used but the analysis is limited by a 'floor and ceiling' effect (Gifford et al., 2008). In fact, there were patients scoring 0% in S/N +10-5 in both CG and SG groups. With regard to the It-Matrix test, mean values were lower in SG patients and differences between the groups were greater than 1 dB, which is considered a meaningful difference for outcome comparison (Puglisi et al., 2015).

Although audiological performances were excellent, IMIED CI users showed, on average, higher impedance values compared to controls. Impedance values vary among different manufacturers, depending on follow-up timing and type of electrodes. Prenzler et al (2018) reported an impedance value <10 kΩ at 12 month follow-up in patients implanted with Med-El Flex28 synchrony devices. Wang et al (2017) found similar results in patients implanted with Med-El Standard electrode array in round window approach surgery. De Ceulaer et al (2003) found impedance values <10 kΩ in Nucleus straight and contour electrodes. AB impedance values for both CII and 90K implants are < 10 kΩ at initial activation (Masoud et al., 2009), while follow-up at > 24 months ranged between 7.8 and 8.95 kΩ for basal, 6.4 and 7.8 kΩ for medium and apical electrodes in 1J and Helix electrode carriers respectively (Filipo et al., 2008). It could therefore be assumed that impedance values in most devices are normally placed < 10 kΩ and that CG impedance values at 12-18 months are in line with those described in the literature.

SG mean impedance values were higher at 3 months following surgery, remained higher over time up to the 18-month follow-up and were generally significantly different from CG values for the mid and apical electrode segments. In the basal segment, the impedance values were not significantly different between the groups. This result may be because even in CG patients the average impedances for the basal turn are higher than in the other cochlear segments. Regardless of the type of surgical access, round window or cochleostomy (Atturo et al., 2014), trauma arising from the insertion of the electrode could induce an inflammatory reaction, fibrous deposition and increased electrode impedance. It is also possible that there are differences in the capacity for inflammatory response in the different regions of the cochlea, due to anatomical variations such as vascular drainage through the inferior cochlear vein (Atturo et al., 2018) or even the width of the cochlear duct. Furthermore, there are many more immune competent cells in the basal turn of the cochlea compared to the other segments (Seyyedi & Nadol, 2014). This suggests that if an inflammatory response were to arise within an implanted cochlea it would probably begin at the basal turn of the cochlea. Similar results were described by Tubishi et al (2011) who reported a significant increase in impedances of all electrodes after surgery and up to 3 months follow-up, while a stable reduction in electrode impedance values at one year was observed only for the apical and middle segments. Although the purpose of the study was not to make a comparison between the different devices, the impedance values for AB and Cochlear implants patients, as study group, were on average higher than for Med-El, while for the latter more electrodes in each single carrier were involved in impedance variation. No statistical analysis was attempted due to the small size of the study groups, and because mean values could possibly depend upon technical differences between devices. This finding may depend on the patient's anatomy and the degree of inflammatory involvement of the cochlear segments (Keithley et al., 1998). However, this finding could also be the result of the characteristics of each type of electrode: their surface size, the surrounding tissue and the position of its contact could all influence impedance values and therefore, they may vary between manufacturers (Busby et al., 2002). The way in which the electrode lies in the cochlea,

perimodiolar or lateral wall and closer to the modiolus in AB and cochlear devices, also seems to be very important: De Ceulaer et al (2003) suggested that the modiolus-hugging design, with a closer and more permanent contact between the electrodes and the modiolus, could play a role in higher impedance values.

A further finding of the present study was an abnormal impedance fluctuation recorded during subsequent fitting sessions. Eight patients, defined as *active patients* (4 s- and 3 os-IMIED), required a greater number of CI fittings due to changes in listening that coincided with a worsening of systemic symptoms or vertigo attacks and / or instability. Of these subjects 4 subjects were AB (1 bilateral) and 3 Med-El (3 bilateral) for a total of 10 ears. Indeed, these *active patients* showed an increase of 8 times the average value found in CG, and an impedance variation ≥ 4 kΩ involving 33-56 % of the electrodes. The reference value of 4 kΩ (defined as "peak") was described by Choi et al (2017) in a large cohort of CI patients and corresponded to a median increase in the impedances correlated, once again, to the subjective variation of hearing loss, dizziness or tinnitus. Nevertheless, it should not be considered as an absolute reference value as it more likely depends upon the characteristics of the study groups and the devices employed in the analysis.

Although the impedance changes observed in *active patients* from this study do not always reach the 4 kΩ value described by Choi et al, these changes were significantly different when compared to CG, and these sudden changes were significant enough to affect the perception of the active patients in this study (Newbold et al, 2014; Wilk et al., 2016).

It has been suggested that impedance peaks may be a biomarker of inner ear pathology, due to the association with vertigo (Neuburger et al., 2009) or sudden loss of all residual hearing (Tubishi et al., 2011; Shaul et al., 2019). In the present study, systemic and vestibular symptoms were reported by IMIED *active patients*. Unfortunately, these patients, due to their worsening clinical symptoms, are often not willing to undergo audiological evaluation, and therefore these changes cannot be adequately quantified over time. These patients were treated with the standard steroid dosage recommended to improve symptoms, reduce inflammatory processes and ultimately prevent fibrosis

of the inner ear. Despite the improvement in symptoms following therapy, in 6.45% of patients there was, over time, an overall progressive increase in impedance values.

A major factor in determining impedances is the volume and composition of bulk tissue surrounding the implanted electrode array (Tykocinski et al., 2005). Clark et al (1995) described how high levels of impedance values significantly correlated with the amount of tissue surrounding the electrode contacts and with the presence of inflammatory cells. Clark et al recommended that routine monitoring of impedance levels should be undertaken as an indicator of cochlear tissue changes and electrode surface roughening. In addition, in an animal model of chronic high-rate stimulation (Xu et al., 1997) higher levels of fibrosis were found in the cochleae as well as the presence of inflammatory cells that exhibited greater impedance levels.

A limitation to the present study is its retrospective nature, which has, by its construct, impeded its capacity to record impedance variations utilising the same timing and number of access points between SG and CG. Despite this, SG showed higher overall impedance values and number of visits to the centre usually corresponding to the variations in their symptoms, which were never observed in CG.

To our knowledge, the present study is the only retrospective analysis which has focussed on variations in impedance in autoimmune patients with cochlear implants. The data suggest that impedance fluctuations may be considered a sign of reactivation of the autoimmune inner ear pathology: electrodes are a privileged point of observation within the cochlea and impedance values can provide information on the biology surrounding the implant. The increase in impedance in patients with a history of immune disease could be addressed through medical therapy to arrest the progression of fibrosis.

Patients affected by IMIED represent good candidates for CI surgery: good audiological performances can be achieved just as with non-IMIED patients. Inner ear pathology reactivation may require more access to the CI unit for appropriate pharmacological approaches and CI fittings. Impedance evaluation could be used as an early warning sign or indicator of IMIED reactivation

and could also aid in the decision-making process when considering therapeutic approaches.

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DECLARATION OF INTEREST STATEMENT

The authors declare that they have no conflicts of interests.

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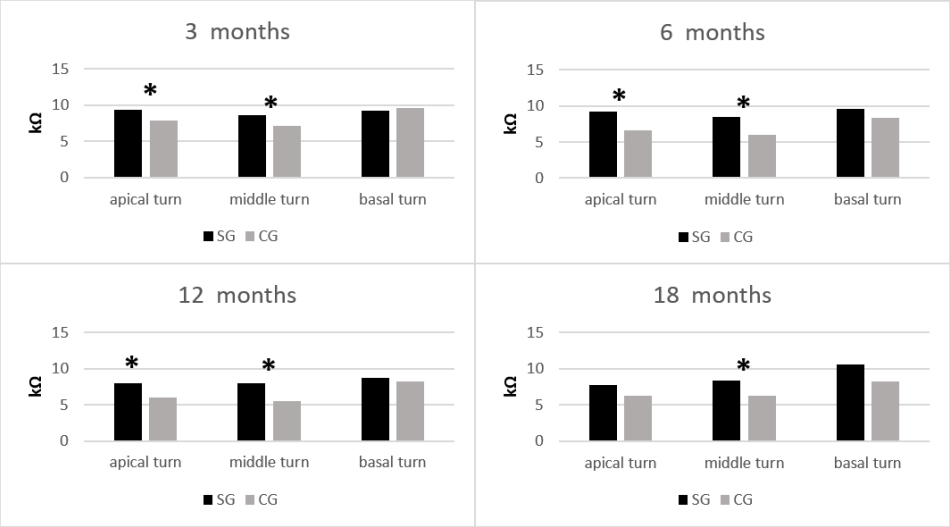
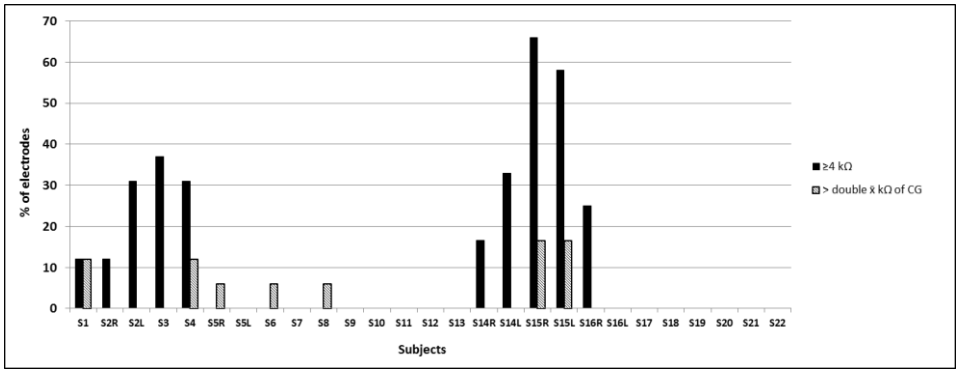
FIGURES

Figure 1



Impedance values for apical, middle and basal electrode segments in the Study Group (SG) and Control Group (CG) after 3, 6, 12 and 18 months following surgery. * shows the significant values ($p<0.05$).

Figure 2

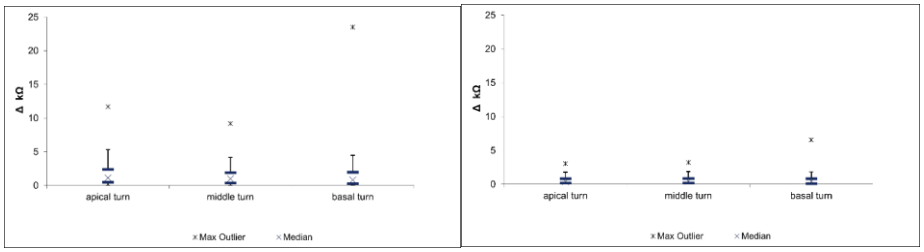


The study group histogram represents the percentage of electrodes showing impedance variations (Δ kΩ) > 4 kOhms or double the mean impedance value of the control group. Single device impedance variation was recorded at 12 and 18 months.

S1-S13: AB devices; S14-S22: Med-El devices. For bilateral subjects implanted side was labeled for R (right) and L (left) ears. No Cochlear device (S23-26) subjects were represented because no patient reached the 18-month follow-up.

Black columns indicate a variation > 4 kΩ , striped columns indicate variations equivalent to double the mean value ($\bar{x}$) of CG. Patients with Δ kΩ > 4 kOhms have been considered as active patients [10 ears, 5 AB (4 subjects) and 5 Med-El (3 subjects)].

Figure 3



Impedance variations (Δ kΩ) for apical, middle and basal electrode segments in different fitting sessions obtained for *active patients* (3a) and CG (3b). The whiskers represent the highest and lowest values recorded, indicating variability outside the upper and lower quartiles, between which lies the median distribution.

TABLES

Table 1 Clinical criteria for AIED [27]

Major criteria	**Minor criteria**
Bilateral involvement	Unilateral involvement
Presence of systemic autoimmune disease	Young middle aged female
High levels of Antinuclear antibody	Serum reactivity against HSP70
Reduced number of naïve T cells (CD4RA) Recovery rate of more than 80%	Positive response to steroid treatment (recovery rate < 80%)

Table 2. Characteristics of study group (SG) and control group (CG). Results are represented as average and minimum-maximum. Bold indicates statistical significance.

	SG	**CG**	**p***
	Average (min-max)	**Average (min-max)**	
Subjects	26 (5 bilateral)	26 (5 bilateral)	
Sex (male)	10	10	
CI number	31	31	
Age at implant (years)	47 (22-74)	55 (24-80)	>0.05
Time between onset of hearing loss and CI surgery (months)	36 (7-552)	360 (4-864)	**<0.001**
Deprivation (months)	17.28 (0-72)	14.19 (0-72)	>0.05

**Mann–Whitney U test*

Table 3. Audiological outcomes in SG and CG. Audiologic outcomes. Results are represented as median and minimum and maximum. Bold indicates statistical significance. [a] Not all participants were able to complete the It-Matrix test (14 subjects in SG and 18 in CG).

	SG	CG	p
	Median (min-max)	**Median (min-max)**	
PTA pre-surgery (dB)	111.56 (85-125)	108.38 (73.66-125)	>0,05
CI free field PTA (dB)	35.8 (21-50)	36 (21.7-64.8)	>0,05
Words quiet (%)	77.47 (41-100)	62.22 (10-92.5)	**<0.001**
in noise SNR+10	42.69 (0-97)	37.59 (0-90)	>0,05
in noise SNR +5	31.06 (0-83)	23.87 (0-87.5)	>0,05
Sentences quiet (%)	86.25 (50-100)	70.18 (8-100)	**<0.05**
in noise SNR+10	44.88 (0-100)	34.98 (0-100)	>0,05
in noise SNR +5	24.82 (0-100)	19.93 (0-100)	>0,05
It-Matrix (dB) [a]	7.61 (-2.0 -28)	10.15 (1.9-21.2)	>0,05
Slope	7.36 (2-16)	5.9 (2-10)	>0,05

Mann–Whitney U test

Table 4. Δ kΩ characteristics in *active patients* and CG. Results are represented as median and minimum-maximum-standard deviation. Bold indicates statistical significance.

	Active patients	**CG**	**p**
	Median	**Median**	
	(min; max; st.dev.)	**(min-max- st.dev.)**	
Apical segment	1.12 (0; 11.7; 2.44)	0.37 (0; 3.01; 0.62)	**<0.001**
Middle segment	1.00 (0; 9.2; 1.79)	0.46 (0; 3.1; 0.59)	**<0.001**
Basal segment	0.8 (0; 23.5; 2.26)	0.46 (0; 6.57; 1.00)	**<0.001**

Mann–Whitney U test