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Human Otopathologic Findings in Cases of Folded Cochlear Implant Electrodes

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Abstract

Hypothesis—We hypothesize that human cases of cochlear implantation (CI) with folding of the electrode array will demonstrate greater degrees of intracochlear ossification, lower spiral ganglion neuron (SGN) counts, and poorer audiometric outcomes.

Background—CI electrode array folding, such folding of the proximal array, is a relatively common surgical complication that can occur with forceful electrode insertion and may be an important and avoidable factor affecting implant outcomes. However, otopathologic findings and audiologic outcomes of human cases where folding of the implant electrode array is observed remain undefined.

Methods—Specimens from a human temporal bone repository having undergone CI during life were evaluated. Specimens with folding of the electrode array on histological analysis constituted study cases. Electrode-matched specimens without array folding constituted controls. All specimens were examined by light microscopy and histopathologically described. Intracochlear fibrosis, osseous tissue and SGN counts were measured. Pre- and post-operative word recognition scores were also compared.

Results—Cases with folded electrodes showed greater volumes of intracochlear osseous tissue than controls, which was most prominent in areas adjacent to folding. Both cases and controls demonstrated similar amounts of fibrous tissue. Folded cases showed decreased SGNs when compared to the contralateral ear, whereas controls showed stable SGN populations between ears. In this small cohort, post-operative hearing outcomes were similar between groups.

Conclusion—Atypical fibro-osseous changes and lower SGN counts are observed in cases of CI electrode folding. Future studies are necessary to determine if recognition and correction of folding can prevent long-term intracochlear changes.

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Keywords

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Introduction

Cochlear implantation (CI) provides hearing restoration to patients with severe to profound sensorineural hearing loss.^{1–3} Atraumatic electrode placement is a desired surgical technique that has increasingly been felt to be an important factor in post-operative implant performance. Many studies have shown that insertional trauma, over insertion, and interscalar electrode translocation from scala tympani (ST) into scala vestibuli (SV) lead to poorer audiometric outcomes.^{1–3}

Both acute and long-term mechanisms have been proposed to lead to poor functional results.^{1,2} Acute consequences of insertional trauma may include disruption of intracochlear structures, such as the osseous spiral lamina, with traumatic loss of spiral ganglion neurons.¹ Suboptimal electrode placement leads to initially poorer hearing outcomes that improve with deactivation of overlapping electrodes, but in severe cases this complication may require electrode removal and reimplantation.^{3,4} Studies of human temporal bones (TBs) of patients having undergone CI show additional long-term intracochlear changes following implantation, including fibrous proliferation around electrode arrays and neo-ossification within the cochlear lumen.⁵ Preliminary evidence suggests that these post-implant sequelae may intensify in cases with acute traumatic electrode placement and may correlate with worse post-implant word recognition scores.^{6,7}

Recently, cochlear device manufacturers have designed new electrodes with precurved conformations that allow for perimodiolar placement within the ST. Using a sheath or stylet, these electrodes may be placed atraumatically into the ST; however, precurved designs also present a greater potential for folding of the electrode array than with straight designs^{4–6,8,9} At the time of insertion, surgeons may identify tactile feedback with significant intracochlear trauma,⁸ but subtle changes from electrode folding from over insertion may not be appreciated. Ultimately, folding of the array may cause damage to intracochlear structures leading to both acute and long-term intracochlear changes.

We hypothesize that folding of the CI electrode array constitutes a severe form of acute intracochlear trauma that may lead to intracochlear ossification, SGN loss, and ultimately, poor audiometric performance. To date long-term intracochlear changes, such as new fibro-ossification and SGN counts have not been investigated in cases of CI electrode array folding. Herein, we examine the histologic findings and audiologic outcomes of human CI cases where folding of the implant electrode array is observed.

Materials and Methods

Specimens

A total of 80 TB specimens from the Otopathology Laboratory at Massachusetts Eye and Ear Infirmary from patients having undergone unilateral or bilateral cochlear implantation

during life were evaluated. Inclusion criteria were: 1) right and left TBs available, 2) insertion of the electrode through an extended round window approach as determined by evidence of drilling anterior and inferior to and incorporating the round window membrane on serial histologic examination, 3) comparable pre-operative interaural speech detection (<15dB difference) and word recognition scores (WRS) (<15% difference), 4) similar etiology and duration of hearing loss between ears, and 5) available post-operative WRS. Specimens with evidence of 1) intracochlear fibro-ossification on pre-implant imaging or 2) osseous change to the otic capsule due to other pathologies were excluded.

All specimens that met the above criteria were histologically analyzed: 1) “Folded” specimens exhibited folding and overlap of the intracochlear electrode array and 2) “Control” specimens exhibited electrode placement entirely within the ST without evidence of electrode folding or gross intracochlear damage (basilar membrane disruption or fracture of the osseous spiral lamina or modiolus).

Histological Techniques

All TBs were fixed in 10% buffered formalin and decalcified in ethylene diamine tetra-acetic acid. The TBs were dehydrated in alcohol and embedded in araldite with the electrode *in-situ* (Patients 2,4 & 5)⁹ or in celloidin with the electrode removed, for sectioning. Sections were cut in a horizontal plane (20 µm thickness) and stained with osmium (Patients 2&4), toluidine blue (Patient 5)⁹ or hematoxylin and eosin. Sections were then mounted on glass slides and histopathologically described.¹⁰

2-D Reconstruction of the Cochlea

Every tenth section of the TBs were studied and the cochlear duct and Rosenthal’s canal were reconstructed by conventional 2-D methods.¹⁰ Segmental and total numbers of SGN were counted and normalized by age-matched controls of specimens with no known cochlear neuronal disease.⁵

‘SGN count’ was quantified as the difference in normalized SGN (% age-matched controls) between the implanted ear of interest and contralateral ear within each patient:

$^{11} (SGN_{\text{implanted ear of interest}}(\%) - SGN_{\text{contralateral ear}}(\%)) \times 100\%$. This permitted a comparison across patients who had otherwise widely different absolute SGN populations.¹¹ Patient 4 was excluded from this analysis because pre-implantation testing did not meet criteria for comparable degrees of hearing loss between ears.

The angle of insertion (AOI) was determined by evaluating the most apical section of the cochlea containing a fibrous sheath around the electrode tip and the entry point of the electrode array at the extended round window opening on 2-D reconstructions.⁶ If no fibrosis was observed along the course of the electrode, the AOI was estimated from intraoperative radiographs.

3-D Reconstruction of the Cochlea

The technique for 3-D reconstruction of the cochlea has been previously described and is demonstrated in Figure 1.^{6,12} Digital images of every tenth slide were captured at 1.25×

magnification under a light microscope with a high-resolution camera (Olympus BX51, Olympus DP71). Images were aligned, converted to greyscale, and segmented using Amira software (version 6.0.0, FEI, Hillsboro, OR). A range of 30–40 images were used for 3-D reconstruction of each specimen. An image of a scale at 1.25× magnification was uploaded with ImageJ software (<http://rsbweb.nih.gov/ij>, Bethesda, MD) to determine the distance per pixel for images.

All images were analyzed to identify new osseous tissue (dark-purple bone and bright-pink osteoid) and fibrous tissue (light pink) within the cochlear lumen, as has been previously described.^{6,10} Differentiation of new osseous tissue from fibrous tissue was performed under high (4–10×) magnification. Osteoid can be clearly seen as staining intensely and homogeneously with eosin (dark pink), whereas fibrous tissue stains less intensely with eosin (light pink, less dense). Each 2-D image was segmented into the cochlear lumen spiral lamina, electrode, osseous tissue, and fibrous tissue (Figure 1A). The cochlear lumen was not differentiated into separate scalae as these were frequently indistinguishable in cases: (ie: cases with extensive fibro-ossification of all three scalae). 3-D reconstructions were used to determine absolute volumes of all materials. Percent volumes of osseous and fibrous tissue were defined as the volume of (osseous or fibrous) tissue divided by the volume of the

cochlear lumen not occupied by the electrode: $\frac{V_{tissue}}{V_{lumen} - V_{electrode}} \times 100\%$.⁷ All values were

measured within each segment and throughout the entire cochlea (Figure 1). The length of array folding was quantified from 3-D reconstructions of the electrode array (Figures 2A–D).

Hearing Outcomes

Pre-operative hearing was assessed bilaterally by reported speech reception/detection thresholds and WRS (Northwestern University Auditory Test Number 6 Word (NU-6W)¹³/Central Institute for the Deaf (CID) W-22¹⁴/Iowa sentences¹⁵). Available post-operative monosyllabic WRS (NU-6W or Consonant-Nucleus-Consonant Whole Word (CNCWW)¹⁶ scores), which have been shown to be comparable,¹⁷ were recorded from a range of 1.5–6 years following implantation. To assess for potential hearing changes occurring as the result of progressive intracochlear fibro-ossification, we evaluated the trajectory of post-operative hearing in cases from early (< 12 months) to late (> 2 years) follow-up for patients with available scores within both time-frames.

Statistical Analysis

Quantitative values were reported as the mean and standard deviation of each group. Student's t-test (unpaired, two-tailed) and Fisher's exact test were used to compare quantitative and qualitative variables, respectively, between two groups. Pearson's correlation coefficient and bivariate analyses were used to determine correlations between quantitative variables. Statistical significance for all tests was set as $p < 0.05$. All analysis was performed using GraphPad Prism (v.7.0, La Jolla, CA).

Results

Patient and Implant Characteristics

Four cases with folding of the electrode array within the basal turn were identified: two cases with bilateral implants and two cases with unilateral implants. In bilateral cases, the contralateral electrode was found to be without folding. One unilateral case was implanted twice on the same side: the first implant showed folding of the distal array on post-operative imaging and was explanted 1 year later with reimplantation of an electrode that resulted in recurrent folding of the array in the basal turn. Five controls with unilateral, normal electrode conformation were also identified. Folded and control electrode contours are shown in Figure 2.

All included patients experienced progressive SNHL and were post-lingually deafened. Additional patient characteristics were comparable between folded and control groups: duration of hearing loss (3.8 ± 1.7 vs. 9.6 ± 5.3 yr), age at implantation (70 ± 7 vs. 73 ± 7 yr) and duration of implant use before death (8.3 ± 4.3 vs. 10.3 ± 2.2 yr) (Table 1). Within the folded group, a higher proportion of patients were implanted with a curved electrode ($n=3$, $\text{AOI}=300 \pm 160^\circ$) compared to a straight electrode ($n=1$, $\text{AOI}=390^\circ$), whereas in the control group, the converse was observed ($n=1$ curved electrode, $\text{AOI}=360^\circ$ and $n=4$ straight electrodes, $\text{AOI}=330 \pm 40^\circ$).

Increased Ossification in Cases with Folding of CI Electrode Array

Throughout the ascending basal turn of the cochlea, folded cases qualitatively showed more osseous tissue compared to controls (Figure 3). Quantitatively, there was greater neo-ossification within Segment I of folded cases versus controls ($29.2 \pm 12.2\%$ vs $6.6 \pm 4.9\%$, $p < 0.05$), which corresponds to the region of array folding. (Figure 4A) Additionally, little to no osseous tissue formation was observed within the basal turn of 4 of 5 control cases. Intracochlear structures, apart from the drilling site of the otic capsule, remained identifiable and relatively normal in appearance (Figure 3B).

In terms of degree of proximal array folding, there was some variability between the four folded cases (Table 1). When the degree of folding was compared with the degree of new ossification, a strongly positive relationship was identified ($r=0.97$, $p < 0.05$). No significant association was identified between degree of neo-ossification and patient age at the time of surgery or AOI ($r=0.11$, $p=0.8$; $r=0.19$, $p=0.6$, respectively). In this small cohort, intracochlear ossification was also independent of the type of electrode (straight vs. curved) ($p=0.4$).

Similar Fibrosis in Cases with and without Folding of the CI Electrode Array

We quantified the amount of fibrosis within the cochlea similarly to osseous tissue and found no difference in fibrosis between folded cases and controls (Figure 4B). In contrast to results for osseous tissue, there was a strong, but non-significant association between degree of fibrosis and length of array folding ($r=0.90$, $p=0.1$). Additionally, we found weak and non-significant correlations between the degree of fibrosis and patient age at time of surgery, type of electrode, or AOI ($r=0.41$, $p=0.3$; $p=0.3$; $r=-0.34$, $p=0.4$, respectively).

Spiral Ganglion Neuronal Survival

SGN counts were decreased in folded cases ($-14.1 \pm 13.4\%$), while controls showed no interaural SGN count differences ($0.7 \pm 5.2\%$) (Figure 4C). When differentiating between segments of Rosenthal's canal, folded cases showed the greatest difference in SGN counts in Segment I and II ($-21.6 \pm 16.5\%$ and $-28.3 \pm 17.0\%$, respectively), which correspond to the locations of folding of the electrode array in each case. In contrast, SGN counts in Segments I and II were similar or slightly higher for all control cases ($7.3 \pm 14.6\%$ and $4.8 \pm 4.9\%$). Additionally, within the folded group, the specimen with the greatest length of array folding showed the greatest SGN count difference in Segment I and II SGN (-44.7% , -52.3%). The other two specimens showed lower SGN counts, but to a lesser degree (Seg I: -7.7% , -16.3% , and Seg II: -12.4% , -16.2%).

Both ossification and lower SGN counts were more pronounced in folded cases than controls. SGN counts in Segments I, II, and throughout the entire cochlea were negatively correlated with the amount of ossification within these areas ($r = -0.72, p < 0.05$; $r = -0.71, p = 0.05$; $r = -0.87, p < 0.01$, respectively). SGN count was not significantly correlated with intracochlear fibrosis, CI use, or AOI and no difference in SGN count was observed between electrode types ($r = -0.05, p = 0.9$; $r = 0.69, p = 0.07$; $r = -0.47, p = 0.2$; $p = 0.5$, respectively).

Hearing Outcomes

Pre-operatively, both groups had minimal WRS bilaterally (Table 1) and the mean post-implantation follow-up time was comparable for folded and control cases (3.5 ± 1.5 yr vs. 4.1 ± 1.3 yr, $p = 0.68$). Absolute post-operative WRS (NU6/CNC) were comparable between folded and control cases ($34 \pm 24\%$ vs. $44 \pm 32\%$), but scores were highly variable within both groups (Figure 5A).

Analysis of early to late post-operative hearing results was performed on one folded and four control cases, given available data. The patient with folded electrode showed a decrement in WRS of 29% while four patients (control group) showed a mean improvement in WRS of $14 \pm 10\%$ over time (Figure 5B). Specimens with greater volumes of osseous tissue within Segment I and throughout the cochlea showed less improvement from early to late post-operative WRS ($r = -0.92, p < 0.05$; $r = -0.95, p = 0.01$, respectively). No significant correlations were found between post-operative WRS or trajectories of WRS and age at surgery ($r = -0.35, p = 0.4$; $r = 0.38, p = 0.5$, respectively), duration of CI use ($r = 0.46, p = 0.2$; $r = -0.14, p = 0.8$, respectively), or AOI ($r = 0.38, p = 0.4$; $r = 0.07, p = 0.9$, respectively).

Discussion

In this TB study, we found significantly different intracochlear histopathological changes in specimens with folding of the CI electrode array when compared to cases without folding of the electrode array. Overall, folded cases showed greater volumes of intracochlear osseous tissue than controls, which was most prominent in areas adjacent to sites of folding. In these same areas, folded cases showed lower SGN counts when compared to the contralateral ear, whereas controls showed stable interaural SGN populations. Interestingly, the degree of intracochlear fibrosis was not significantly different between cases and controls. While post-

operative hearing outcomes were similar between groups, a dramatic post-operative decline in hearing function was observed in one case of electrode folding.

We find that the length of array folding correlated with intracochlear ossification throughout the entire cochlea. This variable may partially explain the range of intracochlear changes observed within our cohort and further strengthens the association between array folding and intracochlear damage. Our cases demonstrate a correlation between the amount of intracochlear ossification and local SGN counts, and SGN loss was most notable in two cases with the largest length of electrode folding and most substantial degree of intracochlear ossification. In fact, a similar association between severe ossification and SGN loss has been found in other pathologies causing intracochlear ossification.¹⁸

Folding of an electrode array appears to represent a form of severe acute intra-cochlear trauma, with resultant osseous deposition and SGN loss. While bony drilling at the extended round window opening site was performed in both cases and controls, and may result in severe damage to the basal cochlear turn, in our series, severe intracochlear trauma was observed only in cases of electrode folding. Previous studies have investigated the effect of CI placement on intracochlear anatomy in human TBs and have shown a positive association between gross intracochlear trauma and new osseous tissue formation within the scala media and SV.⁷ Our findings are consistent with this study and additionally demonstrate that folding of a CI electrode array leads to local intracochlear osseous change that is dependent on the degree of electrode folding. In terms of functional outcomes, there is conflicting evidence regarding the impact of such intracochlear changes on hearing. This may be due, in part, to small sample sizes, variation in follow-up times and variable post-operative hearing gains between patients.^{6,7,19} A more accurate method of evaluating slowly progressive, chronic intracochlear changes may be the trajectory of post-operative CNC scores. Initial hearing gains may not be sustained if progressive cochlear ossification occurs, leading to SGN loss and decreased efficacy of electrical stimulation. While we provide initial evidence of this relationship, a larger study is necessary to fully answer the question.

As CI function depends on populations of SGNs,^{7,11} many groups have investigated whether electrical stimulation results in survival or death of SGN. Animal studies have shown progressive degeneration of SGN following inner hair cell death,²⁰ with a potential protective effect of electrical stimulation of CI.²¹ Human TB studies have shown that in CI patients with symmetric hearing loss a mean overall degeneration in SGNs occur; however, within segments of the cochlea receiving stimulation there appeared to be a local protective effect. In areas not receiving stimulation there appeared to be larger SGN loss.^{22,23} In line with these studies, we showed that in the absence of electrode folding and with minimal intracochlear damage, stable populations of SGNs are observed. Therefore, loss of SGNs in our cases of electrode folding may not be due to electrical stimulation, but could potentially result from trauma and osseous tissue deposition; suggesting that electrode misplacement may override protective effects of electrical stimulation. Additionally, intracochlear ossification may have detrimental effects on SGN populations by partially occluding the inferior cochlear vein. This vein sits in close proximity to the round window membrane and receives drainage from the spiral ganglion and scala tympani through the posterior spiral vein.¹⁰

Our findings show that folding of CI electrodes causes significant acute intracochlear damage, but a clinically important question remains: does early recognition and correction of CI misplacement prevent long-term degeneration? Multiple mechanisms have been proposed to explain implant-induced ossification, and animal models support the idea that damage to and exposure of the endosteum of the otic capsule or soft tissues within the cochlea may stimulate intracochlear ossification, potentially through an osteoprotegerin-mediated pathway.^{24,25} Considering this mechanism in our study, insertional damage from misplaced electrodes could stimulate immediate osseous changes. Alternatively, chronic placement of a folded array may exert pressure on intracochlear structures leading to long-term damage and progressive ossification. If the latter is the case, then withdrawal and reinsertion of a CI electrode in the proper configuration could prevent further degeneration. While all specimens in our study were implanted for multiple years before death, TB studies of specimens with shorter implant durations may provide more insight into the timing of intracochlear changes observed following CI. Such findings may also be translatable to precurved devices, which are at increased risk for array folding at insertion.²⁶

This study is limited by its retrospective nature, small sample size and available clinical data. We attempted to be consistent with the timing of post-operative outcomes, but reported WRS varied between 1–6 years after surgery. Electrode model and stimulation mode may affect results and our inclusion criteria prevented comparison of a single type of electrode. However, both groups contained specimens implanted with straight and precurved Nucleus-type electrodes. Our findings suggest that electrode type does not appear to be associated with hearing outcomes, although it should be noted that included electrode models represent those available in the 1990s, when implantations occurred. An important assumption in our analysis is that folding of the electrode array occurred on insertion, leading to intracochlear damage and long-term degeneration. Although less likely, we cannot exclude the possibility that electrodes were placed correctly and intracochlear tissue formation (for unrelated reasons) caused subsequent array folding. Unfortunately, immediate post-operative imaging was not available to investigate this. A thorough review of our temporal bone collection did not reveal any cases of distal tip foldover. Further study is needed in histologically prepared cases of distal tip foldover to determine whether or not this complication results in intracochlear changes similar to those found in cases of proximal electrode folding. Finally, due to the limited number of specimens available, two cases in the folded group were implanted bilaterally, which may affect calculations of interaural SGN counts; however, in both cases the contralateral implant was placed without folding.

Despite these limitations, our study is the first to describe intracochlear changes following folding of CI electrode arrays. We find that this complication leads to local intracochlear ossification and SGN loss, which is influenced by the degree of array folding and appears to be limited to the cochlear segment affected by folding. These findings may impart negative consequences for long-term hearing outcomes, and highlight the need for proper, atraumatic initial insertion of CIs. Further analysis is necessary to determine if intracochlear degeneration may be prevented via immediate identification through intra-operative imaging^{26,27} with rapid correction of CI electrode placement.

Conclusion

Histological analysis of human temporal bone specimens identified intracochlear ossification and decreased SGN populations adjacent to areas of and in proportion to the degree of folding of CI electrode arrays.

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References

1. Finley CC, Skinner MW. Role of electrode placement as a contributor to variability in cochlear implant outcomes. *Otol Neurotol*. 2008; 29:920–928. [PubMed: 18667935]
2. Wardrop P, Whinney D, Rebscher SJ, Roland JT Jr, Luxford W, Leake PA. A temporal bone study of insertion trauma and intracochlear position of cochlear implant electrodes. I: Comparison of Nucleus banded and Nucleus Contour electrodes. *Hear Res*. 2005; 203:54–67. [PubMed: 15855030]
3. Zuniga MG, Rivas A, Hedley-Williams A, et al. Tip fold-over in cochlear implantation: case series. *Otol Neurotol*. 2016; 38:199–206.
4. Lassig AAD, Zwolan TA, Telian SA. Cochlear implant failures and revision. *Otol Neurotol*. 2005; 26
5. Schuknecht HF. Surgical Pathology: Cochlear Implantation. In: Merchant SN, Nadol JB, editors. *Schuknecht's Pathology of the Ear*. Shelton, CT: People's Medical Publishing House-USA; 2010. 842–850.
6. Li PM, Somdas MA, Eddington DK, Nadol JB. Analysis of Intracochlear New Bone and Fibrous Tissue Formation in Human Subjects With Cochlear Implants. *Ann Otol Rhinol Laryngol*. 2007; 116:731–738. [PubMed: 17987778]
7. Kamakura T, Nadol JB Jr. Correlation between word recognition score and intracochlear new bone and fibrous tissue after cochlear implantation in the human. *Hear Res*. 2016; 339:132–141. [PubMed: 27371868]
8. Kratchman LB, Schuster D, Dietrich MS, Labadie RF. Force Perception Thresholds in Cochlear Implantation Surgery. *Audiol Neurotol*. 2016; 21:244–249. [PubMed: 27576674]
9. Nadol JB, Ketten DR, Burgess BJ. Otopathology in a case of multichannel cochlear implantation. *Laryngoscope*. 1994; 104:299–303. [PubMed: 8127186]
10. Schuknecht HF. *Pathology of the Ear*. Philadelphia, PA: 1993.
11. Seyyedi M, Viana LM, Nadol JB Jr. Within-subject comparison of word recognition and spiral ganglion cell count in bilateral cochlear implant recipients. *Otol Neurotol*. 2014; 35:1446–1450. [PubMed: 25120196]
12. Somdas MA, Li PM, Whiten DM, Eddington DK, Nadol JB Jr. Quantitative evaluation of new bone and fibrous tissue in the cochlea following cochlear implantation in the human. *Audiol Neurotol*. 2007; 12:277–284. [PubMed: 17536196]
13. Tillman TW, Carhart R. An expanded test for speech discrimination utilizing CNC monosyllabic words. Northwestern University Auditory Test No. 6. SAM-TR-66-55. Tech Rep SAM-TR. 1966:1–12.
14. Hirsh IJ, Davis H, Silverman SR, Reynolds EG, Eldert E, Benson RW. Development of materials for speech audiometry. *J of Speech and Hear Disorders*. 1952; 17:321–337.
15. Tyler R, Holstad B. A closed set speech perception test for hearing-impaired children. Iowa City: University of Iowa. 1987

16. Peterson GE, Lehiste I. Revised CNC lists for auditory tests. *J of Speech and Hear Disorders*. 1962; 7:62–70.
17. Causey GD, Hermanson CL, Hood LJ, Bowling LS. A comparative evaluation of the Maryland NU 6 auditory test. *J Speech Hear Disord*. 1983; 48:62–69. [PubMed: 6620995]
18. Nadol JB, Hsu W. Histopathologic correlation of spiral ganglion cell count and new bone formation in the cochlea following meningogenic labyrinthitis and deafness. *Ann Otol Rhinol Laryngol*. 1991; 100:712–715. [PubMed: 1952661]
19. Kawano A, Seldon HL, Clark GM, Ramsden RT, Raine CH. Intracochlear factors contributing to psychophysical percepts following cochlear implantation. *Acta Otolaryngol*. 1998; 118:313–326. [PubMed: 9655204]
20. Xu SA, Sheper Rk, Chen Y, Clark GM. Profound hearing loss in the cat following the single co-administration of kanamycin and ethacrynic acid. *Hear Res*. 1993; 70:205–215. [PubMed: 8294265]
21. Leake PA, Hradek GT, Snyder RL. Chronic electrical stimulation by a cochlear implant promotes survival of spiral ganglion neurons after neonatal deafness. *The Journal of Comparative Neurology*. 1999; 412
22. Seyyedi M, Eddington DK, Nadol JB Jr. Effect of monopolar and bipolar electric stimulation on survival and size of human spiral ganglion cells as studied by postmortem histopathology. *Hear Res*. 2013; 302:9–16. [PubMed: 23660399]
23. Xu HX, Kim GH, Snissarenko EP, Cureoglu S, Paparella MM. Multi-channel cochlear implant histopathology: are fewer spiral ganglion cells really related to better clinical performance? *Acta Otolaryngol*. 2012; 132:482–490. [PubMed: 22264101]
24. Tinling SP, Colton J, Brodie HA. Location and timing of initial osteoid deposition in postmeningitis labyrinthitis ossificans determined by multiple fluorescent labels. *Laryngoscope*. 2004; 114
25. Zehnder AF, Kristiansen AG, Adams JC, Merchant SN, McKenna MJ. Osteoprotegerin in the inner ear may inhibit bone remodeling in the otic capsule. *Laryngoscope*. 2005; 115:172–177. [PubMed: 15630389]
26. Trakimas DR, Kozin ED, Ghanad I, Barber SR, Curtin H, Remenschneider AK. Pre-curved cochlear implants and tip foldover: a cadaveric imaging study. *Otolaryngol Head Neck Surg*. 2017
27. Razafimahefa-Raelina T, Farinetti A, Nicollas R, Triglia JM, Roman S, Anderson L. Self- and parental assessment of quality of life in child cochlear implant bearers. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2016; 133:31–35. [PubMed: 26520481]
28. Rabinowitz WM, Eddington DK, Delhorne LA, Cuneo PA. Relations among different measures of speech reception in subjects using a cochlear implant. *J Acoust Soc Am*. 1992; 92:1869–1881. [PubMed: 1401531]

Figure 1. Method of 3-dimensional reconstruction

A: Example of horizontal section of TB with the cochlear lumen (Segment I: orange, Segment II: green, Segment III: red, Segment IV: blue), spiral lamina (purple), electrode (black), osseous tissue (yellow), and fibrous tissue (pink) segmented. This was completed for an average of 30–40 sections per case. B: Subsections of the cochlea where volumes of new tissue and spiral ganglion neurons were quantified: Segment I (orange), Segment II (green), Segment III (red), Segment IV (blue).

Figure 2. 3-D reconstructions of electrode array in folded and control cases

A-D: 3-D reconstructions of the electrode array (green) were used to measure the length of folding in Patients 1 (A), 2 (B), 3 (C), and 4 (D). Panels A-C represent Nucleus 22 and 24 electrodes, while D is a Clarion 1.0 electrode. E-G: 3-D reconstructions of a 'properly placed' electrode array (black) in a control patient. The trajectory of the electrode array can be seen through the translucent cochlea (F). The arrays of all control specimens enter and remain within the ST (yellow) (G). F&G: SV (blue), spiral ligament (red).

Figure 3. Histology of TB specimens

A: Example of haematoxylin and eosin (H&E) stained folded case showing an electrode (black arrow) entering the cochlea and folding over within the basal turn. Extensive new osseous tissue (yellow arrows) is seen within the cochlear lumen and fibrous tissue (red arrow) surrounds the electrode path. B: Example of H&E stained control case showing an electrode (black arrow) entering the ST of the basal turn. Minimal osseous tissue (yellow arrows) is observed within the cochlear lumen and a thin layer of fibrous tissue (red arrow) surrounds the electrode path. Inset: osteoid (*) is differentiated from fibrous tissue (>) as it

stains more intensely and homogenously with eosin. This is apparent at higher (4–10×) magnifications.

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Figure 4. Quantification of intracochlear changes following CI

A: New osseous tissue: Individual and mean values of % volume of the cochlear lumen filled with osseous tissue for folded cases and controls within Segments I-IV. Black and blue symbols correspond to folded and control cases, respectively. Error bars represent standard error of the mean. B: New fibrous tissue: Individual and mean values of % volume of the cochlear lumen filled with fibrous tissue for folded cases and controls within Segments I-IV. C: SGN counts: Individual and mean values of SGN counts reported as interaural differences in % of age-matched control values (implanted ear of interest – contralateral ear) within each segment of Rosenthal's canal. *SGN counts were significantly less than zero within Segment I, II, and overall in folded cases. For Patient 4: normalized SGN (% age-matched controls) on implanted side of interest (I: 49%, II: 85%, III: 83%, IV: 44%, total: 70%) and contralateral side (I: 24%, II: 63%, III: 63%, IV: 53%, total: 56%). Black and blue symbols correspond to folded and control cases, respectively. Error bars represent standard error of the mean.

Figure 5. Post-operative hearing outcomes

A: Mean post-operative monosyllabic WRS were comparable between groups. *NU-6 score estimated as 10% from sentence score.²⁸ B: Trajectories of post-operative WRS from early follow-up (≤ 12 months) to late follow-up (≥ 24 months) in a subset of cases with available scores. All controls showed stable hearing outcomes over time while a single folded case showed a decrement in long-term hearing. Black and blue symbols correspond to folded and control cases, respectively. Error bars represent standard error of the mean.

Table 1

Comparison of patient and CI electrode characteristics between groups

Pt #	Study Group	Age at Death (yr)	Age at HL Onset (yr)	Age at HL "Documented" Profound HL (yr)	Etiology of HL	Duration of Deafness (yr)	Pre-operative WRS (%)			Side of Interest			Contra-lateral Side		
							AD	AS	Side	CI	Age at Implant (yr)	Duration of Use (yr)		AOI (°)	Length of Folding (mm)
1	Folded	71	9 AU	56 AD 57 AS	Bulbar polio, PSNHL	3	0	0	AD	Nucleus 24M	59	11.6	360	4.4	Nucleus 24M
2	Folded	78	20 AU	72 AU	Mumps, Chemo-therapy	4	0	0	AD	Nucleus 22	76	3.6	390	6.5	-
3	Folded	83	65 AU	71 AU	Meniere's Disease	6	20	8	AD	Nucleus 24M	71	12.3	420	2.8	Nucleus 24M
4	Folded	78	? AU	70 AD *	Noise exposure, PSNHL	2 *	0	0	AS	Clarion	72	5.7	120	3.4	-
5	Control	80	49 AU	63 AU	Suspected genetic, PSNHL	8	0	0	AD	Nucleus 24M	71	9.4	360	-	-
6	Control	83	Childhood AU	69 AU	Unknown, PSNHL	7	0	12	AD	Nucleus 22	76	6.8	360	-	-
7	Control	74	21 AU	55 AU	Suspected genetic, PSNHL	7	0	0	AD	Nucleus mini-22	62	11.6	340	-	-
8	Control	84	? AU	64 AU	Unknown, PSNHL	7	2	0	AD	Nucleus 22	71	12.4	360	-	-
9	Control	91	? AU	61 AU	Meniere's Disease	19	0	0	AS	Nucleus 22	80	11.1	270	-	-
Folded: Mean (SD)						3.8 (1.7)					70 (7)	8.3 (4.3)	320 (140)		
Control: Mean (SD)						9.6 (5.3)					73 (7)	10.3 (2.2)	340 (40)		
p-value						0.07					0.58	0.45	0.84		

HL: hearing loss, AD: right ear, AS: left ear, AU: both ears, PSNHL: progressive sensorineural hearing loss, WRS: word recognition scores, CI: cochlear implant, Nucleus 24M (curved electrode), Nucleus 22 or mini-22 (straight electrode), Clarion (curved electrode), AOI: angle of insertion, SD: standard deviation.

* Patient 4 was documented with profound deafness on the right (non-implanted) side, but moderate-severe hearing loss in the low and mid-frequencies on the left (implanted) side 2 years prior to implantation.