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Risk factors for loss of ipsilateral residual hearing after Hybrid cochlear implantation

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Cochlear implant; hearing preservation; hearing loss; noise

Introduction

Cochlear implants (CIs) restore sound perception to individuals with severe to profound hearing loss by using electrical current to directly stimulate surviving auditory neurons. The S8 Hybrid CI, a 10mm long version of the original 24mm CI, was developed and validated in a recent FDA trial from 1999 to 2009^{1,2}. Shallow insertion of a shorter array at the base of the cochlea allows preservation of functional cochlear structures towards the apex. Thus with a hearing preservation CI, low-frequency or apical residual hearing is preserved, while the impaired high-frequency or basal regions are bypassed with electrical stimulation from the device. Patients with residual low-frequency hearing, common with age-related hearing loss (presbycusis), benefit from this device by using acoustic and electrical modes of hearing together.

Ipsilateral post-implantation hearing loss has been described in every patient series of hearing preservation cochlear implantation. This hearing loss is generally mild ~12dB and coincident with implantation. Recently our group described a subset of these patients for whom hearing loss accelerates after activation, hypothesizing that high amplitude electric-acoustic stimulation (EAS) may cause excitotoxic damage to the peripheral afferent auditory system³. Here we analyze the same cohort of 85 patients from the FDA hearing preservation array multicenter trial and correlate ipsilateral post-implantation hearing loss with patient-specific medical risk factors known to be associated with presbycusis, such as age and the use of prescription medications. We also seek to assess the relative clinical significance of

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Conflicts of Interest: Author BJG holds a patent on the Hybrid Cochlear Implant. No royalties are received. Additionally he is a consultant for both Advanced Bionics and Cochlear Corporation.

this post-implantation hearing loss for overall auditory function in hearing preservation CI recipients.

Materials and Methods

Design

Retrospective chart review.

Subjects

Audiometric data of 85 patients who underwent Iowa/Nucleus 10mm Hybrid cochlear implantation as part of the adult FDA multi-center clinical trial in the USA from 1999 to 2008 were reviewed. All participants had severe to profound hearing loss above 2000 Hz and were implanted in the worse hearing ear. Detailed candidacy information is described in Gantz *et al.* 2009. The total population comprised 39 males and 46 females, aged between 19 and 82 years at the time of implantation (mean = 59). Duration of high frequency hearing loss ranged from 3 to 66 years (mean = 26). Etiology of hearing loss was categorized as follows: Hereditary (31%), Noise induced (20%), Infectious (5%), Unknown (42%) and Other (2%). The last category comprised one patient with hearing loss ascribed to endolymphatic hydrops and one with known ototoxin exposure. Patients whose hearing loss was of a relapsing type i.e. autoimmune, were omitted from the study (n=2).

More detailed medical and audiometric records were available from 22 patients who participated in this trial at the University of Iowa Hospital and Clinics (UIHC). In total, this subset of patients included 11 males and 11 females, aged 19 to 80 years (mean = 57) at surgery.

Audiometry

Audiometric data consisted of standard pure-tone audiograms collected pre-operatively and then at activation (1 month postoperatively). Additional audiograms were collected at 3, 6 and 12 months after activation. Frequencies tested included 125, 250, 500, 750 and 1000 Hz for both implanted and contralateral ears. Using a linear mixed model with unstructured correlation between frequencies, differences in hearing loss by frequency was significant for the implanted ear ($p < .001$) but not for the non-implanted ear ($p = .212$). A separate model on the difference between hearing loss in the implanted ear versus the non-implanted ear was also significant ($p = .030$). Correlation between the frequencies using all 86 subjects was high (all $r > 0.65$). Follow-up tests using Tukey-Kramer adjusted p-values were used to examine which frequencies in fact differed. The results indicate that the only significant differences in hearing loss were seen between frequencies 500 and 1000 Hz for the implanted ear ($p < .0001$) and for the difference between the implanted and non-implanted ear ($p = .016$). Because there were so few differences by frequency, threshold was averaged across frequency at each audiogram time-point to simplify further analyses. It was also assumed that threshold averages across frequency for the 22 Iowa patients would have few differences. Threshold shift at each time point was assayed by subtracting pre-operative average threshold from the last post-operative average threshold at that time point. Contralateral threshold shift was then subtracted in order to correct for natural progression

of premorbid disease in the implanted ear. These calculations were used to generate an ear-specific frequency-averaged measure of hearing loss, reported here as either threshold shift (a positive value) or hearing loss (a negative value). Appreciable hearing threshold was defined as an absolute (uncorrected) threshold of 90dB or less.

Patient Records

More detailed patient charts of hearing preservation implantees at UIHC were reviewed for the purpose of discerning the impact of health-related factors on acoustic hearing loss subsequent to implantation. Using the Framingham criteria for cardiovascular disease risk as a guide⁴, both continuous and categorical pre-implantation variables were assessed for potential correlation with post-implantation hearing loss severity. Continuous variables available from the national patient database included age at the time of implantation, duration of hearing loss, duration of severe to profound hearing loss, and pre-operative audiometric thresholds. Additional data gleaned from records of patients from the UIHC cohort included body mass index (BMI:kg/m²), systolic blood pressure (SBP) at pre-operative appointment, number of allergies, number of medications, and total number of comorbidities. We defined comorbidity as any ongoing non-psychiatric medical condition at the time of implantation e.g. obstructive sleep apnea, hypertension. Categorical variables examined in the national cohort included gender and etiology of hearing loss. In the UIHC cohort, history of tobacco use, treatment status of hypertension, incidence of hyperlipidemia, known cardiac disease, and diabetes mellitus were all separately examined. Use of peri-operative intravenous steroids (Dexamethasone 10mg IV) was noted as well.

Efficacy Measures

Changes in test scores on efficacy measures utilized in the FDA trial across repeated testing sessions have been previously reported². Here we correlated changes in these efficacy measures with patient-specific changes in hearing as well as absolute acoustic thresholds after 12 months of electrical stimulation with a CI.

The CNC (Consonant-Nucleus-Consonant) word recognition test was the primary speech perception measure for the FDA trial Phase 1 and 2 studies (N = 80). The CNC test consists of 10 lists with 50 monosyllabic words in each list. Two lists were administered for a total of 100 words per test condition. Subject responses were scored for the total number of words correct, expressed as a percentage. CNC scores were collected under unilateral acoustic (implanted ear pre-implantation) and bilateral acoustic hearing conditions pre-operatively, and under unilateral hybrid (electric plus acoustic in the implanted ear) and bilateral hybrid (electric plus acoustic in both ears) hearing conditions post-operatively, at activation (1 month post-operatively), as well as 3 and 12 months post-activation. Scores collected with unilateral or bilateral hybrid listening conditions were compared to their respective pre-operative unilateral or bilateral acoustic listening scores.

For some subjects, recorded sentence materials from the Hearing-In-Noise Test (HINT) were also used to measure sentence recognition in quiet. The HINT sentences consist of 25 lists, designed to be of equal difficulty. Each test list contains 10 sentences that vary from 3 to 7 words in length. Scoring is based upon the total number of correctly identified words in

the sentence and expressed as a percent-correct score. Results were available from 52 patients under best listening conditions. Of these, 42 listened using bilateral hybrid hearing (electric plus acoustic in both ears), 5 listened with electric hearing along with acoustic hearing in the contralateral ear, 4 listened with ipsilateral acoustic and electric hearing. HINT scores were collected preoperatively and 6 months post-activation.

Statistical Analysis

All error bars were calculated using standard error of the mean (SEM). Differences in hearing threshold variations between groups were evaluated for each frequency and across frequencies with Student's t-tests and ANOVA. Univariate correlations were assessed using Pearson product moment correlation. Multivariate regression analyses were performed to determine the variables that best account for variation in hearing and efficacy measure outcomes. Variable selection for the full audiometric dataset was determined using backward model selection, an automated procedure that starts with all factors and eliminates them one by one to keep only the most important factors. Highly collinear variables were also identified. In the Iowa group, small sample size and the large number of predictors did not allow for multivariate analysis.

Results

Premorbid factors relating to general health and hearing were examined for correlation with post-implantation hearing loss at 12 months. Whenever possible, data from the national cohort were used (n=85). Specific medical data was available only from the 22 patients implanted at our institution.

Continuous variables were individually analyzed for association with post-implantation hearing loss using Pearson product moment correlations for the national cohort and Spearman rank correlations for the smaller cohort implanted at Iowa. For example, Figure 1 shows a characteristic plot of post-operative hearing loss as a function of age at the time of implantation. In this case a negative association is apparent (Pearson $R = -0.31$, $p < 0.01$) such that older age at the time of implantation is associated with increased severity of post-implantation hearing loss. Table I shows individual correlation statistics for all continuous variables. In the smaller subset of patients implanted at UIHC, no medical variables were significantly associated with hearing besides age.

Categorical variables were also analyzed for association with post-implantation hearing loss using paired student's t-tests (Table II). For instance, Figure 2 shows a comparison of gender. In the national cohort, male implantees had a significantly ($p < 0.001$) higher degree of post-implantation hearing loss (mean threshold shift = 24 ± 3.4 dB) than female implantees (mean = 11 ± 2 dB). Figure 3 shows a comparison of etiology. Etiology of hearing loss was known for 49 implantees. Including unknown etiology as a separate category, comparisons between hereditary, noise-induced, infectious and unknown etiologies were performed. Patients with an etiology of NIHL had significantly more hearing loss after implantation than other etiologies ($p < 0.03$, ANOVA).

Multivariate regression analysis was also performed to assess relative predictive value of the above premorbid factors for post-implantation hearing loss after correction for interactions between variables (Tables III–IV). For the national group, age and gender were found to be the most important predictors accounting for 18% of variation in HL at 12 months post-activation. NIHL as an etiology was an insignificant predictor of HL but was significantly correlated with both age and gender ($R=.28$ $p=.008$, $R=.37$ $p=.001$). Regression that included NIHL as a predictor provided a marginal improvement in model accuracy - accounting for 20% of variation in outcome. Table III contains parameter estimates for the model with age and gender.

Functional measures of combined electric and acoustic hearing were performed serially for this cohort as previously reported in Gantz *et al.* 2009. Here, we correlate the change in individual subject's scores on CNC word and HINT tasks from pre-operative sessions to 9 or 12 months post-activation with total loss of hearing over the same interval. Both unilateral and bilateral listening conditions were analyzed. As shown in Figure 4, a significant correlation exists in the unilateral listening condition, such that performance on the CNC task declined in subjects with more post-implantation hearing loss (open circles: Pearson = 0.37, $p < 0.001$). As seen in Gantz *et al.* 2009, most subjects improved in CNC word scores when similarly tested in the bilateral listening mode (gray triangles) irrespective of hearing loss (Pearson = 0.11, $p > 0.05$). Similarly, HINT scores (Figure 5), obtained under combined bilateral listening conditions for most subjects, were poorly correlated with loss of acoustic hearing (Pearson = 0.13, $p = 0.32$). Thus, even patients with loss of acoustic hearing derive significant benefit from the CI.

Three multivariate linear regressions were performed to determine what set of variables, including pre-operative test scores, are most related to these functional outcomes. 79 people had serial values for CNC word tested both bilaterally and unilaterally. 51 people had serial values for HINT.

Table Va shows that the best combination of predictors for the change in bilateral CNC word scores in order of descending impact are (1) pre-operative threshold in the implanted ear, (2) pre-operative bilateral CNC score, (3) NIHL as an etiology of HL and (4) post-implantation hearing loss. This model explains 25.5% of the variation in bilateral CNC word scores. Post-implantation hearing loss is marginally non-significant ($p = 0.08$) and has been left as a predictor to allow us to see the relationship between hearing loss and bilateral CNC word scores. For example, assume the values for all other factors are identical between two hybrid implantees. If one person loses 10dB of hearing averaged across frequencies 12 months after activation and another loses 20dB, then we expect the person who lost 10dB to recognize 2% more words than the person who lost 20dB.

Table Vb shows that the best combination of predictors for the change on unilateral CNC word scores in order of descending impact are: (1) age, (2) post-implantation hearing loss, (3) pre-operative unilateral CNC word score and (4) NIHL etiology. Pre-operative unilateral CNC word score is marginally non-significant, but since we want to control for the initial unilateral score, we keep this predictor in the final model. The other predictors are significant at the $p < 0.05$ level. From this we can infer the relationship between hearing loss

at 12 months after activation and performance on ipsilateral CNC word. Assuming two hybrid implantees have identical values for all other factors, if one person loses 10dB over the year subsequent to activation and the other loses 20dB, then we expect the latter to recognize approximately 5% fewer words than the former.

The best predictor of improvement in HINT score was initial HINT score; however, this model did not meet linear assumptions well. Thus, this finding was corroborated by examining individual spearman rank correlations, which confirmed that the sole variable significantly related to change in HINT score is initial HINT. Neither mode of listening (bimodal, hybrid, or combined) nor total hearing loss was significant to the model in either case. Overall, this indicates that individuals with higher initial HINT scores are expected to have a larger improvement in HINT. However since the model was nonlinear we cannot quantify the amount.

Discussion

Medical data from the time of surgery support the idea that post-implantation hearing loss is more likely in cochleae susceptible to damage. Older age, male gender and NIHL correlate with loss of residual hearing in the largest patient cohort for hearing preservation cochlear implantation to date. Cardiovascular risk factors including age and male gender potentiate noise-induced hearing loss, possibly as a result of microvascular insufficiency^{5,6,7,8}. While comorbidities are limited in the small and generally healthy population of implant recipients, the correlation of the above variables with loss of residual hearing suggests an association between cardiovascular health and susceptibility to post-implantation hearing loss. Other medical factors, such as the the number of medications at the time of surgery, used as an easily quantified albeit imprecise indicator of medical comorbidity, smoking status and treatment for hypertension, trended toward correlation but were hampered by low sample size. Thus medical data, while not predictive of clinical outcome in completely deaf implantees, may be salient to loss of residual hearing in cochlear implantees.

Etiology appears to be significant and interrelated with health status. Patients with known noise induced hearing loss lost more hearing after implantation and ultimately performed worse on our clinical measures of CI performance (CNC, HINT). Noise exposure increases free radical production in the cochlea and subsequently reduces cochlear blood flow and causes cell death in the organ of Corti⁹. Furthermore, recent experiments in mice show that even reversible noise-induced threshold shifts may cause ongoing degeneration of afferent neurons¹⁰. Finally, because the plurality of our subjects had unknown etiology (42%), our study may under-represent the number of patients for whom noise damage increased susceptibility to post-implantation hearing loss.

We recently reported increased hearing loss in a subset of hearing preservation CI recipients following the onset of electrical stimulation, which may be related to high levels of electric stimulation. In an *in vitro* model, high levels of electrical stimulation primarily damaged the afferent neural processes innervating the organ of Corti³. Significantly, noise trauma results in a similar type of damage to the afferent cochlear innervation¹¹. Exacerbation of existing

damage to afferent neural structures by electrical stimulation may account for the increased risk of post-implantation hearing loss in patients with noise induced hearing loss.

Residual hearing status in the implanted ear is not strongly correlated with bilateral measures of speech comprehension. As seen in other series, CNC and HINT scores, when tested in bilateral listening conditions, improve irrespective of post-operative hearing loss in the implanted ear¹². This improvement is immediate² and as we have shown here, sustained. Under unilateral acoustic+electric listening conditions, however, loss of acoustic hearing predicts diminished CNC performance accounting for 30% of variance in CNC word performance. These results suggest both that preserved acoustic hearing in the contralateral ear is sufficient to provide the benefits of acoustic+electric hearing when ipsilateral residual hearing is lost, and that unilateral electrical hearing alone is superior to pre-operative acoustic hearing for some patients. Even in the few patients that lose low frequency hearing in the ipsilateral ear, high frequency hearing provided by a CI imparts benefit over hearing aids alone.

Conclusions

Age, male gender, and noise-induced hearing loss appear to increase susceptibility to post-implantation loss of residual hearing. These factors should be kept in mind when counseling candidates for hearing preservation CIs. In order to minimize this risk, these implantees should be counseled to use hearing protection when needed, and avoid noisy environments and high stimulus levels post-operatively. Even in those cases with significant hearing loss in the ipsilateral ear, most patients will achieve significant improvement in speech understanding following implantation, in that patients benefit from combined bilateral listening irrespective of hearing loss in the implanted ear. This outcome suggests that while ipsilateral acoustic hearing is of benefit, acoustic hearing in the contralateral ear also contributes to overall audition, and further reinforces current practice of implanting the worse hearing ear in hearing preservation cochlear implantees.

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Figure 1.

Hearing loss 1 year after implantation as a function of age at time of implantation. With regression analysis, a negative association is apparent (dotted line, Pearson $R = -0.31$, $p < 0.01$) such that older age at the time of implantation is associated with increased severity of post-implantation hearing loss. Similar univariate analyses were performed for all continuous variables.

Figure 2.

Post-implantation hearing loss at 12 months as a function of gender. Males lost significantly more hearing than females. Male implantees had a significantly ($p < 0.001$) higher degree of post-implantation hearing loss (mean threshold shift = 24 ± 3.4 dB) than female implantees (mean = 11 ± 2 dB). Similar univariate analyses were performed for all categorical variables.

Figure 3.

Post-implantation hearing loss at 12 months as a function of etiology of hearing loss (n=85). Patients with a known etiology of noise induced hearing loss (NIHL) were more likely to lose hearing after implantation than those with hearing loss due to hereditary (Her, $p=0.025$) or unknown causes (UNK, $p=0.01$) according to ANOVA. There were no significant differences in HL due to infectious (Infect) and any other etiology.

Figure 4.

Functional measures of performance – CNC word. When tested solely with ipsilateral hearing, decrease in CNC word score is correlated with increased loss of hearing. Pearson $\rho=0.37$, $p<0.001$. Open circle post-operative CNC word scores were obtained under unilateral hybrid listening conditions ($n=79$), regression indicated by solid line. When tested with bilateral hearing (bilateral hearing aids with cochlear implant), the correlation with post-operative hearing loss is insignificant. Most subjects improved in score irrespective of hearing loss: black triangles, regression indicated by dashed line.

Figure 5.

Functional measures of performance - HINT. Change in HINT percentage correct score as a function of hearing loss in the implanted ear by 12 months post-activation. HINT score collected in best listening mode, primarily bilateral listening conditions. No correlation is seen. Most subjects improved irrespective of hearing loss (n=59).

Table I

Continuous variables: Univariate analysis

	n	Correlation statistic	p value
Age	85	Pearson R = -0.31	0.004
Duration of hearing loss	85	Pearson R = -0.07	0.513
Duration of severe to profound hearing loss	85	Pearson R = -0.07	0.527
Systolic blood pressure (mmHg)	22	Spearman rank = 0.017	0.941
Number of medications	22	Spearman rank = -0.275	0.216
Number of comorbidities	22	Spearman rank = -0.062	0.783
Number of allergies	22	Spearman rank = -0.139	0.537

Table II

Categorical variables: Univariate analysis

	n	Category mean threshold increase (n)		Student's t-test unpaired p value
Gender	85	M = 24dB (39)	F = 11dB (46)	0.0005
Treated for hypertension	22	+ = 18dB (13)	- = 8 dB (9)	0.154
Smoking history	22	+ = 24dB (4)	- = 12dB (18)	0.184
Cardiac disease	22	+ = 13dB (4)	- = 14dB (18)	0.893
Peri-operative IV steroids	22	+ = 17dB (7)	- = 13dB (15)	0.596
Diabetes Mellitus	22	+ = 7.5dB (2)	- = 13dB (20)	0.856
Hyperlipidemia	22	+ = 15dB (10)	- = 10.5dB (12)	0.905

Table III

Multivariate regression for national cohort

National Group Parameter Estimates (n=85)		
Variable	Parameter Estimate	Pr > t
Intercept	5.371	0.5
Age	−0.282	0.04
Gender	−11.481	0.004

Table IV

a: Functional scores using binaural hearing		
CNC word Bilateral		
Variable	Estimated Effect	Pr > t
Intercept	71.96	<.0001
Initial bilateral CNC	−0.53	0.0002
Initial threshold (ipsi)	−0.59	0.02
HL at 12 months	0.20	0.08
NIHL	15.55	0.004

b: Functional scores using monaural hearing			
CNC word Unilateral			
Variable	Estimated Effect	Standard Error	Pr > t
Intercept	63.76	11.24	<.0001
HL at 12 months	0.46	0.13	0.001
initial unilateral CNC	−0.41	0.21	0.05
age	−0.48	0.18	0.01
NIHL	17.73	6.14	0.01