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Intracochlear Inflammatory Response to Cochlear Implant Electrodes in the Human

Mohammad Seyyedi^{1,2} and Joseph B. Nadol Jr., M.D.^{1,2}

¹Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA

²Department of Otolaryngology and Laryngology, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Hypothesis—This study evaluates the types and degree of tissue response adjacent to the electrode of multichannel cochlear implants.

Background—cochlear implant electrodes have been classified as biocompatible prostheses. Nevertheless, in some reports, electrode extrusion, chronic inflammation and even soft failure of the implant system have been attributed to a tissue response to the electrode.

Methods—All celloidin embedded temporal bones with multichannel cochlear implants from the temporal bone collection of the Massachusetts Eye and Ear Infirmary were included in the study. A total of 28 temporal bones from 21 subjects were identified and processed for histology. The severity of cellular response including eosinophil and lymphocytic infiltration, giant cell reaction, new bone formation and fibrosis were scored on a scale from 0 to 3 at three 1mm-segments along the electrode: 1- first 1mm at the cochleostomy, last 1mm from the tip of electrode, and midway between these proximal and distal segments. The values were compared using the Wilcoxon test.

Results—A granulomatous reaction to the electrode was observed in 27 (96.4%) temporal bones. Eosinophil infiltration was observed in 7 (25%) temporal bones, suggesting an allergic reaction. The inflammatory response to the electrode was significantly greater at the basal turn of cochlea close to the cochleostomy ($p < 0.05$) than distal to it.

Conclusion—An inflammatory response is common after cochlear implantation and it is more robust at the cochleostomy than distal to it, suggesting the role of trauma of insertion as a contributing factor.

Keywords

tissue response; cochlear implant; giant cell; foreign body; endocochlear; Labyrinthitis

Introduction

Cochlear implants (CI) have been considered well-tolerated and biocompatible auditory prostheses with a low rate of complications that can restore the hearing of the patients with severe to profound hearing impairment (1-6). Nevertheless, there have been a number of case reports in which a pronounced inflammatory/allergic reaction to cochlear implants resulted in implant failure, extrusion, explantation and reimplantation. Puri et al. (7), Kunda et al. (8) and others (1,9-12) reported a delayed hypersensitivity or an allergic reaction to the electrode array or the receiver-stimulator unit. In addition, some reports suggested local tissue reaction as a possible explanation for cochlear implant soft failures (12,13). On the other hand, in a meta-analysis of 7132 cochlear implant recipients, 0.55 % of them (n=39) experienced extrusion of the device (1). All these studies indicated that for a number of CI users, biocompatibility of the device was an issue. Considering the incidence of the implant extrusion and pronounced inflammatory reaction to the electrode, it is reasonable to study the interaction between the electrode and its adjacent tissue within the cochlea. The histopathology of the temporal bones in cochlear implant recipients has been published previously and all reported fibrotic and neo-osteogenic reaction to cochlear implants (14-24). Nevertheless, the degree and types of inflammatory response and the locations with maximal reaction to the intracochlear portion of the electrode has not been studied systematically. In this study, using a grading system, the severity of the inflammatory response and the locations of maximal reaction were determined. The correlation between the severity of the inflammatory response and the duration of implantation, type of electrode and the tissue used for sealing the cochleostomy were also evaluated.

Methods and Materials

All temporal bones in the temporal bone collection of the Massachusetts Eye and Ear Infirmary with multi-channel electrode embedded in celloidin were included in the study. Twenty eight temporal bones from 21 individuals (Table 1) who had undergone cochlear implantation during life were identified. The temporal bones were removed after death, fixed in 10% buffered formalin and decalcified in ethylene diamine tetra acetic acid (EDTA). The electrodes were removed at this point, and then the specimens were embedded in celloidin (25). The temporal bones were sectioned at a thickness of 20 μ m in the horizontal plane, and every fifth section was stained with hematoxylin and eosin and mounted on a glass slide. Rosenthal's canal and the cochlear duct were reconstructed in two dimensions (Figure 1) by a method described by Schuknecht (26) and Otte et al. (27), and the length of Rosenthal's canal, cochlear duct, the depth and the location of electrode insertion were determined using MATLAB® software. Three 1mm-segments along the track of each electrode were selected to evaluate the degree of tissue response and cellular infiltration, namely: 1- at the cochleostomy, 2- at the tip of electrode and 3- midway along the intracochlear segment of the electrode (Figure 1). The slides associated with these three different 1mm segments were examined for fibrosis, new bone formation and lymphocyte, eosinophil and giant cell infiltration. Using a grading system, as illustrated in Figure 2, the degree of tissue response and cellular infiltration were determined for each element at these three segments by a blinded otopathologist (Table 2).

The Wilcoxon signed-rank test was used to compare the severity of tissue reaction at these three locations. The Mann-Whitney U Test was used to compare the severity of tissue reaction between different electrode types (Cochlear Nucleus® vs. Advanced Bionics®) and a similar method was used to compare the degree of inflammatory response based on the tissues used to seal the cochleostomy (fascia vs. muscle). The correlation between the duration of implantation and the severity of tissue reaction was evaluated using Spearman's rank correlation analysis.

Results

Twenty eight temporal bones from 21 profoundly hearing-impaired patients who had undergone cochlear implantation during life met inclusion criteria. There were 7 females and 14 males with an average age of 78 years ranging from 57 to 92 (Table 1). In all cases electrodes were inserted through a bony cochleostomy. There were six Advanced Bionics electrodes® (Sylmar, CA) and 22 had Cochlear Nucleus® electrodes (Cochlear Corp., Sydney Australia). The duration of implantation ranged from 1 to 23 years with an average of 11 years. All patients had uneventful implantation except cases 2 and 18. The right cochlear implant in case# 2 was explanted 12 years after implantation because of the development of cholesteatoma. In case# 18 there was soft failure bilaterally, as previously described (12). With the exception of one temporal bone (case # 27), all other 27 temporal bones had a foreign body giant cell infiltration in at least 1 segment. Case# 18 had the most severe reaction which caused a severe granulomatous reaction with necrosis (12). Lymphocytic infiltration was observed in 25 temporal bones (89.2%). In 7 temporal bones there was eosinophil infiltration (25%).

The severity of infiltration by foreign body giant cells, lymphocytes and eosinophils, new bone formation and fibrotic reaction were compared across different points of the electrode track in each temporal bone by the Wilcoxon Signed-Rank test (Table 3). As shown in Table 3, the infiltration of foreign body giant cells, lymphocytes and eosinophils at the cochleostomy was significantly more severe than the cellular response at the middle of the intracochlear segment of the electrode and at the tip of the electrode. However, the difference in eosinophilic reaction between the tip of the electrode and the cochleostomy did not reach significance (p-value= 0.129). The cellular reaction at the tip and the middle of the electrode did not differ significantly (p-values> 0.05). As can be seen in the Table 3, fibrosis and new bone formation were less severe with increasing distance from the cochleostomy.

The Mann Whitney test (Table 4) did not demonstrate a significant difference in the cellular, fibrotic and osteogenic reactions between the two types of electrode (Cochlear Nucleus® vs. Advanced Bionics®) with the exception of the foreign body giant cell infiltration which was less pronounced at the tip of the Cochlear Nucleus® electrodes. There was no difference in inflammatory response between fascia and muscle grafts (Table 4).

As indicated in Table 5, Spearman's correlation analysis did not demonstrate any correlation between the duration of implantation and the cellular, fibrotic and osteogenic reactions.

Discussion

Although cochlear implants have been widely accepted as biocompatible prostheses (2-6), there have been several reports describing the extrusion of implants and a severe allergic reaction to intracochlear and the receiver-stimulator segments of the electrode resulting in explantation and soft failure (1,7-9,12,13). In a review (1), device-associated complications occurred in 311 individuals of 7132 patients. Of these 311 patients, 39 experienced device extrusion due to severe local tissue response.

It has been also suggested that the severity of local tissue response may be inversely correlated with survival of the spiral ganglion cells (19), performance after implantation, and preservation of the residual acoustic hearing (28,29). The current study was designed to examine the local tissue response and its severity caused by the intracochlear segment of the implanted electrodes at three different locations (Figure 1 and Table 2). The association between the extent of inflammatory response and different types of electrode arrays as well as the duration of implantation was also evaluated.

Cochlear implantation is always accompanied by surgical injury, which initiates an acute inflammatory response to the electrode. The acute phase of inflammation may be replaced by a chronic phase due to a foreign body reaction induced by components of the electrode array involving macrophages and their derivatives (epithelioid cells and foreign body giant cells) and lymphocytes (30-33). A macrophage is able to phagocytize particles up to 5 μm (34). If the particle size is larger, macrophages coalesce to form foreign body giant cells (35,36). The chronic inflammatory response includes granulation tissue identified by the presence of macrophages, infiltration of fibroblasts, and angiogenesis. Granulation tissue is the precursor of fibrous capsule formation, and granulation tissue is separated from the implant by the cellular components of the foreign body reaction, a one to two-cell layer of macrophages, and foreign body giant cells (30).

In contrast to the hypothesis that a foreign body reaction is rare around cochlear implant electrodes (1,5,37), in the current study foreign body giant cell infiltration and granulomatous reaction was observed in 27 of 28 temporal bones (96.4 %) which is significantly higher than the previous reports (12,24,38). In two separate studies, Nadol et al. observed foreign body granulomatous reaction in the presence of an intracochlear electrode in 75 % (n= 8) and 57 % (n= 21) of temporal bones (12,24). Migirov et al. (38) reported chronic inflammatory response with foreign body giant cells in the presence of the receiver/stimulator segment of the implant in 46.7 % of the patients (n= 15). In the present study, the foreign body giant cells appeared as linear multinucleated cells between the electrode array and the fibrous capsule (Figure 2d).

As shown in Table 3, the lymphocytic and giant cell infiltrations were significantly greater at the cochleostomy compared to the middle and the tip of the electrode. The eosinophil granulocyte infiltration (Figure 2) that was seen in 25 % of the implanted temporal bones was not reported in previous studies. The presence of eosinophils in chronic inflammation suggests type I hypersensitivity mediated by IgE and an allergic reaction to components of the electrode array in these 7 temporal bones. The eosinophilic reaction was also

significantly more robust at the cochleostomy compared to the middle of the electrode. It was also more pronounced at the cochleostomy compared to the tip of the electrode but did not reach a significant level (Table 3).

In the current study similar to previous studies (12,15,17,19,38), all electrodes at the cochleostomy were surrounded by a fibrous sheath (Figure 2). The severity of the fibrotic reaction and new bone formation adjacent to the intracochlear part of the electrode was significantly more apparent at the cochleostomy compared to the middle and the tip of the electrode (Table 3), which is consistent with the result of previous studies (39,40). The local tissue reaction may alter the normal anatomy and cause malfunction of cochlear implant and poorer performance after cochlear implantation (14,19,28,29,41). Nadol reported negative correlation between the severity of new bone formation and survival of spiral ganglion cells in deafened ears (42). Deleterious effect of fibrosis and new bone formation in implanted temporal bones was reported by Fayad et al. (39) especially at the cochleostomy where the local tissue response was more robust. Seyyedi et al. (43) reported significantly fewer spiral ganglion cells in the implanted human ear as compared to the unimplanted side suggesting that insertion trauma and resultant local tissue response were contributing factors.

Our data suggests that the duration of implantation, the type of electrode and the tissue used to seal the cochleostomy do not have any correlation with the severity of cellular and stromal reactions. Similarly, Migirov et al. did not find any association between the duration of implantation and the presence of foreign body reaction (38). Nadol et al. (24) did not find correlation between the presence of foreign body reaction and duration of implantation, type of electrode and the tissue used to seal the cochleostomy.

The heightened reaction at the cochleostomy compared to more apical regions of the cochlea suggests that the trauma of insertion, violation of the normal anatomy, disruption of the intracochlear endosteum and release of inflammatory mediators may accentuate the local tissue response and foreign body reaction. Less traumatic techniques of electrode insertion such as insertion through round window membrane may decrease the severity of local tissue response (44,45).

Conclusion

The current study showed that a cellular immune response after cochlear implantation is more common than previously reported. In 25 % of temporal bones, an allergic type I reaction may be involved. A heightened cellular immune response at the cochleostomy suggests that trauma of insertion may be a contributing factor.

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Figure 1.

Two dimensional reconstruction of left cochlear duct, Rosenthal's canal and path of electrode array of case 5. The vertical line divides Rosenthal's canal to 4 segments. The black circles on Rosenthal's canal and on the cochlear duct are 1 mm apart. Three 1mm-segments of the cochlea (highlighted in blue) were studied to determine the extent of local tissue response toward the electrode: 1- 1mm-segment adjacent to the cochleostomy 2- 1mm-segment at the tip of electrode 3- 1mm-segment at the middle of the electrode track.

Figure 2.

Photomicrograph of 3 cochleae at three locations along electrode array (tip, middle, cochleostomy). a: Asterisk shows the outline of the electrode in case# 6 (left) close to the tip of the electrode (T) with mild fibrosis (grade 1) and no new bone formation (grade 0). b: same temporal bone at higher magnification which shows mild foreign body giant cell formation (grade 1) with mild lymphocytic infiltration (grade 1). c: Asterisk shows the outline of the electrode in case# 14 close to the middle of the electrode array (M) with moderate fibrosis (F) (grade 2) and no evidence of new bone formation (grade 0). d: same cochlea at higher magnification which shows moderate foreign body giant cell formation (grade 2) and moderate lymphocytic infiltration (grade 1). e: Asterisk shows the outline of the electrode in case # 19 (left) close to the cochleostomy with severe fibrosis (grade 3) and severe new bone formation (grade 3). f: case# 19 cochlea at higher magnification which shows severe giant cell formation (grade 3) and intense lymphocytic infiltration (grade 3). g: asterisk shows the outline of the electrode in case # 19 (left) close to the cochleostomy. Lymphocytic infiltration, fibrosis and new bone formation can be recognized. h: Higher magnification of area within black box in Figure g. The lymphocytic (grade 3) and

eosinophilic infiltration (grade 2) can be recognized. i: Higher magnification of area within black box in Figure h. Many eosinophils with bilobed nuclei and cytoplasm filled with large, red refractile granules can be recognized. (Thick arrow: lymphocytes; Thin arrow: foreign body giant cells; Hollow arrow: eosinophil; M: middle of the electrode; T: tip of the electrode; F: fibrosis; B: new bone formation)

Table 1

Demographic characteristics of 21 patients (seven patients were implanted bilaterally).

	Age/Gender	Diagnosis	Implanted ear	Device	Duration of implantation	Tissue used to seal cochleostomy
1	89/F	Unknown	AS	Nucleus	11	Fascia
2	73/F	Otosclerosis	AD	Nucleus	12	Muscle
2	73/F	Otosclerosis	AS	Nucleus	1	Fascia
3	83/M	Meniere's disease	AD	Nucleus	12	Fascia
3	83/M	Meniere's disease	AS	Nucleus	12	Fascia
4	89/F	Unknown	AS	Advanced Bionics	9	Fascia
5	80/M	Unknown	AS	Nucleus	6	?
6	88/M	Meniere's disease	AD	Advanced Bionics	6	Muscle
6	88/M	Meniere's disease	AS	Nucleus	17	?
7	78/M	Unknown	AS	Nucleus	7	Fascia
8	83/M	Unknown	AD	Nucleus	7	Fascia
9	71/F	Unknown	AD	Nucleus	12	Fascia
9	71/F	Unknown	AS	Nucleus	12	Fascia
10	70/M	Acoustic neuroma	AD	Nucleus	11	Fascia
11	74/M	Unknown	AD	Nucleus	12	Fascia
12	82/F	Unknown	AS	Advanced Bionics	8	Fat graft
13	83/M	Otosclerosis	AS	Nucleus	23	Muscle
14	82/M	Unknown	AS	Advanced Bionics	8	Fascia
15	76/M	Unknown	AS	Nucleus	18	Fascia
16	74/F	Otosclerosis	AS	Advanced Bionics	8	?
16	74/F	Otosclerosis	AD	Advanced Bionics	8	?
17	57/M	Superficial siderosis	AD	Nucleus	7	Fascia
18	71/M	Unknown	AD	Nucleus	13	Muscle
18	71/M	Unknown	AS	Nucleus	12	Fascia
19	68/M	Skull fracture	AD	Nucleus	20	Fascia
19	68/M	Skull fracture	AS	Nucleus	3	?
20	84/F	Unknown	AD	Nucleus	13	Muscle

Age/Gender	Diagnosis	Implanted ear	Device	Duration of implantation	Tissue used to seal cochleostomy
21 92/M	Meniere's disease	AS	Nucleus	11	Fascia

AS: left, AD: right; F: female; M: male; “?”: not known.

Table 2

Inflammatory cell infiltration, fibrotic reaction and new bone formation scaling at three different 1mm-segments: 1- at the cochleostomy 2- middle of the electrode 3- the tip of the electrode.

	At the cochleostomy				Middle of electrode				Tip of the electrode						
	L	GC	E	F	B	L	GC	E	F	B	L	GC	E	F	B
1	3	2	0	2	3	1	2	0	2	2	1	2	0	1	0
2	0	1	0	2	2	0	0	0	2	0	0	0	0	1	0
2	1	2	0	2	2	0	1	0	1	1	0	1	0	1	0
3	2	3	0	3	2	0	1	0	1	0	0	1	0	1	0
3	3	2	0	2	3	0	2	0	2	0	0	1	0	1	0
4	2	3	0	3	3	2	2	0	3	3	2	2	0	2	2
5	0	1	0	3	3	0	1	0	2	2	0	1	0	2	2
6	2	2	0	3	3	1	3	0	2	2	1	2	0	1	1
6	2	2	0	3	3	1	1	0	2	2	1	1	0	1	0
7	2	2	0	3	3	0	1	0	1	0	0	1	0	1	0
8	2	1	2	2	1	0	0	0	1	1	0	0	0	1	0
9	2	2	0	3	3	0	1	0	0	0	0	1	0	0	0
9	2	2	0	3	3	0	1	0	1	0	0	1	0	1	0
10	2	2	1	3	3	1	1	0	3	1	1	1	0	2	1
11	0	2	0	2	1	0	0	0	0	0	0	0	0	0	0
12	1	1	0	3	3	1	1	0	2	2	0	2	0	2	2
13	1	2	0	3	3	1	1	0	2	2	1	1	0	2	2
14	2	2	0	2	2	2	2	0	2	0	2	2	0	2	0
15	3	2	0	2	2	1	1	0	2	1	1	1	0	1	1
16	0	1	0	3	3	1	1	0	2	1	0	1	0	1	0
16	1	2	0	3	3	1	2	0	2	1	1	2	0	2	1
17	3	2	1	3	3	2	2	0	2	0	3	2	2	1	0
18	3	3	2	3	3	3	3	2	3	3	3	3	2	2	3
18	3	3	2	3	3	3	3	2	3	3	3	3	2	2	3
19	3	2	2	3	2	0	0	0	2	1	1	1	1	2	1

	At the cochleostomy						Middle of electrode						Tip of the electrode					
	L	GC	E	F	B	L	GC	E	F	B	L	GC	E	F	B			
19	3	3	2	3	2	2	2	0	3	1	2	3	0	1	0			
20	2	0	0	2	3	0	0	0	1	0	0	0	0	1	0			
21	3	2	0	3	3	1	1	0	1	1	1	1	0	1	1			

L: lymphocytic infiltration; GC: foreign body giant cell infiltration; E: eosinophil infiltration; F: fibrotic reaction; B: new bone formation. (0= none, 1= mild infiltration or presence, 2= moderate infiltration or presence, 3= severe infiltration or presence)

Table 3

Wilcoxon rank test results comparing the different elements of local tissue response between different segments.

	$L_M - L_C$	$L_T - L_C$	$L_T - L_M$	$GC_M - GC_C$	$GC_T - GC_C$	$GC_T - GC_M$	$E_M - E_C$	$E_T - E_C$	$E_T - E_M$	$F_M - F_C$	$F_T - F_C$	$F_T - F_M$	$B_M - B_C$	$B_T - B_C$	$B_T - B_M$
MNR	9.82	9.00	2.50	9.09	9.06	3.00	3.00	3.25	.00	9.50	14.00	7.00	12.50	13.50	4.50
MPR	4.00	.00	2.50	7.50	8.00	3.00	.00	2.00	1.50	.00	.00	.00	.00	.00	.00
Z	-3.63	-3.73	0.00	-3.50	-3.53	-0.45	-2.07	-1.52	-1.34	-3.87	-4.69	-3.50	-4.36	-4.52	-2.64
P-value	<0.01	<0.01	1.00	<0.01	<0.01	0.66	0.04	0.13	0.18	<0.01	<0.01	<0.01	<0.01	<0.01	0.01

L: lymphocyte infiltration; GC: foreign body giant cell infiltration; E: eosinophil infiltration; F: fibrotic reaction; B: new bone formation; M: middle of the electrode; C: cochleostomy; T: tip of the electrode; MNR: mean negative rank; MPR: mean positive rank.

Mann Whitney test results comparing the effect of different types of cochlear implant electrodes (Cochlear Nucleus® vs. Advanced Bionics®) as well as tissue used to seal the cochleostomy (fascia vs. muscle) on different elements of foreign body reaction near the electrode.

Table 4

	L _C	GC _C	E _C	F _C	B _C	L _T	GC _T	E _T	F _T	B _T
MR _{CN}	15.84	14.86	15.45	13.91	13.86	14.00	12.93	15.05	13.23	13.68
MR _{AB}	9.58	13.17	11.00	16.67	16.83	16.33	20.25	12.50	19.17	17.50
MWU _D	36.50	58.00	45.00	53.00	52.00	55.00	31.50	54.00	38.00	48.00
Z _D	-1.74	-0.51	-1.55	-0.90	-0.96	-0.66	-2.09	-1.11	-1.79	-1.13
P-value _D	0.08	0.61	0.12	0.37	0.34	0.51	0.04	0.27	0.07	0.26
N _D	28	28	28	28	28	28	28	28	28	28
MR _F	12.38	12.18	11.68	11.47	10.91	11.35	11.68	11.41	11.06	10.71
MR _M	8.50	9.20	10.90	11.60	13.50	12.00	10.90	11.80	13.00	14.20
MWU _S	27.50	31.00	39.50	42.00	32.50	40.00	39.50	41.00	35.00	29.00
Z _S	-1.27	-1.10	-0.30	-0.05	-0.92	-0.21	-0.25	-0.18	-0.67	-1.20
P-value _S	0.21	0.27	0.76	0.96	0.36	0.83	0.80	0.86	0.50	0.23
N _S	22	22	22	22	22	22	22	22	22	22

MRCN: mean rank in Cochlear Nucleus® group; MRAB: mean rank in Advanced Bionics® group; MRF: mean rank in fascia group; MRM: mean rank in muscle group; MWU: Mann-Whitney U; L: lymphocyte infiltration; GC: foreign body giant cell infiltration; E: eosinophil infiltration; F: fibrotic reaction; B: new bone formation; C: cochleostomy; T: tip of the electrode; D: comparison based on the device used to stimulate cochleae (Cochlear Nucleus® vs. Advanced Bionics®); S: comparison based on the tissue used to seal the cochleostomy (muscle vs. fascia).

Table 5

Spearman's analysis results evaluating correlation between duration of implantation and different elements of foreign body reaction.

Duration of implantation			
	Coefficient of correlation	P-value	N
L_C	.207	.290	28
GC_C	.115	.560	28
E_C	-.021	.916	28
F_C	-.062	.753	28
B_C	.030	.881	28
L_T	.057	.774	28
GC_T	-.277	.153	28
E_T	.208	.288	28
F_T	.035	.860	28
B_T	.157	.426	28

L: lymphocyte infiltration; GC: foreign body giant cell infiltration; E: eosinophil infiltration; F: fibrotic reaction; B: new bone formation; C: cochleostomy; T: tip of the electrode.