宇佐美真一	残存聴力活用型人工内耳(electric acoustic stimulation)	日本耳鼻咽喉科学会専門医通信	106	14-15	2011
宇佐美真一	補聴器と人工内耳の融合　残存聴力活用型人工内耳について	耳鼻咽喉科・頭頸部外科	83	393-401	2011
宇佐美真一	残存聴力活用型人工内耳（EAS: electric acoustic stimulation）	Clinical Neuroscience	29	1376-1378	2011
塚田景大、岩崎聡、茂木英明、工　穣、宮川麻衣子、西尾信哉、宇佐美真一	乳突皮質形成による残存聴力活用型人工内耳の術後聴力への影響	耳鼻咽喉科・頭頸部外科	84	91-95	2012

IV.　研究成果の刊行物・別刷

Acta Oto-Laryngologica, 2011; 131: 405–412

informa
healthcare

ORIGINAL ARTICLE

Achievement of hearing preservation in the presence of an electrode covering the residual hearing region

SHIN-ICHI USAMI[1], HIDEAKI MOTEKI[1], NOBUYOSHI SUZUKI[1], HISAKUNI FUKUOKA[1], MAIKO MIYAGAWA[1], SHIN-YA NISHIO[1], YUTAKA TAKUMI[1], SATOSHI IWASAKI[2] & CLAUDE JOLLY[3]

[1]*Department of Otorhinolaryngology,* [2]*Department of Hearing Implant Sciences, Shinshu University School of Medicine, Matsumoto, Japan and* [3]*MED-EL Headquarters, Innsbruck, Austria*

Abstract

Conclusions: With full insertion with a long electrode, hearing preservation can be achieved even in the presence of a long electrode covering the residual hearing region. *Objectives:* Advances in developing new atraumatic concepts of electrode design as well as surgical technique have enabled hearing preservation after cochlear implantation surgery, and EAS (electric acoustic stimulation) accompanied with hearing preservation is a new trend for patients with residual hearing at the lower frequencies. However, full insertion with a long/medium electrode and hearing preservation is still a challenging field that calls for discussion. *Method:* In this study, round window insertion, an atraumatic electrode, and dexamethasone administration were used and atraumaticity (hearing preservation and conservation of vestibular function) was evaluated with full insertion of the electrode. *Results:* Postoperative evaluation after full insertion of the electrodes showed that hearing at low frequencies was well preserved in all five cases. Combined postoperative imaging with the referential tonotopic map confirmed achievement of full insertion and indicated the corresponding frequencies and the depth of the electrode. Achievement of atraumaticity of round window insertion in the present cases was confirmed from the viewpoint of the minimal drilling time as well as the preserved vestibular function.

Keywords: *EAS, electric acoustic stimulation, high frequency hearing loss, cochlear implantation, deep insertion, atraumaticity*

Introduction

Advances in developing new atraumatic concepts of electrode design as well as surgical technique have enabled hearing preservation after cochlear implantation surgery, and EAS (electric acoustic stimulation) accompanied with hearing preservation is a new trend for patients with residual hearing at the lower frequencies.

However, a recent review collecting the data obtained by previous studies demonstrated that substantial acoustic hearing loss occurred in 24% of the patients, and among them 13% showed total loss [1]. Various techniques to preserve residual hearing at the lower frequencies have been attempted, including soft surgery technique when performing cochleostomy [2], round window insertion [3], use of atraumatic electrodes [4,5], and postoperative steroid administration.

Partial insertion up to 20 mm (where there is no residual hearing) is currently often performed [1], and full insertion with a long/medium electrode and hearing preservation is still a challenging field that calls for discussion. In this study, the method was based on atraumatic concepts and used round window insertion, an atraumatic electrode (in four of five cases), and dexamethasone administration. Hearing preservation and conservation of vestibular function were evaluated with full insertion of the electrode.

Correspondence: Shin-ichi Usami, Department of Otorhinolaryngology, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto 390-8621, Japan. Tel: +81 263 37 2666. Fax: +81 263 36 9164. E-mail: usami@shinshu-u.ac.jp

(Received 12 September 2010; accepted 26 September 2010)

ISSN 0001-6489 print/ISSN 1651-2251 online
DOI: 10.3109/00016489.2010.539266

Material and methods

We performed cochlear implantation with full insertion of the electrode (MEDEL COMBI40+® with a 31.5 mm standard electrode in one case, PULSAR® with a 24 mm FLEXeas® in three cases, and PULSAR® with a 31.3 mm FLEXsoft® in one case). The patients were aged from 38 to 68 years; two male, three female. All cases had post-lingual hearing loss at higher frequencies, starting from 30 to 40 years old and slowly progressive. The round window approach was applied to reduce the insertion damage of the cochlea. All surgeries were performed by a single surgeon (S.U.). Intraoperative infusion of dexamethasone (8 mg) was applied before drilling of the bony edge of the round window niche. Also postoperative dexamethasone treatment was administered for 6 days (8, 8, 4, 4, 2, and 2 mg, respectively). Insertion depth of the electrode and the corresponding frequencies were estimated by using postoperative X-ray (the X-ray digital linear tomosynthesis [6]). For comparison between round window insertion and cochleostomy insertion, drilling time to reach the perilymphatic space was averaged based on the video recording of 21 cases (round window insertion, 12 cases including the present 5 cases; cochleostomy insertion, 9 cases).

In addition to postoperative assessment of audiological testing, vestibular evoked myogenic potential (VEMP) as well as caloric response were analyzed to monitor atraumaticity of the surgery using nine cases (either round window insertion or

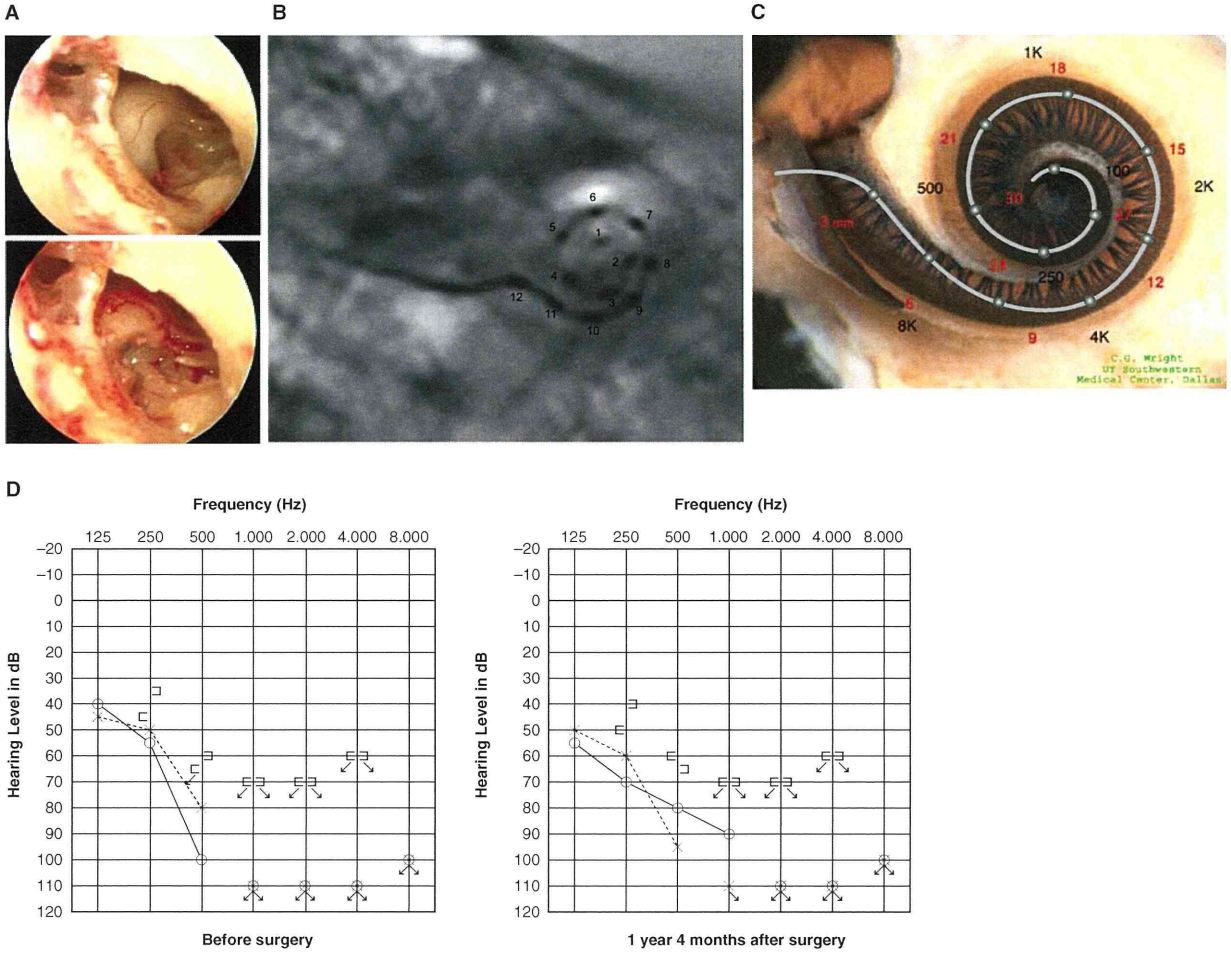

Figure 1. Case 1. A 60-year-old woman presented with slowly progressive bilateral hearing loss from age 40. By age 50 she had only minimal gain from hearing aids and when we first saw her they were nearly useless in her daily life. COMBI40+ with regular electrode was used for this patient on Dec 10, 2008. For insertion, the round window approach was applied, and full insertion was achieved. Complete preservation of residual hearing was obtained. (A) Endoscopic view of round window insertion, (B) postoperative X-ray finding, (C) imaging with putative location of electrode and the referential tonotopic map, (D) preoperative and postoperative audiograms. The image of human cochlea neural tissues stained by osmium tetroxide used in Figures 1–5 was kindly provided by Dr C.G. Wright, USWT, Dallas, USA (red, mm from round window; black, corresponding frequency).

cochleostomy), including the present five cases. In VEMP testing, the electrographic signal from the stimulated side was amplified and averaged using a Neuropack evoked potential recorder (Nihon Kohden Co. Ltd, Tokyo, Japan). Clicks lasting for 0.1 ms at 105 dBnHL were presented through a headphone. The stimulation rate was 5 Hz, the bandpass filter intensity was 20–2000 Hz, and analysis time was 50 ms. The responses to 200 stimuli were averaged twice. In caloric testing, maximum slow eye velocity was measured by cold water irrigation (20°C, 5 ml, 20 s). Postoperative VEMP and caloric responses of the implanted ears and contralateral ears were compared.

Results

Postoperative evaluation after full insertion of the electrodes showed that hearing at low frequencies was well preserved in all 5 cases, and then a speech processor (DUET EAS®) was applied for electric acoustic stimulation (EAS). Combined postoperative imaging with the referential tonotopic map confirmed achievement of full insertion and indicated the corresponding frequencies and the depth of the electrode (Figures 1–5). Audiological testing showed preservation of residual hearing, especially for bone conduction hearing (Figures 1–5).

Drilling time to reach the perilymphatic space based on the video recording was significantly less in the cases with round window insertion compared with cochleostomy cases (Figure 6, $p = 0.00001$, t test). VEMP responses could be recorded in four of five cases and were well preserved postoperatively. VEMP responses were decreased postoperatively in the cases with cochleostomy, in contrast to the round window insertion cases where the responses were maintained (Figure 7A). The ratio of the corrected amplitude value of cochlear implantation side divided by the normal side value was

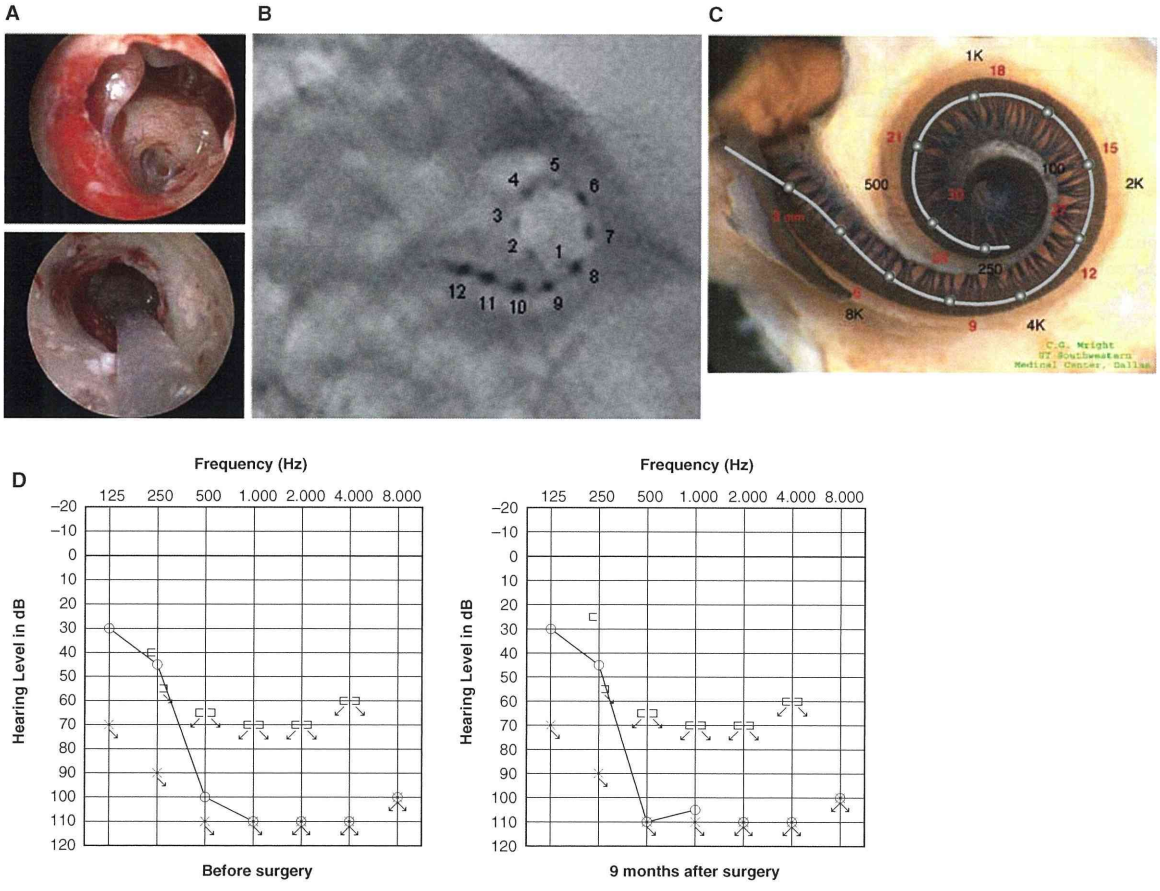

Figure 2. Case 2. This 39-year-old man was congenitally deaf in the left ear. Mild hearing loss in his right ear was noticed in childhood, and he presented with progressive hearing loss of 10 years duration. FLEXeas/RW approach was applied on Nov 16, 2009. Preservation of residual hearing was obtained. (A) Endoscopic view of round window insertion, (B) postoperative X-ray finding, (C) imaging with putative location of electrode and the referential tonotopic map, (D) preoperative and postoperative audiograms.

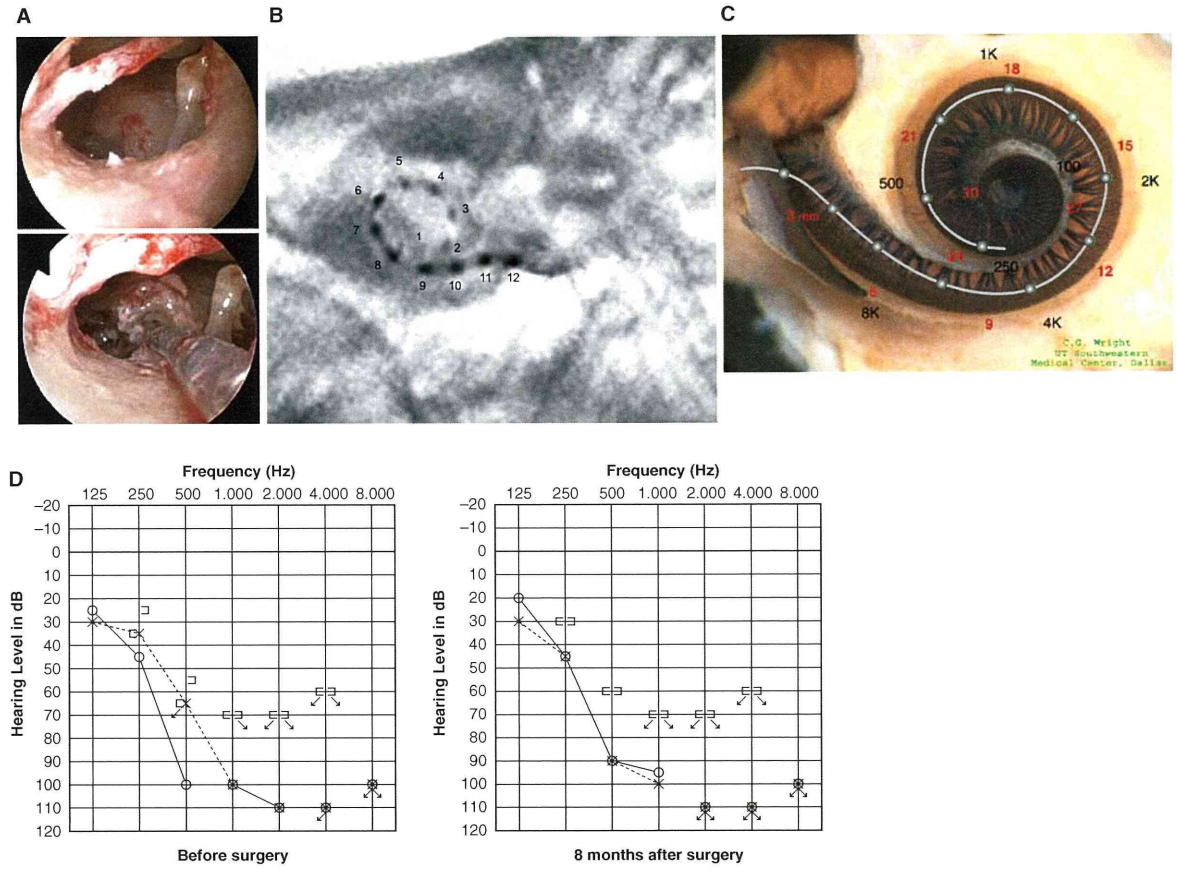

Figure 3. Case 3. This 45-year-old woman became aware of bilateral hearing loss and tinnitus around age 25. When she presented to us it had been slowly progressing for 10 years. PULSAR FLEXeas/RW approach was applied on Nov 18, 2009. Preservation of residual hearing was obtained. (A) Endoscopic view of round window insertion, (B) postoperative X-ray finding, (C) imaging with putative location of electrode and the referential tonotopic map, (D) preoperative and postoperative audiograms.

significantly lower in the cochleostomy cases than in the round window insertion cases ($p = 0.0001$, t test). Caloric response was well preserved and no difference was found between the two groups (Figure 7B, $p = 0.51$, t test).

Discussion

Hearing loss in the majority of these patients is more or less progressive, although the speed of progression, i.e. rapid or rather stable, may be dependent on their etiology. An unresolved issue is the prediction of progressiveness based on the etiology of individual hearing loss, but we have recently reported at least four genes that are responsible for the candidates for EAS, and therefore there is not a single etiology but rather a great genetic heterogeneity involved in this particular type of hearing loss [7]. Since shallow insertion of short electrodes cannot recruit neurons in the apical region, deep insertion would be the best solution to prevent future hearing deterioration at the lower frequencies. Full insertion with a long/medium electrode for the patients with residual hearing at the low frequencies is still a controversial field because of possible loss of their residual hearing due to mechanical trauma of the corresponding area.

In the present series, combined postoperative imaging with the referential tonotopic map clearly indicated that hearing preservation is achievable even in the presence of a long electrode covering the residual hearing region. Due to individual variation in the length of the cochlear turn, it is not sufficient to describe the length of the inserted electrode for estimating the corresponding frequencies of the tip of the electrode. In the present study, the X-ray digital linear tomosynthesis, which is known to have less artifacts and provide better understanding of the morphological relationship with the cochlear turn, indicated tonotopic orientation.

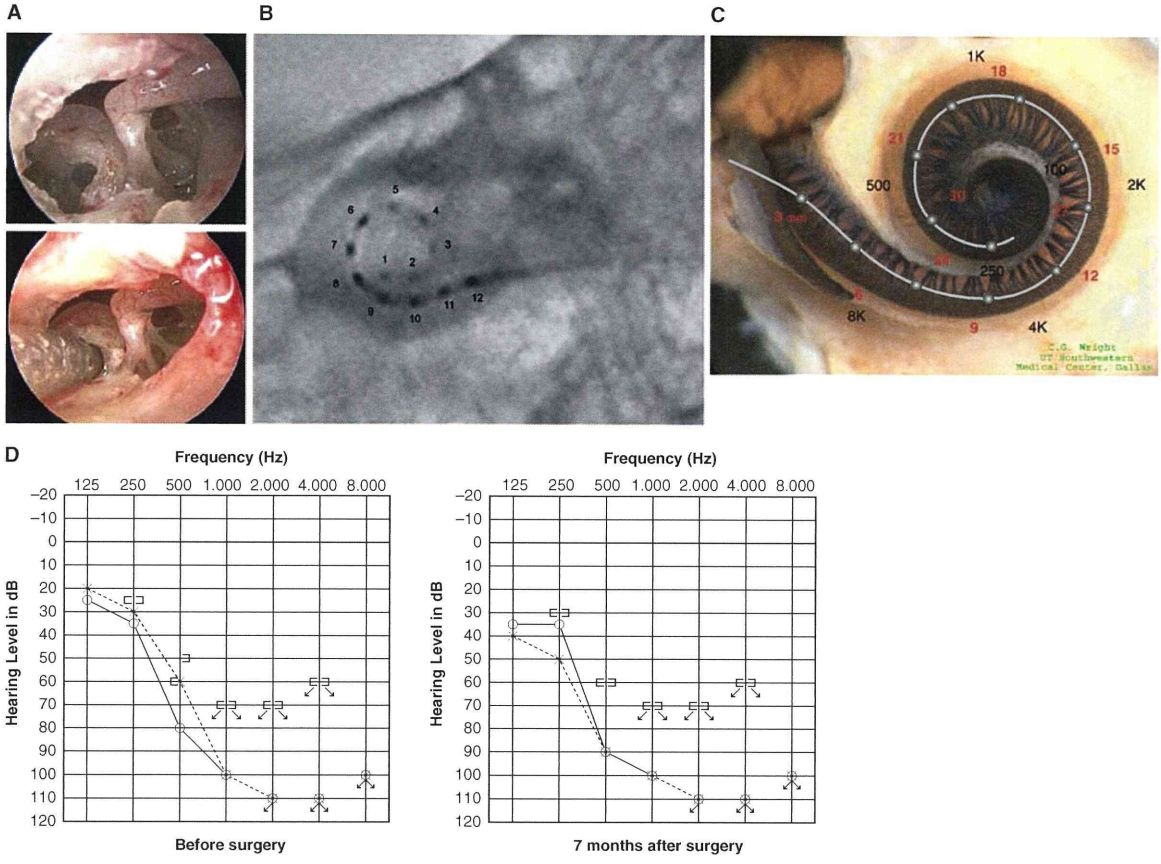

Figure 4. Case 4. This 38-year-old woman had hearing loss detected by mass screening in primary school. It appeared to slowly progress as she grew up, and by age 25 she suffered inconvenience in hearing and communication, mainly using only her left ear. The PULSAR FLEXeas/RW approach was applied on Dec 21, 2009. Preservation of residual hearing was obtained. (A) Endoscopic view of round window insertion, (B) postoperative X-ray finding, (C) imaging with putative location of electrode and the referential tonotopic map, (D) preoperative and postoperative audiograms.

With regard to the vibrations of the basilar membrane in the presence of the electrode, based on histological observations of morphologic changes in temporal bone studies, a close contact or even a slight lifting of the basilar membrane in the ascending basal and middle turns of the cochlea has been described [8]. However, in most cases, in adjacent regions, the basilar membrane was not in direct contact with the electrode, and lower frequencies were not affected by fixation in the basal and middle turn of the cochlea. Kiefer et al. [8] also reported the interesting phenomenon that audiological testing of the patients showed slightly better thresholds of the corresponding frequencies after implantation. Acoustic energy may increase perception in regions adjacent to the fixed regions, and basilar membrane behavior may be altered, i.e. some frequencies are redistributed and more amplified. In this series, some frequencies of the patients represented improvement after cochlear implantation (see Figure 1, air conduction hearing at 500 and 1000 Hz and bone conduction hearing at 500 Hz and Figure 2, bone conduction hearing at 250 Hz), supporting this phenomenon. On the other hand, in some cases, an air–bone gap was slightly recognized postoperatively (air conduction hearing was slightly elevated), perhaps due to a slight lifting of the basilar membrane in the middle turn observed in the temporal bone study [8].

These hearing improvement/deterioration results are not conclusive, because they could also be considered as within the margin of error. Serial testing as well as long follow-up observation period will resolve this issue, and we are currently working on this aspect.

Dexamethasone is known to have protective effects against insertion trauma as well as inflammatory process after implantation [9]. In this series, intraoperative infusion and postoperative dexamethasone treatment was administered systemically.

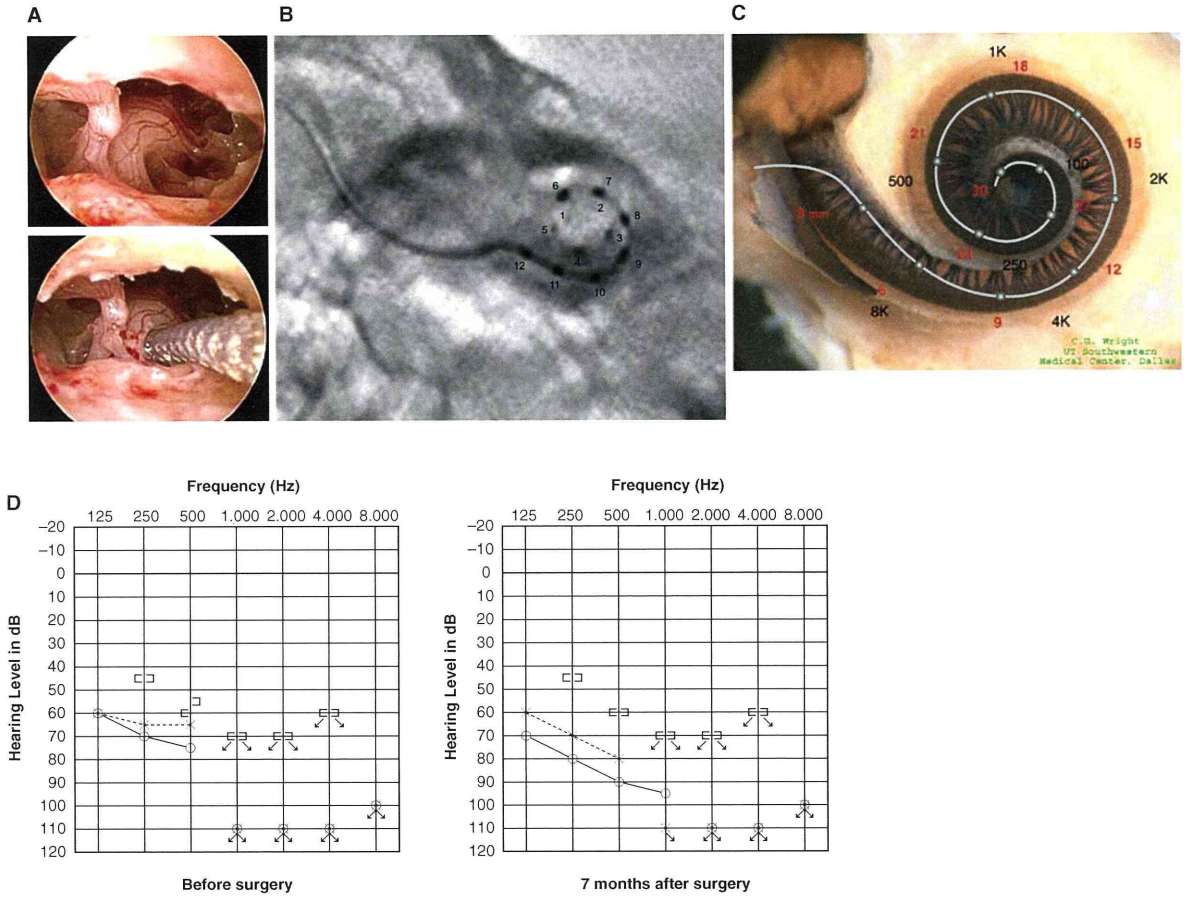

Figure 5. Case 5. This 68-year-old man presented with slowly progressive bilateral hearing loss from around age 40. He had only minimal gain from hearing aids. The PULSAR FLEXsoft/RW approach was applied on May 17, 2010. Preservation of residual hearing was obtained. (A) Endoscopic view of round window insertion, (B) postoperative X-ray finding, (C) imaging with putative location of electrode and the referential tonotopic map, (D) preoperative and postoperative audiograms.

There have been a series of trials with the goal of minimizing intracochlear trauma, by both cochleostomy insertion and round window insertion. For cochleostomy insertion, to avoid trauma, much attention has been paid to the cochleostomy site with the aim of avoiding the critical structures of the inner ear [10,11]. According to Lane et al. [12], by using 64-slice multidetector computed tomography (CT), localization of the electrode in the scala vestibuli as well as migration of the electrode array from the scala tympani to the scala vestibuli, which may influence hearing preservation, was observed in the patients with cochleostomy. On that basis, round window insertion was chosen in the present series.

Detailed clinical evaluation has confirmed the atraumaticity of the surgical approach in the present cases from the point of drilling time as well as of vestibular function.

During cochleostomy, noise levels were reported ranging from 114 to 128 dB SPL, indicating that during inner ear surgery they reach levels that can cause noise-induced hearing loss [13].

Our measurements clearly showed that drilling time to reach the perilymphatic space is significantly less for the round window approach compared with cochleostomy insertion, suggesting reduced influence of noise-induced trauma that may cause sensorineural hearing loss.

The importance of conservation of vestibular function is recognized, especially for bilateral cochlear implantation. A recent study suggested that dysfunction of the saccular macula, an integral component of the otolith system, likely resulting from insertion trauma of the cochlear implant electrode, can cause chronic dizziness after cochlear implantation [14]. In the present series, postoperative assessment of VEMPs as well as caloric response also supported

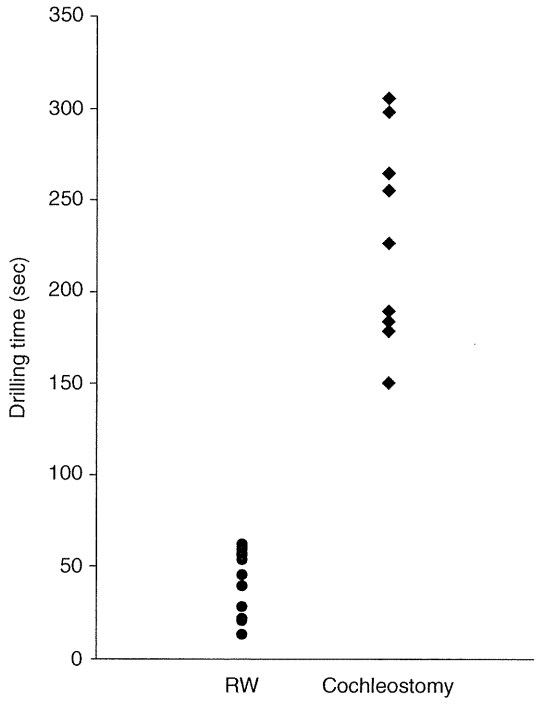

Figure 6. Video recording showing that drilling time to reach the perilymphatic space is significantly shorter for the round window approach compared with cochleostomy insertion.

achievement of atraumatic surgery from the vestibular functional point of view. Comparison with the cochleostomy insertion cases showed symmetrical VEMP scores in round window cases. The cochleostomy cases showed poorer response postoperatively, indicating that saccular function may be affected by the cochleostomy. These data support the recent report that for the sacculus, which is known to be the most vulnerable vestibular organ, the round window approach is preferable from the viewpoint of vestibular function [15].

Conclusion

In our series of experiences with full insertion with a long electrode we were able to preserve residual hearing at low frequencies as well as the vestibular function. Combined postoperative imaging with the referential tonotopic map clearly indicated that hearing preservation can be achieved even in the presence of a long electrode covering the residual hearing region and indicated that development of atraumatic procedures, including fine flexible electrodes, surgical technique (round window insertion), and postoperative steroid application enabled successful hearing preservation.

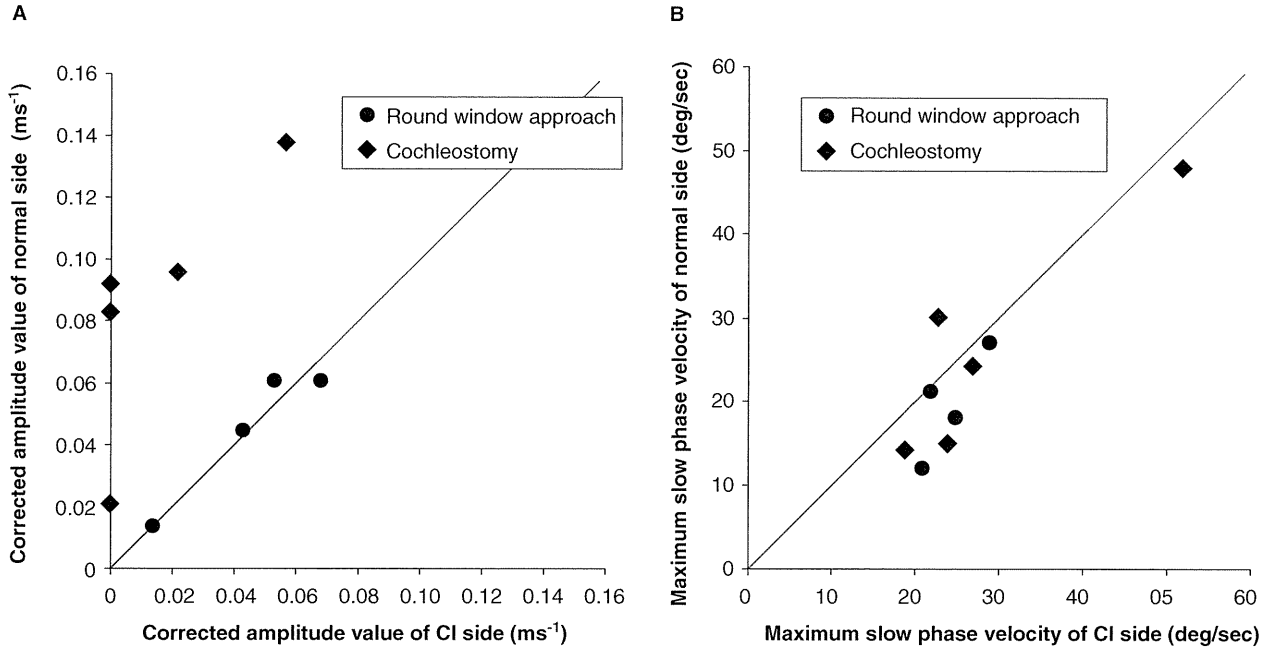

Figure 7. (A) Vestibular evoked myogenic potential (VEMP) responses were recorded in four of five cases and were well preserved postoperatively. VEMP responses decreased postoperatively in the cochleostomy cases while they were maintained in the round window insertion cases. Corrected amplitude value Cp13-n23 (ms^{-1}) = amplitude Cp13-n23 (micro V)/background electromyographic activities (micro V ms). (B) Caloric response was well preserved and there were no differences between the two groups. MSV, maximum slow eye velocity.

Acknowledgments

We thank Ms A.C. Apple-Mathews for help in preparing the manuscript. This study was supported by a Health Sciences Research Grant (Research on Eye and Ear Science, Immunology, Allergy and Organ Transplantation) from the Ministry of Health and Welfare of Japan.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Talbot KN, Hartley DE. Combined electro-acoustic stimulation: a beneficial union? Clin Otolaryngol 2008;33:536–45.

[2] Lehnhardt E, Laszig R. 1994. Specific surgical aspects of cochlear implant soft surgery. In: Hochmair-Desoyer IJ, Hochmair ES, editors. Advances in cochlear implants. Vienna: Manz. p 228–9.

[3] Skarzynski H, Lorens A, Piotrowska A, Anderson I. Preservation of low frequency hearing in partial deafness cochlear implantation (PDCI) using the round window surgical approach. Acta Otolaryngol 2007;127:41–8.

[4] Adunka O, Kiefer J, Unkelbach MH, Lehnert T, Gstoettner W. Development and evaluation of an improved cochlear implant electrode design for electric acoustic stimulation. Laryngoscope 2004;114:1237–41.

[5] Baumgartner WD, Jappel A, Morera C, Gstöttner W, Müller J, Kiefer J, et al. Outcomes in adults implanted with the FLEXsoft electrode. Acta Otolaryngol 2007;127: 579–86.

[6] Gomi T, Hirano H, Umeda T. Evaluation of the X-ray digital linear tomosynthesis reconstruction processing method for metal artifact reduction. Comput Med Imaging Graph 2009; 33:267–74.

[7] Usami S, Miyagawa M, Suzuki N, Moteki H, Nishio S, Takumi Y, et al. Genetic background of candidates for EAS (Electric-Acoustic Stimulation). Audiol Med 2010;8: 28–32.

[8] Kiefer J, Böhnke F, Adunka O, Arnold W. Representation of acoustic signals in the human cochlea in presence of a cochlear implant electrode. Hear Res 2006;221:36–43.

[9] van de Water TR, Dinh CT, Vivero R, Hoosien G, Eshraghi AA, Balkany TJ. Mechanisms of hearing loss from trauma and inflammation: otoprotective therapies from the laboratory to the clinic. Acta Otolaryngol 2010; 130:308–11.

[10] Briggs RJ, Tykocinski M, Stidham K, Roberson JB. Cochleostomy site: implications for electrode placement and hearing preservation. Acta Otolaryngol 2005;125:870–6.

[11] Adunka OF, Pillsbury HC, Buchman CA. Minimizing intracochlear trauma during cochlear implantation. Adv Otorhinolaryngol 2010;67:96–107.

[12] Lane JI, Witte RJ, Driscoll CL, Shallop JK, Beatty CW, Primak AN. Scalar localization of the electrode array after cochlear implantation: clinical experience using 64-slice multidetector computed tomography. Otol Neurotol 2007;28: 658–62.

[13] Strömberg AK, Yin X, Olofsson A, Duan M. Evaluation of the usefulness of a silicone tube connected to a microphone in monitoring noise levels induced by drilling during mastoidectomy and cochleostomy. Acta Otolaryngol 2010;130: 1163–8.

[14] Basta D, Todt I, Goepel F, Ernst A. Loss of saccular function after cochlear implantation: the diagnostic impact of intracochlear electrically elicited vestibular evoked myogenic potentials. Audiol Neurootol 2008;13:187–92.

[15] Todt I, Basta D, Ernst A. Does the surgical approach in cochlear implantation influence the occurrence of postoperative vertigo? Otolaryngol Head Neck Surg 2008; 138:8–12.

Acta Oto-Laryngologica, 2012; 132: 377–384

informa
healthcare

ORIGINAL ARTICLE

Patients with *CDH23* mutations and the 1555A>G mitochondrial mutation are good candidates for electric acoustic stimulation (EAS)

SHIN-ICHI USAMI[1], MAIKO MIYAGAWA[1], SHIN-YA NISHIO[1], HIDEAKI MOTEKI[1,2], YUTAKA TAKUMI[1,2], MIKA SUZUKI[1], YOKO KITANO[3] & SATOSHI IWASAKI[2]

[1]*Department of Otorhinolaryngology, Shinshu University School of Medicine,* [2]*Department of Hearing Implant Sciences, Shinshu University School of Medicine, Matsumoto, Japan and* [3]*School of Health Sciences, Tokai University, Isehara, Japan*

Abstract

Conclusions: CDH23 mutations and the 1555A>G mitochondrial mutation were identified among our series of electric acoustic stimulation (EAS) patients, confirming that these genes were important in hearing loss with involvement of high frequency. Successful hearing preservation as well as good outcomes from EAS indicated that patients with this combination of mutations are good candidates for EAS. *Objectives:* Screening for gene mutations that possibly cause hearing loss involving high frequency was performed to identify the responsible genes in patients with EAS. In addition to a review of the genetic background of the patients with residual hearing loss, the benefit of EAS for patients with particular gene mutations was evaluated. *Methods:* Eighteen patients (15 late-onset, 3 early-onset) with residual hearing who had received EAS were included in this study. Genetic analysis was performed to identify *GJB2, CDH23, SLC26A4,* and the 1555 mitochondrial mutations. *Results:* Three early-onset patients had *CDH23* mutations. One late-onset patient had the 1555 A>G mitochondrial mutation.

Keywords: *Residual hearing, hearing preservation, gene, mitochondria, 12S rRNA*

Introduction

Hearing loss in the majority of patients with residual hearing at lower frequencies is more or less progressive, although the speed of progression, i.e. rapid or rather stable, may be dependent on the etiology. An unresolved issue is the prediction of progressiveness based on the etiology of individual hearing loss. We have recently reported at least four genes that are responsible for the candidates for electric acoustic stimulation (EAS), and therefore there is not a single etiology but rather a great genetic heterogeneity involved in this particular type of hearing loss [1]. In this study, screening for mutations of four genes (*GJB2, CDH23, SLC26A4,* and the 1555 mitochondrial mutations), which possibly cause high frequency hearing loss, was performed to identify the responsible genes for 18 patients with EAS.

Material and methods

Eighteen patients (8 males and 10 females, aged 1–68 years) were included in this study. Clinical features of the subjects are summarized in Table I. As regards onset of hearing loss, 15 patients were late-onset (10–50 years old) and 3 patients were early-onset (most probably congenital). Anamnestic evaluation and/or serial audiogram indicated that all of the patients had progressive sensorineural hearing loss. No patients had any anomalies such as enlarged vestibular aqueduct. All patients had some residual hearing in the lower frequencies, and therefore received EAS. The round window approach was applied for all the patients, and intraoperative and postoperative intravenous administration of dexamethasone was used as described in a previous report [2]. For genetic analysis, direct sequencing for *GJB2, SLC26A4, CDH23,* and

Correspondence: Shin-ichi Usami, Department of Otorhinolaryngology, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto 390-8621, Japan. Tel: +81 263 37 2666. Fax: +81 263 36 9164. E-mail: usami@shinshu-u.ac.jp

(Received 29 September 2011; accepted 13 November 2011)

ISSN 0001-6489 print/ISSN 1651-2251 online
DOI: 10.3109/00016489.2011.649493

Table I. Clinical features of subjects in study.

Case no.	Gender	Age (EAS)	Onset (age)	Progressiveness	Inheritance mode	Responsible gene	Implant	Insertion depth (mm)
1	F	59	Late (43)	+	Sporadic	N/I	PULSAR FLEXeas	24
2	F	71	Late (30)	+	AD	N/I	PULSAR FLEXeas	24
3	F	45	Late (25–30)	+	Sporadic	N/I	PULSAR FLEXeas	24
4	F	38	Late (34)	+	Sporadic	N/I	PULSAR FLEXeas	24
5	F	46	Late (30)	+	AD	N/I	PULSAR FLEXeas	24
6	M	29	Late (10)	+	AD	N/I	PULSAR FLEXeas	24
7	M	39	Late (20)	+	AD	N/I	PULSAR FLEXeas	24
8	F	35	Late (25)	+	Sporadic	N/I	PULSAR FLEXeas	24
9	M	52	Late (25)	+	Mitochondrial	*Mit. 1555A>G*	PULSAR FLEXeas	24
10	F	51	Late (30)	+	AD	N/I	PULSAR FLEXeas	24
11	M	39	Late (6)	+	Sporadic	N/I	PULSAR FLEXeas	24
12	F	45	Late (25)	+	Sporadic	N/I	PULSAR FLEXeas	24
13	F	38	Late (10)	+	AR	N/I	PULSAR FLEXeas	24
14	F	60	Late (40)	+	AD	N/I	Combi 40+ standard	31.5
15	M	68	Late (50)	+	Sporadic	N/I	PULSAR FLEXsoft	31.5
16	M	12	Early (3)*	+	AR	*CDH23*	PULSAR FLEXsoft	31.5
17	M	12	Early (1 year 8 months)*	+	AR	*CDH23*	PULSAR FLEXsoft	31.5
18	M	1	Early (0)†	NA	Sporadic	*CDH23*	PULSAR FLEXsoft	31.5

N/I, not identified within four genes.
*Most probably congenital.
†Newborn hearing screening.

the 1555 mitochondrial mutation was performed. Detailed methods are described elsewhere [3-6].

Results

All three early-onset patients had *CDH23* mutations (case nos 16, 17, and 18; Figures 1,2,3). One post-lingual patient had the 1555 A>G mitochondrial mutation (case no. 9; Figure 4). Hearing in the low frequencies after cochlear implantation was well preserved in all 18 cases including these 4 cases.

Case nos 16 and 17 (Figures 1 and 2)

The patients were 12-year-old twins, had the same mutations in the *CDH23* gene, and showed similar audiograms and a slowly progressive nature confirmed by serial audiograms. Both had some residual hearing in the lower frequencies and used hearing aids, but due to the progression of their hearing loss, they received cochlear implants (Nucleus CI24M device, with complete insertion of a straight array through cochleostomy) for the left ear at the age of 5 (no. 16) and 6 (no. 17). In one of the twins (no. 16) residual hearing was successfully preserved (Figure 1D), but the other (no. 17) lost his air-conduction thresholds after cochlear implantation even though the bone-conduction threshold remained stable (Figure 2D). Their audiological performance was good with the cochlear implantation (electric stimulation only). They wanted to have cochlear implants on the other sides, considering their residual hearing and the progressive nature of the hearing loss, and we decided to use a longer atraumatic electrode (MEDEL PULSAR CI100/FLEXsoft electrode) to cover the low frequencies (Figure 1A, B, C; Figure 2A, B, C). Hearing was well preserved 6 months postoperatively (Figures 1D and 2D). Both had compound heterozygous mutations (p.P240L/p.R301Q), and their parents were found to be carriers for these mutations (Figure 2E). After identification of the *CDH23* mutations, they were referred for ophthalmologic examination including electroretinography (ERG) and visual field analysis. Both had normal ERG response and no visual field deficits, confirming the nonsyndromic phenotype (DFNB12). Furthermore, they did not have any vestibular problems and showed normal responses in caloric testing. Their hearing thresholds improved to 30 dB and 35 dB (nos 16 and 17, respectively)

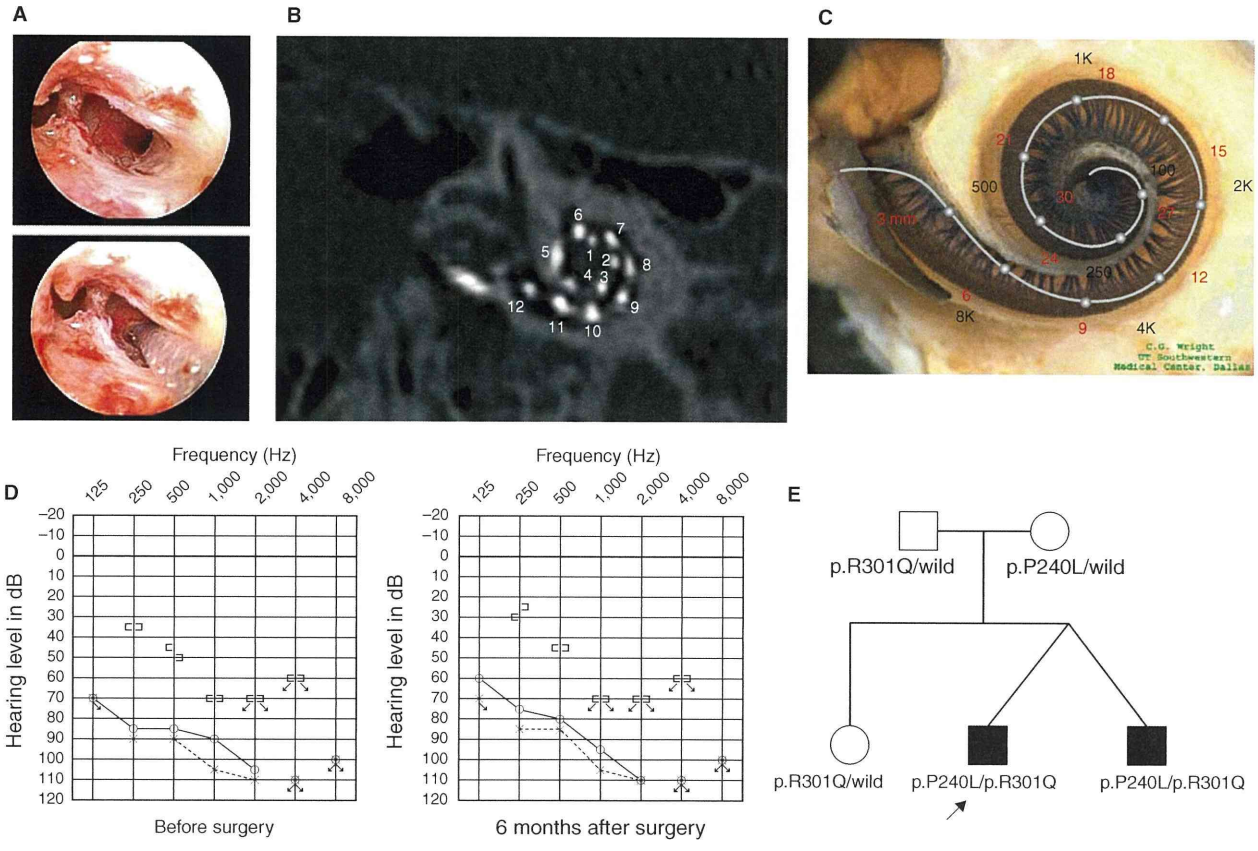

Figure 1. Case no. 16. (A) Endoscopic view of round window insertion, (B) montage CT image, (C) imaging with putative location of electrode and the referential tonotoic map, (D) preoperative and postoperative audiograms. The image of human cochlea neural tissues stained by osmium tetroxide used in Figures 1,2,3,4 was kindly provided by Dr C.G. Wright, USWT, Dallas, USA (red, mm from round window; black, corresponding frequency). (E) Pedigree and the mutations found in the CDH23 gene.

(average for all frequencies from 125 to 8000 Hz) 1 year after cochlear implantation. Their word recognition scores in quiet improved from 64% to 76% (no. 16) and from 60% to 76% (no. 17) at 1 year postoperatively.

Case no. 18 (Figure 3)

This case was a 1-year-old boy with the *CDH23* mutations. Auditory steady-state response (ASSR) evaluated at the age of 4 and 7 months showed some residual hearing at 500 Hz in the right ear (Figure 3D). He first received a left cochlear implant (MEDEL PULSAR CI100/standard electrode) at the age of 9 months. The parents wanted him to use a cochlear implant on the right side as well, and we decided to use a more atraumatic electrode (MEDEL PULSAR CI100/FLEXsoft electrode) because of the possible residual hearing in the low frequencies (Figure 3A, B, C). The second cochlear implant surgery was performed at the age of 12 months. Residual hearing measured by conditioned orientation reflex (COR) audiometry [7] was well preserved 1 year after cochlear implantation (Figure 3D). This patient had compound heterozygous mutations (p.[D1216A; V1807M]/p.Q1716P) and the parents were found to be carriers for these mutations (Figure 3E). Although the patient was too young to undergo ophthalmologic examination, he did not have any problems in vision or any vestibular problems, and there is no indicative evidence for Usher syndrome at this time.

In this very young case, auditory behavioral development was assessed by using the LittlEARS® Auditory Questionnaire, which has been designed for children under the age of 2 years [8,9]. The development curve showed a rapid increase in auditory behavior and reached the score seen in normally developed children (c 3F).

Case no. 9 (Figure 4)

This case was a 52-year-old male with the 1555A>G mitochondrial mutation. He noticed hearing loss around age 38 and used hearing aids, but his hearing loss was slowly progressive as evaluated by serial audiograms. Due to residual hearing in the lower frequencies,

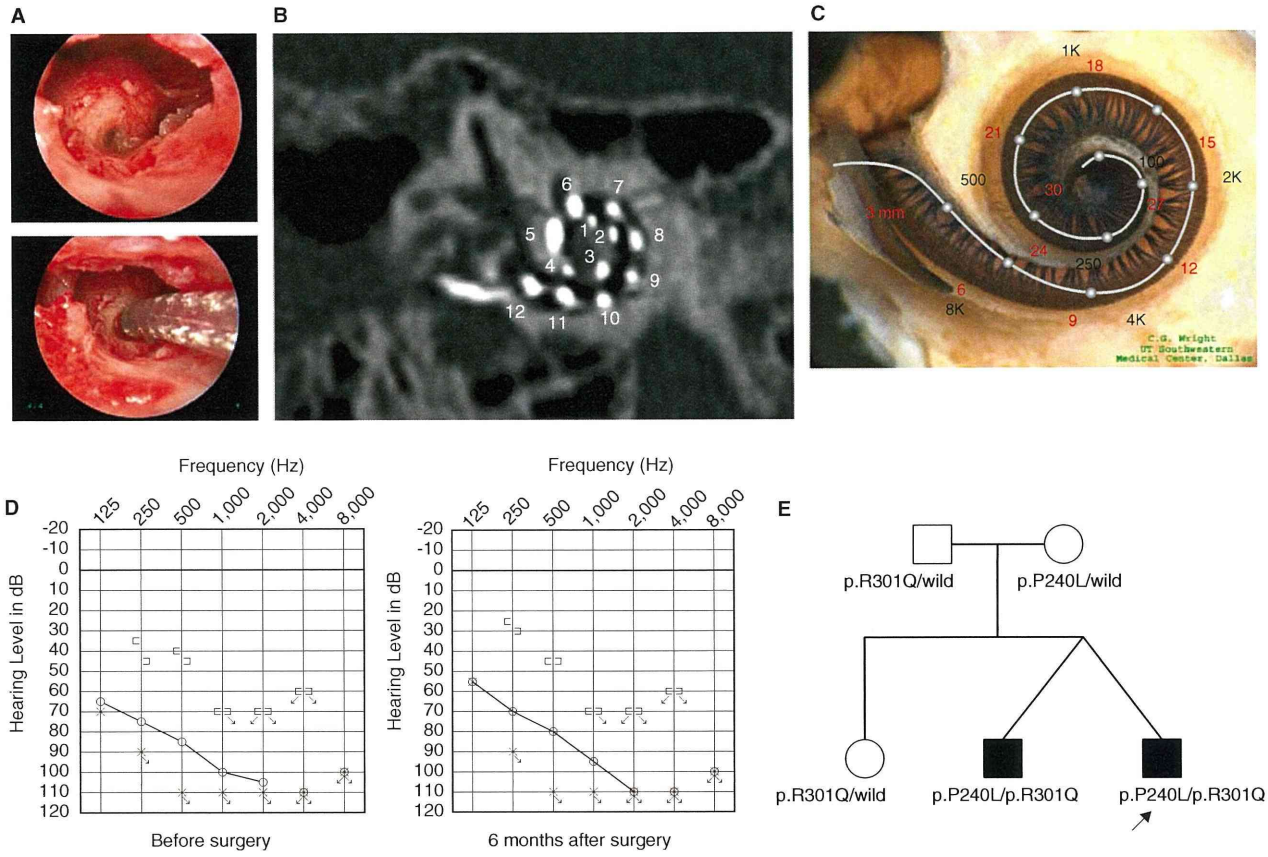

Figure 2. Case no. 17. (A) Endoscopic view of round window insertion, (B) montage CT image, (C) imaging with putative location of electrode and the referential tonotoic map, (D) preoperative and postoperative audiograms. (E) Pedigree and the mutations found in the *CDH23* gene.

an atraumatic electrode (MEDEL PULSAR CI100/FLEXeas electrode) was chosen (Figure 4A, B, C). Residual hearing was well preserved at 2 months postoperatively (Figure 4D). His parents had hearing loss, and the pedigree was consistent with mitochondrial inheritance (as well as autosomal dominant inheritance) (Figure 4E). Genetic screening detected the 1555 mitochondrial mutation in the patient and his mother. He had no history of exposure to aminoglycoside antibiotics. No vestibular symptoms were noted, and no abnormal findings were seen in vestibular testing including caloric response and vestibular evoked myogenic potential (VEMP). His hearing threshold improved to 30 dB (average for all frequencies from 125 to 8000 Hz) 2 months after cochlear implantation. Due to an insufficient follow-up period, his speech recognition score has not yet been evaluated.

Discussion

As predicted from our previous study [1] using patients who fulfilled the criteria for EAS, the *CDH23* mutations and the 1555A>G mitochondrial mutation were in fact found among our series of EAS patients.

Our previous study indicated that the *CDH23* mutations were frequently found in patients with recessive inheritance and the presence of residual hearing is one particular phenotypic feature of the patients with *CDH23* mutations [5], and actually all of the early-onset patients had the mutations in this gene.

The *CDH23* gene encodes cadherin 23, a protein thought to be a molecule that forms the lateral links between the stereocilia of hair cells [10]. One remarkable result in this study is that function of the lateral links remained stable even after deep insertion of the electrode of the cochlear implant. Such functional preservation enabled hearing preservation even in the presence of an electrode covering the corresponding frequency region.

As suggested by genotype–phenotype correlation study, USH1D, which has a more severe phenotype including severe to profound hearing loss, vestibular dysfunction, and retinitis pigmentosa, is usually associated with nonsense, splicing-site, and frameshift

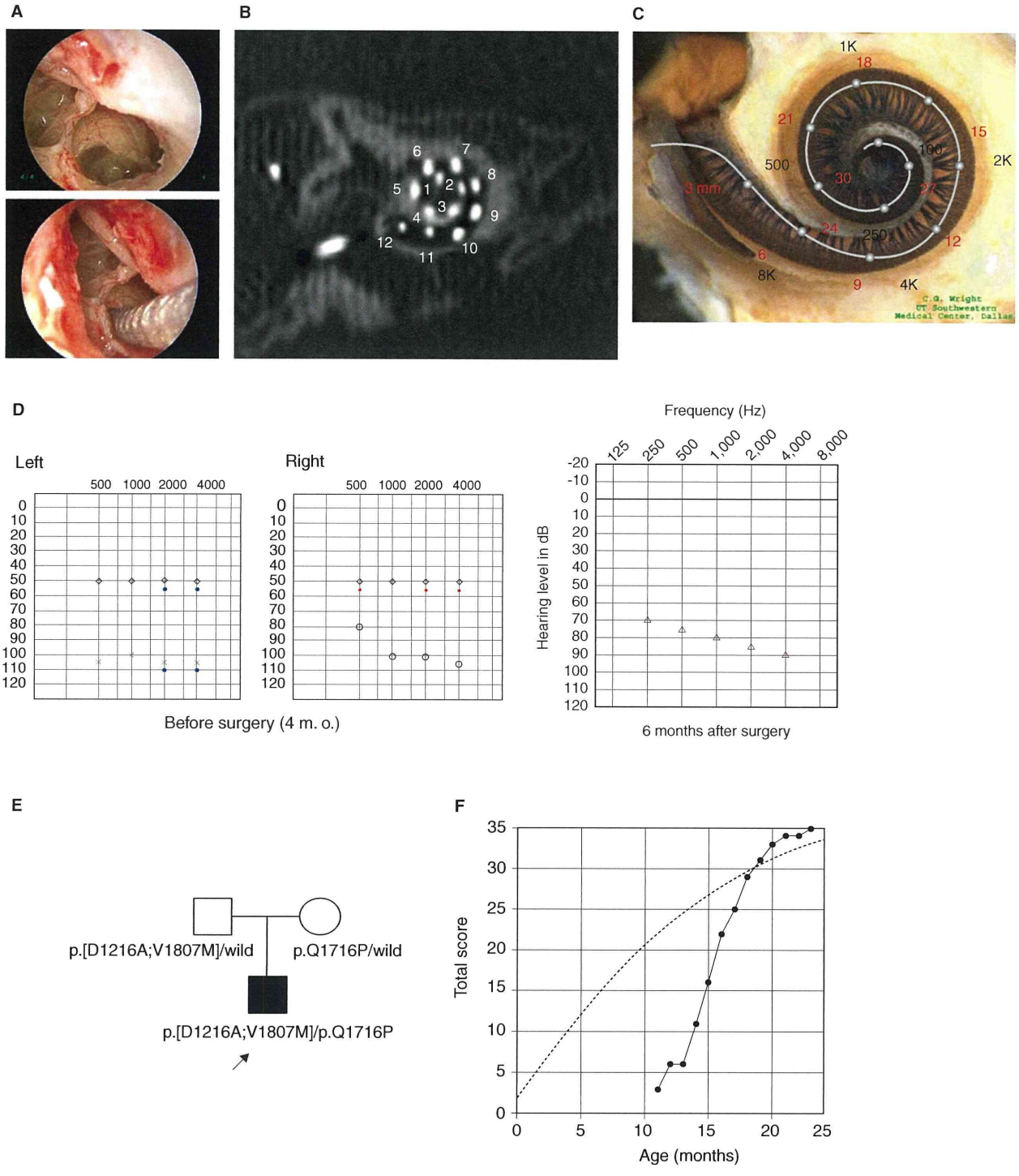

Figure 3. Case no. 18. (A) Endoscopic view of round window insertion, (B) montage CT image, (C) imaging with putative location of electrode and the referential tonotoic map, (D) preoperative ASSR findings (blue, left; red, right) and postoperative COR audiogram finding. (E) Pedigree and the mutations found in the *CDH23* gene. (F) Auditory behavioral development assessed by LittlEARS® Auditory Questionnaire. The development curve shows rapid improvement in auditory behavior reaching the curve of normally developed children.

mutations. In contrast, DFNB12, which has a milder phenotype, is associated with missense mutations [11,12]. The mutations found in the present three cases (we previously reported case nos 16 and 17 as family no. 3 [5]) are consistent with the general genotype–phenotype correlation rule.

In Usher type I patients, known to have the same etiology, improvement in sound detection as well as

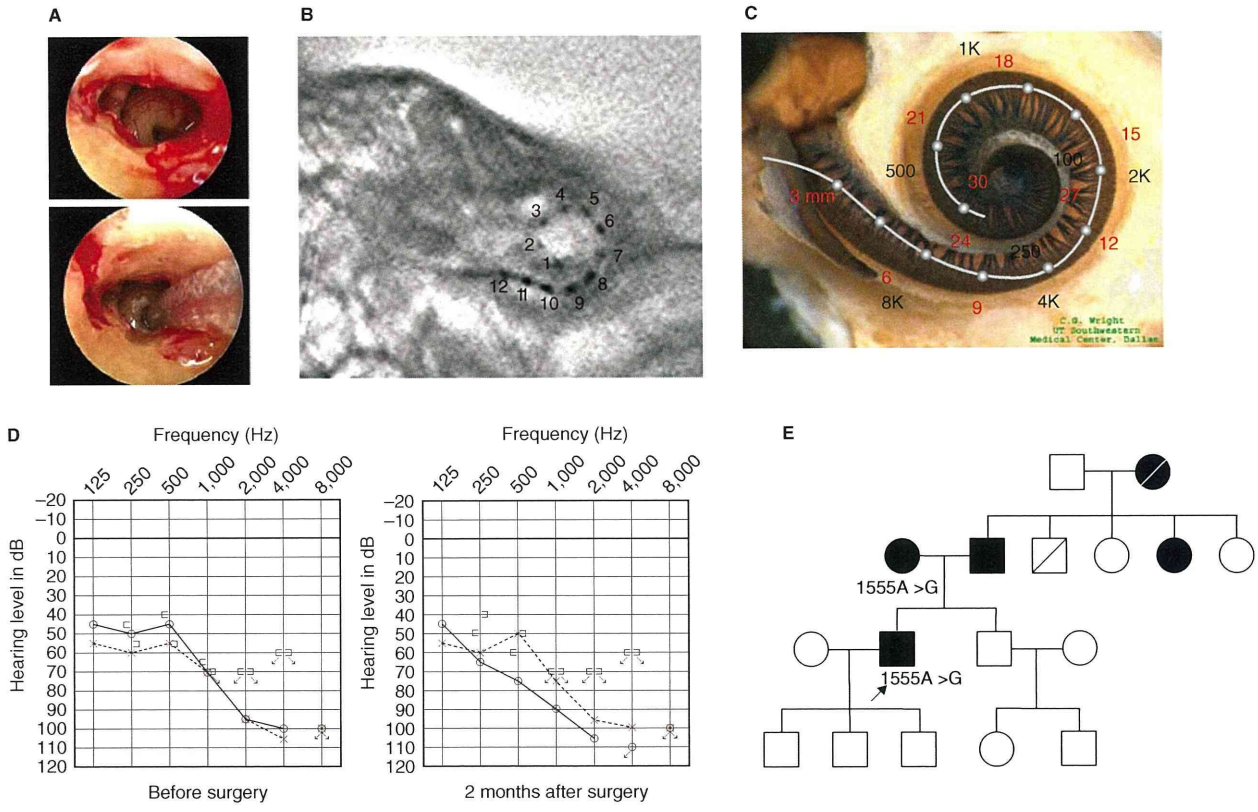

Figure 4. Case no. 9. (A) Endoscopic view of round window insertion, (B) postoperative X-ray finding, (C) imaging with putative location of electrode and the referential tonotoic map, (D) preoperative and postoperative audiograms. (E) Pedigree and the subjects with the mitochondrial 1555 mutations.

speech perception was seen in all patients, especially younger ones [13]. The present study clearly indicates that patients with the *CDH23* mutations are good candidates for EAS. The previous report together with the present cases indicates that progressiveness of hearing loss is a characteristic feature of the patients with this mutation [5,12]. Therefore, deep insertion with longer electrodes is recommended to prevent future deterioration. Successful hearing preservation and prediction of future hearing level by genetic diagnosis may facilitate decision making for early intervention.

It is interesting that *GJB2*, the most prevalent causative gene among the prelingual patients, was not found in the present series of patients. This is probably due to their more or less flat audiograms [1] and therefore they may be good candidates for conventional cochlear implantation.

In very young children, pure tone audiograms are not available. Acoustic brainstem response (ABR) is usually used to evaluate their hearing, but it is difficult to measure residual hearing in the low frequencies. Recently, acoustic steady-state response (ASSR) has been clinically available to measure hearing levels of 500 Hz or 250 Hz, but sometimes the low frequency part is not reliable or convincing [14]. In addition to such hearing testing, genetic testing is useful to predict the residual hearing at low frequencies. Especially for cases with *CDH23* mutations, predicted audiograms can be obtained for the very young patients. Based on this concept, together with consideration of their expected long life (which includes a risk of progression), we chose a longer atraumatic electrode (MEDEL PULSAR CI100/FLEXsoft electrode) for three patients with *CDH23* mutations.

It is known that patients with the 1555A>G mitochondrial mutation are susceptible to aminoglycoside antibiotics [15]. The 1555A>G mutation is one of the most important mutations among the hearing loss population in Japan, and approximately 3% of patients with sensorineural hearing loss possess this mutation [16]. Their hearing loss is known to be slowly progressive [6,17]. This mutation is an important cause in the post-lingual cochlear implant patients, found in 10% of them [16]. It has been reported that a patient with cochlear implantation showed excellent auditory performance [18], indicating that cochlear implantation is a valuable choice of therapy for patients with profound hearing loss caused by this mutation. This mutation was also found in

patients without any aminoglycoside exposure and their hearing loss was usually milder than those with aminoglycoside exposure [19]. Environmental causative factors other than aminoglycoside antibiotics – such as noise or mechanical stress – have been speculated, although not confirmed. The present study provided an important clinical experience that EAS could be safely performed even if the patients have this mutation and therefore possible association of susceptibility for any mechanical stress.

For outcome of EAS, together with successful hearing preservation, all four patients obtained 25–35 dB in average hearing threshold after implantation. Since EAS was implanted as a second cochlear implant for three cases with *CDH23* mutations, it is difficult to evaluate the independent benefit of EAS. However, improvement of word recognition scores after EAS was observed in case nos 16 and 17, indicating that additive benefit was clearly obtained even after a rather long period following the first implants (at 7 years and 6 years, respectively). For case no. 18, although it is also difficult to evaluate the independent benefit of EAS because of the very young age, the auditory behavioral development as assessed by the LittlEARS® Auditory Questionnaire was significantly improved after two consecutive implantations. Since the *CDH23* mutation will be potentially found in rather young candidates, this genetic marker could be available for the existence of residual hearing. For those patients, it is strongly suggested that the surgeon keep in mind the option of performing atraumatic surgery.

In the present series, there are many families with autosomal dominant hearing loss (6 of 18), suggesting that many other genes responsible for dominant hearing loss may be involved. It is also important to note that all of the patients showed progressive hearing loss. We are currently searching for the responsible genes for the patients with high frequency hearing loss.

In conclusion, the *CDH23* mutations and the 1555A>G mitochondrial mutation were identified among our series of EAS patients, confirming that these genes were important in high frequency hearing loss. Successful hearing preservation in these patients as well as good outcomes of EAS indicated that those with these mutations are good candidates for EAS. The present study indicates that genetic testing provides useful information regarding residual hearing and consequent therapeutic options.

Acknowledgments

We thank A.C. Apple-Mathews for help in preparing the manuscript. This study was supported by a Health and Labour Sciences Research Grant for Comprehensive Research on Disability Health and Welfare from the Ministry of Health, Labour and Welfare of Japan (S.U.), by the Acute Profound Deafness Research Committee of the Ministry of Health, Labour and Welfare of Japan (S.U.), and by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan (http://www.mext.go.jp/english/) (S.U.).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Usami S, Miyagawa M, Suzuki N, Moteki H, Nishio S, Takumi Y, et al. Genetic background of candidates for EAS (Electric-Acoustic Stimulation). Audiol Med 2010;8:28–32.

[2] Usami S, Moteki H, Suzuki N, Fukuoka H, Miyagawa M, Nishio SY, et al. Achievement of hearing preservation in the presence of an electrode covering the residual hearing region. Acta Otolaryngol 2011;131:405–12.

[3] Abe S, Usami S, Shinkawa H, Kelley PM, Kimberling WJ. Prevalent connexin 26 gene (GJB2) mutations in Japanese. J Med Genet 2000;37:41–3.

[4] Usami S, Abe S, Weston MD, Shinkawa H, Van Camp G, Kimberling WJ. Non-syndromic hearing loss associated with enlarged vestibular aqueduct is caused by PDS mutations. Hum Genet 1999;104:188–92.

[5] Wagatsuma M, Kitoh R, Suzuki H, Fukuoka H, Takumi Y, Usami S. Distribution and frequencies of CDH23 mutations in Japanese patients with non-syndromic hearing loss. Clin Genet 2007;72:339–44.

[6] Usami S, Abe S, Kasai M, Shinkawa H, Moeller B, Kenyon JB, et al. Genetic and clinical features of sensorineural hearing loss associated with the 1555 mitochondrial mutation. Laryngoscope 1997;107:483–90.

[7] Suzuki T, Ogiba Y. Conditioned orientation reflex audiometry. Arch Otolaryngol 1961;74:192–8.

[8] Tsiakpini L, Weichbold V, Kuehn-Inacker H, Coninx F, D'Haese P, Almadin S. 2004. LittlEARS Auditory Questionnaire. Innsbruck: MED-EL.

[9] Coninx F, Weichbold V, Tsiakpini L, Autrique E, Bescond G, Tamas L, et al. Validation of the LittlEARS ((R)) auditory questionnaire in children with normal hearing. Int J Pediatr Otorhinolaryngol 2009;73:1761–8.

[10] Siemens J, Lillo C, Dumont RA, Reynolds A, Williams DS, Gillespie PG, et al. Cadherin 23 is a component of the tip link in hair-cell stereocilia. Nature 2004;428:950–5.

[11] Bork JM, Peters LM, Riazuddin S, Bernstein SL, Ahmed ZM, Ness SL, et al. Usher syndrome 1D and nonsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of the novel cadherin-like gene CDH23. Am J Hum Genet 2001;68:26–37.

[12] Astuto LM, Bork JM, Weston MD, Askew JW, Fields RR, Orten DJ, et al. CDH23 mutation and phenotype heterogeneity: a profile of 107 diverse families with Usher syndrome and nonsyndromic deafness. Am J Hum Genet 2002;71:262–75.

[13] Liu XZ, Angeli SI, Rajput K, Yan D, Hodges AV, Eshraghi A, et al. Cochlear implantation in individuals with Usher type 1 syndrome. Int J Pediatr Otorhinolaryngol 2008;72:841–7.

[14] Picton TW, Durieux-Smith A, Champagne SC, Whittingham J, Moran LM, Giguère C, et al. Objective evaluation of aided thresholds using auditory steady-state responses. J Am Acad Audiol 1998;9:315–31.

[15] Prezant TR, Agapian JV, Bohlman MC, Bu X, Oztas S, Qiu WQ, et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. Nat Genet 1993;4:289–94.

[16] Usami S, Abe S, Akita J, Namba A, Shinkawa H, Ishii M, et al. Prevalence of mitochondrial gene mutations among hearing impaired patients. J Med Genet 2000;37:38–40.

[17] Lu SY, Nishio S, Tsukada K, Oguchi T, Kobayashi K, Abe S, et al. Factors that affect hearing level in individuals with the mitochondrial 1555A>G mutation. Clin Genet 2009;75:480–4.

[18] Tono T, Ushisako Y, Kiyomizu K, Usami S, Abe S, Shinkawa H, et al. Cochlear implantation in a patient with profound hearing loss with the A1555G mitochondrial mutation. Am J Otol 1998;19:754–7.

[19] Usami S, Abe S, Akita J, Shinkawa H, Kimberling WJ. Sensorineural hearing loss associated with the mitochondrial mutations. Adv Otorhinolaryngol 2000;56:203–11.

Audiology Japan 54, 678～685, 2011

残存聴力活用型人工内耳(EAS：electric acoustic stimulation)の長期装用者3症例における術後成績

茂木英明[1)2)]，西尾信哉[1)]，宮川麻衣子[1)]，工　　穣[1)2)]，岩崎　聡[2)]，宇佐美真一[1)]
[1)]信州大学　医学部　耳鼻咽喉科
[2)]信州大学　医学部附属病院　人工聴覚器学講座

要旨：低音部に残存聴力を有する高音急墜，漸傾型の感音難聴の場合，補聴器を装用しても良好な聴取能が得られない場合が多い。欧米ではこのような症例に対する治療法として，低音部分を経外耳道的に音響刺激を行い，高音部を人工内耳で電気刺激する「残存聴力活用型人工内耳（EAS：electric acoustic stimulation)」が開発されてきた。我々はその有効性を検証するため3症例に対してEAS専用のMED-EL社製FLEXeas電極の埋め込みを行い，術後1年経過した。低音部の残存聴力は1年後でも温存されていた。福田版の単音節では補聴器装用下で平均17.3%が音入れ後12ヶ月で67.7%に改善を認めた。欧米ではその有効性が認められ，すでに臨床応用されているが，日本人においても低音部に残存聴力のある症例に対してEASは有効な治療法になることが示唆された。

ーキーワードー
残存聴力，人工内耳，補聴器，聴取成績

はじめに

低音部に残存聴力を有するが，高音部の難聴が高度である，特に1,000Hzを境とするような高音急墜あるいは漸傾型の聴力像を呈する感音難聴の場合，補聴器を装用しても良好な聴取能が得られない場合が多い。本邦での人工内耳埋込みの適応基準では，補聴器装用効果が得られないことに関する表記はなされているが，聴力レベルとして両耳とも平均聴力レベルが90dB以上とされており，このような高音急墜型の感音難聴に対する適応はない場合もある。しかし，1999年にIlbergらが，低音部のみに残聴がある症例に対し，低音部を音響刺激で，高度難聴の中・高音部を電気刺激するため人工内耳の電極を部分挿入にとどめる手術法を報告[1)]して以降，欧米ではこのような症例に対する治療法として，低音部分を経外耳道的に音響刺激を行い，高音部を人工内耳で電気刺激する「残存聴力活用型人工内耳(EAS：electric acoustic stimulation)」が開発されてきた。コンセプトとして提唱され始めた当初は通常の人工内耳電極を使用し，低音部の聴力を保存するための工夫として蝸牛の基底回転のみに部分的に電極を挿入していた。当科でも2008年に通常の人工内耳電極を用い，同じ手術操作で低音部の残存聴力を温存できた症例を経験している[2)]。その後，多くの検討がなされ，低音部の残存聴力を保存するための手術手技と低侵襲型の人工内耳電極，専用のスピーチプロセッサが開発された。結果，その有効性と安全性が認められヨーロッパではCEマークを取得し，臨床に応用されている。2010年8月より，本邦でもこの「残存聴力活用型人工内耳」（以下，EASと略す）が高度医療（第3項先進医療）の承認を受け，現在までにすでに10症例以上に対し手術が行われている[3)]。

我々はこの高度医療施行前に，その有効性を検証するため3症例に対してEASの埋め込みを行って

いる。これら３症例に関しては，埋め込み後１年以上経過しており，残存聴力の状態や聴取能についての長期成績を検討することができたので，その有用性を含め報告する。

対　　象

当科にて両側感音難聴と診断し，いずれも言語習得後，進行の遅い感音難聴で低音部に聴力を有し，補聴器の装用効果のない症例である。高度医療のEASの適応基準では，純音聴力検査にて，両側とも125Hz，250Hz，500Hzが65dBHL以下，2000Hzが80dBHL以上，4000，8000Hzが85dBHL以上の聴力像となっているが（図１），これら３症例はこの適応基準にあてはまらない，より低音部の残存聴力が失われている症例である。

説明と同意

信州大学医学部倫理委員会の承認（2008年５月13日）後，説明と同意を得た。説明書には(1)EASは本邦では医療機器としては未承認である，(2)治療器具の概要と手術方法，(3)適応は，低音部の聴力が残存しているが高音部が高度難聴であり補聴器の効果が少ない症例である，(4)予想される合併症，等を記載した。

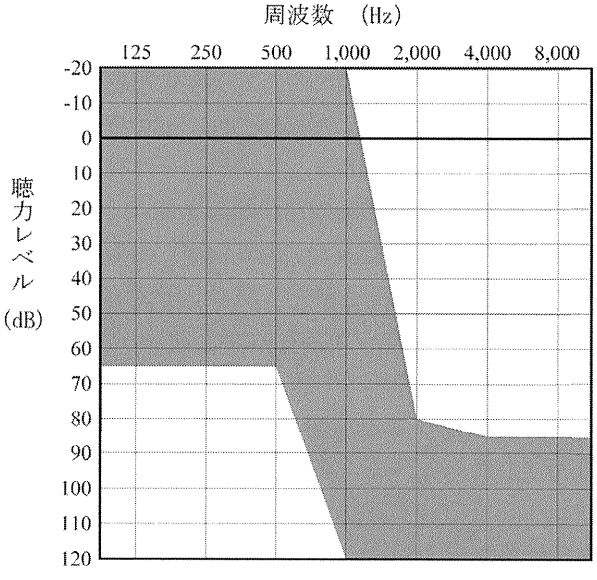

図１　高度医療（第３項先進医療）における残存聴力活用型人工内耳（EAS）の適応聴力

方　　法

１．手術方法

手術はすべて同一術者により行われた。インプラントはMED-EL社製PULSAR CI100，電極はFLEXeasを使用した。これは通常用いるスタンダード電極よりも短く，かつ先端が細く設計されており，蝸牛に対する侵襲を低減させるものである。乳突削開の後，後鼓室開放で中鼓室に到達する。後鼓室開放ののち，正円窓小窩の骨縁を削除，正円窓膜に微小な耳用ピックで小切開を加え，電極を挿入する，いわゆる正円窓アプローチ法（Round window approach)[4]で行った。術中，蝸牛保護を目的としデキサメタゾン（デカドロン）6.6mgを静注した。全電極を挿入し，正円窓膜周囲はフィブリン糊を用いて小筋膜片でシールし固定した。術後翌日よりデキサメタゾンの漸減投与を５日間行った[5]。

２．スピーチプロセッサの装用

術後，中耳腔に貯留した血液や滲出液が消失した４から５週間後に音入れを行った。スピーチプロセッサはEAS専用のMED-EL社製，DUET 2を使用した。これはひとつのプロセッサの中に電気刺激部分と音響刺激部分を内蔵している。プロセッサの調整はMED-EL社のフィッティングガイドラインをもとに行った。低音部の残存聴力が65dBHLにあたる周波数を電気刺激部の下限周波数とし，電気刺激部のマッピングを行った。このスピーチプロセッサは仮に低音部の残存聴力が温存できない場合は，低音部からすべて電気刺激を行うことが可能である。音響刺激部は従来の補聴器と同じように外耳道から音響を入力するため，イヤーモールドを作成した。プログラムコントロールはデジタル制御であり，最大ゲインは43dBで周波数帯域は125Hzから1700Hzである。利得は500Hzの聴力閾値に対しハーフゲインルールを適用し調整を行った。低周波スロープの調整とボリューム調整により電気刺激部とのオーバーラップとラウドネスバランスを調整した。

３．聴取能の評価

音入れ後より１，３，６，12ヶ月目に裸耳の純音聴力検査と電気刺激：Electric stimulation（以下ESと略す），音響刺激：Acoustic stimulation（以下AS