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ORIGINAL ARTICLE

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

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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

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.

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)
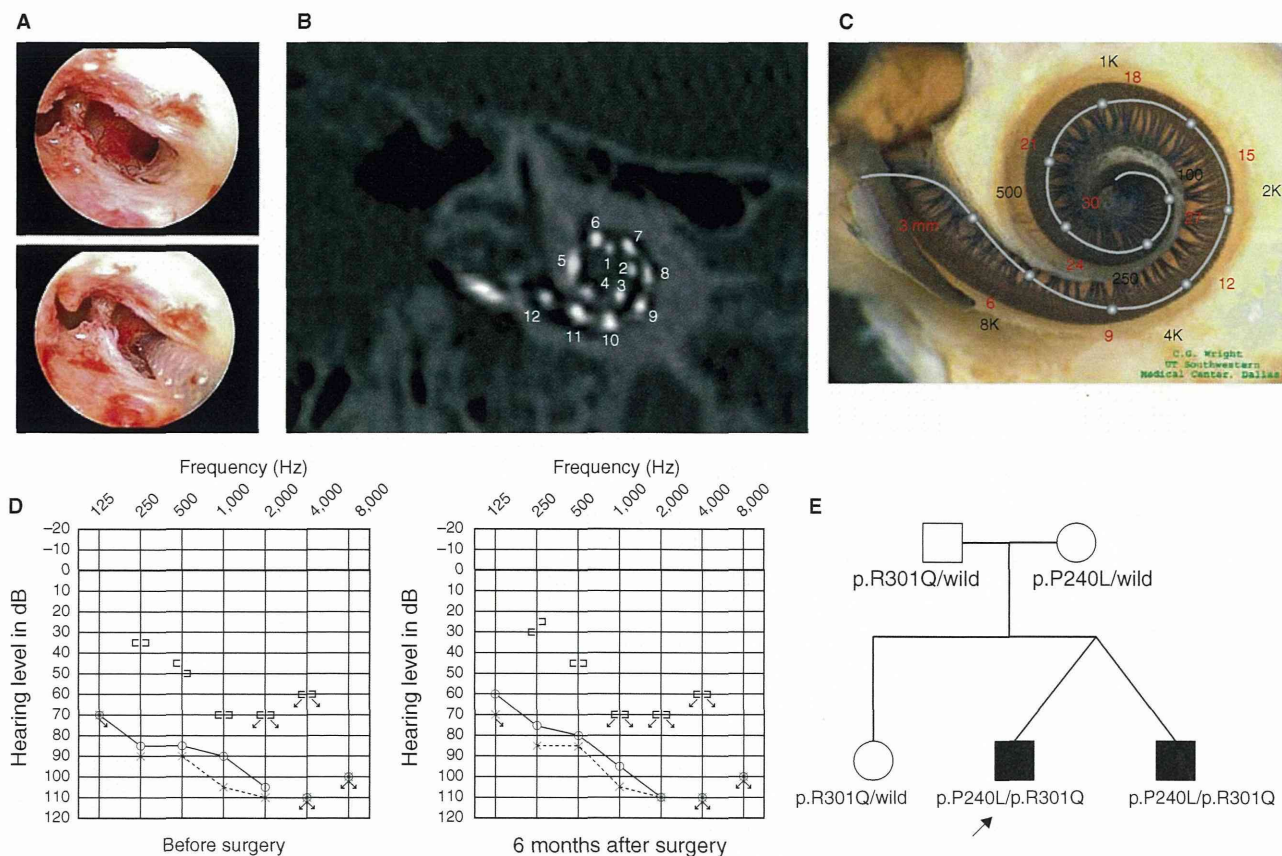
Figure 1. Case no. 16. (A) Endoscopic view of round window insertion, (B) montage CT image, (C) imaging with putative location of electrode and the referential tonotoic map, (D) preoperative and postoperative audiograms. The image of human cochlea neural tissues stained by osmium tetroxide used in Figures 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,
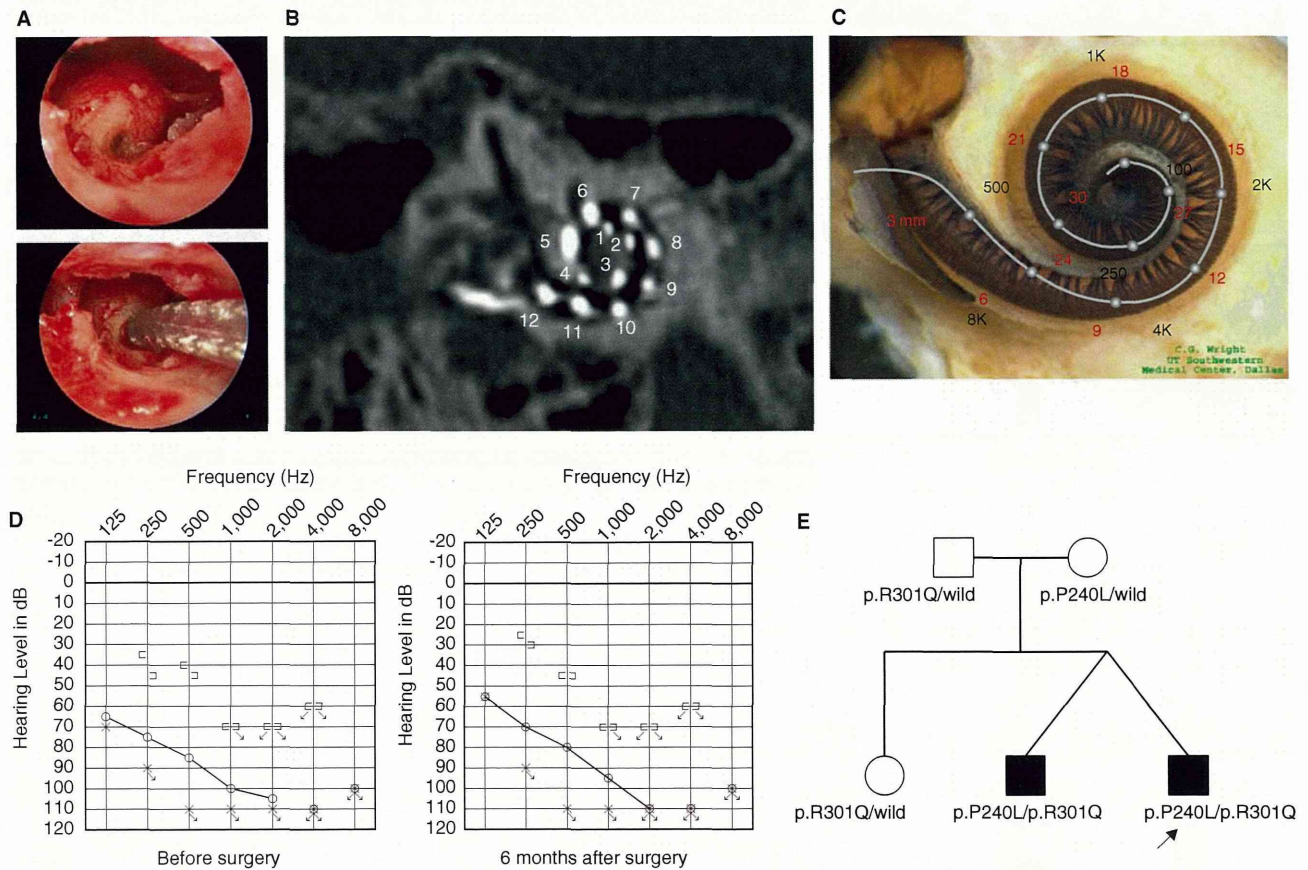
Figure 2. Case no. 17. (A) Endoscopic view of round window insertion, (B) montage CT image, (C) imaging with putative location of electrode and the referential tonotoic map, (D) preoperative and postoperative audiograms. (E) Pedigree and the mutations found in the CDH23 gene.

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
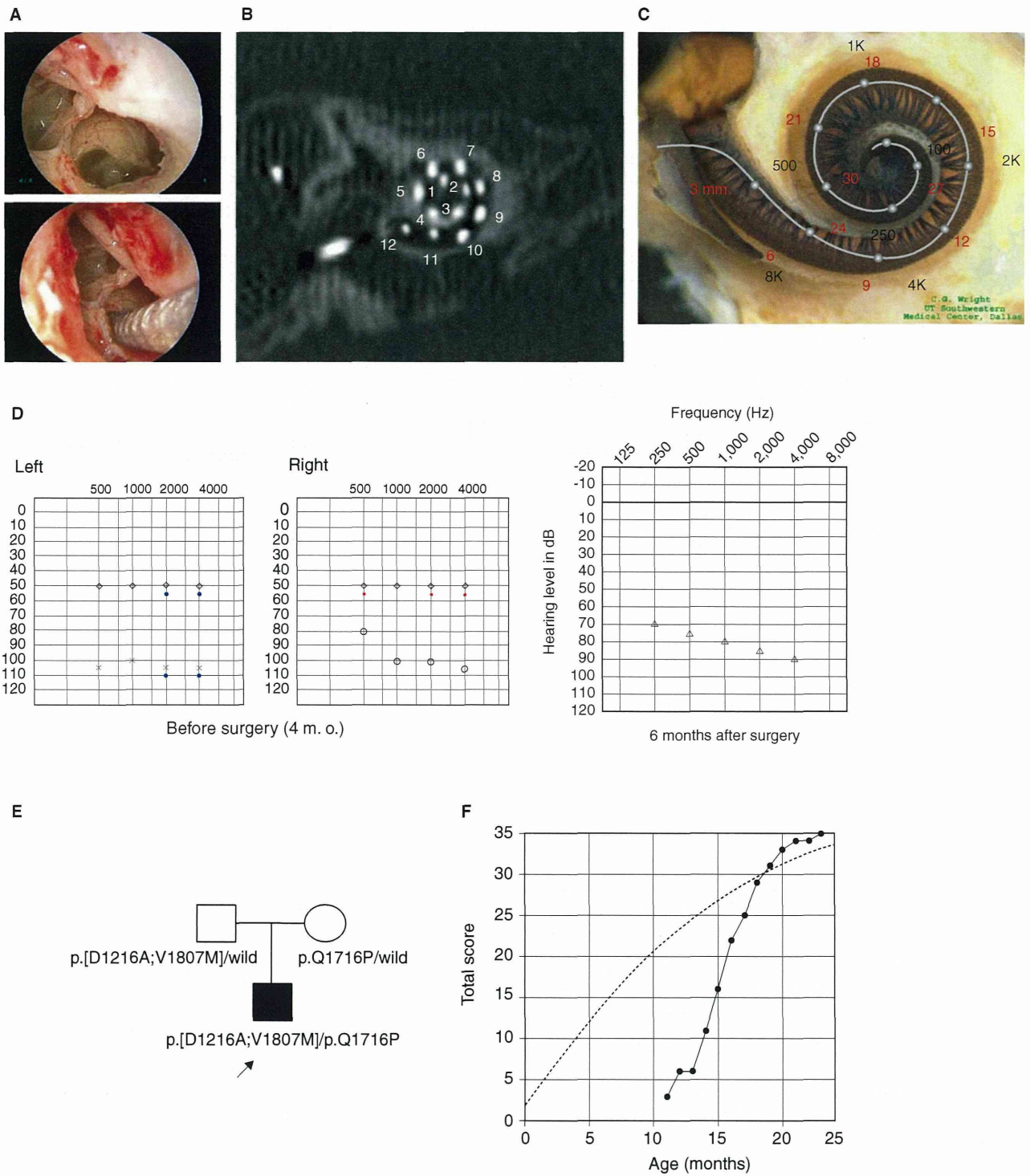
Figure 3. Case no. 18. (A) Endoscopic view of round window insertion, (B) montage CT image, (C) imaging with putative location of electrode and the referential tonotoic map, (D) preoperative ASSR findings (blue, left; red, right) and postoperative COR audiogram finding. (E) Pedigree and the mutations 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
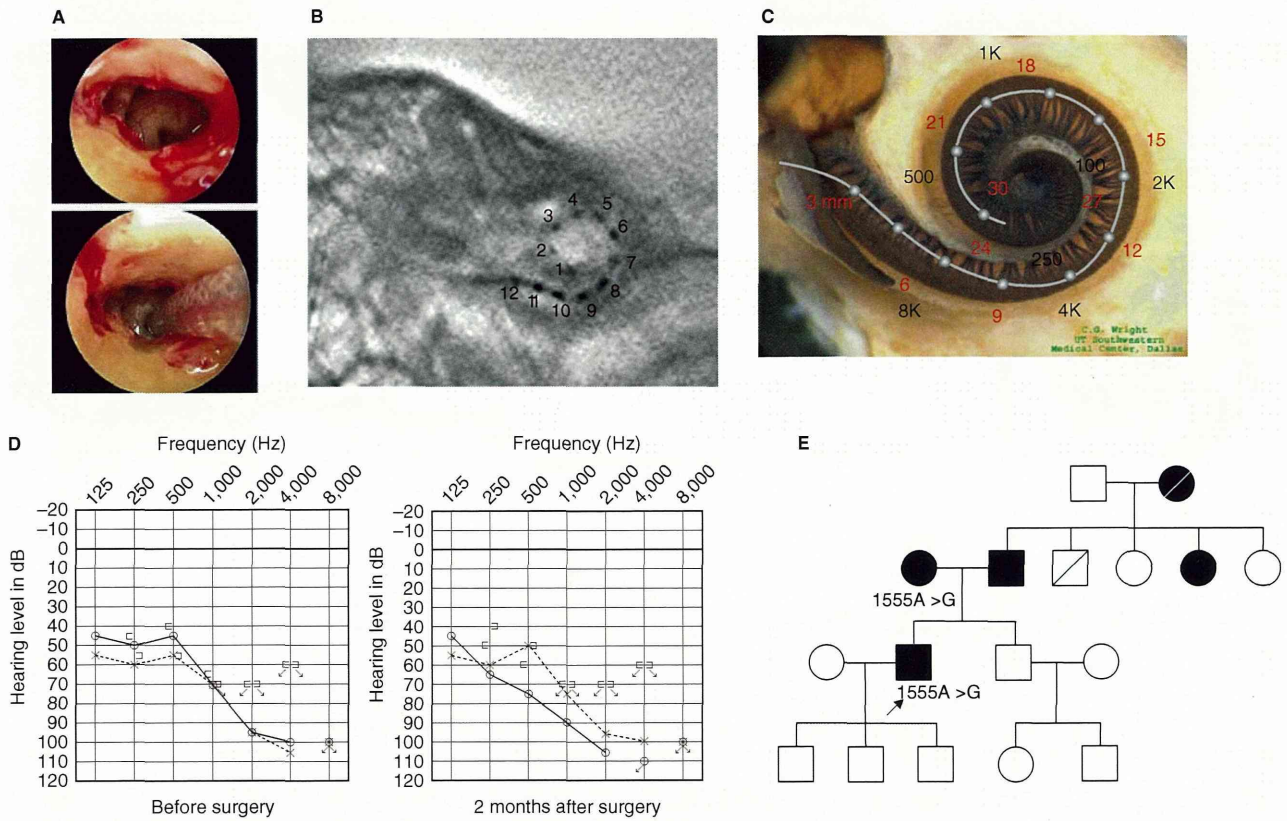
Figure 4. Case no. 9. (A) Endoscopic view of round window insertion, (B) postoperative X-ray finding, (C) imaging with putative location of electrode and the referential tonotoic map, (D) preoperative and postoperative audiograms. (E) Pedigree and the subjects with the mitochondrial 1555 mutations.

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.

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

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Standards of practice in the field of hearing implants

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HEARRING quality standards: an Introduction

In 2005 the World Health Organization estimated that approximately 278 million people suffered from 'moderate to profound hearing impairment,' 80% of whom lived in low- and middle-income countries (WHO, 2010) where there is less access to competent medical professionals and modern medical procedures and technologies than in high-income countries. Furthermore, with the ageing populations in the developed world (United Nations, 2010) and their associated age-related hearing-loss (presbycusis), the need

for assisted hearing solutions – even taking into account a hopefully broader application of preventive measures (e.g. rubella immunization, health education, quieter workplaces, etc.) and health-care infrastructure development – is clearly both significant and continued.

One of such possible hearing solutions is hearing implantation. Indeed, as of December 2010, approximately 219 000 people have been implanted, either uni- or bilaterally (National Institute on Deafness and Other Communication Disorders, 2011). As significant as the benefits of cochlear or middle ear implantation have been for recipients and their families, such implantation is still in its demographic infancy, serving a negligible fraction of those whom

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it could, and will, help integrate or reintegrate into the verbal bustle of everyday life and work.

'The best clinics – providing the best for the patient and comprehensive care' (HEARRING, 2012). With this motto, renowned specialists of four leading hearing implant centers formed the HEARRING group in 2008. Inspired by the collaborative nature of comprehensive cancer center networks, they sought a closer network to better pool their expertise and share information instead of relying solely on medical literature and – beneficial as they are – the individual personal contacts that medical congresses and conferences provide. In the following years, other centers from around the world have joined HEARRING: as of 2012, 23 clinics with numerous surgeons, audiologists, rehabilitationists, and other skilled professionals are collaborating under the HEARRING umbrella.

The 23 clinics in the HEARRING network are committed to creating and maintaining the highest standards of quality. We believe that consensus- and evidenced-based standards are essential to providing each potential implant user, regardless of age or where in the world he/she is treated, with the best possible hearing implant solution for the treatment of her/his individual hearing loss.

In order to try to ensure the best outcomes and the highest safety levels for every present or potential implant user in every clinic, the HEARRING group – under the direction of experts Prof. Christopher H. Raine, MD, Prof. Dr Rudolf Hagen, Prof. Dr Joachim Müller, Prof. Dr Benoit Godey, and Jane Martin – has created a series of standards that covers all aspects of the hearing implant solution process. These quality standards are based on the British Cochlear Implant Group's (BCIG) own quality standards and can be considered current best practice; indeed they have been approved and adopted by participating HEARRING clinics. These standards are not, however, a static picture; as technology and treatment options continually develop, these standards will be continually updated.

The BCIG was founded in 1989 – not long after implantation became common – to promote good practice and provide information and advice to professionals and the public on cochlear implant solutions. They, with the Royal National Institute for the Deaf, published 'Quality Standards for Adult Cochlear Implantation' (British Cochlear Implant Group and Royal National Institute for the Deaf, 2009), a series of 16 guidelines that are meant to be the *minimum* and *realistically achievable* baseline standards for clinics. HEARRING has used this original document as a blueprint for developing a series of six related sets of evidence-based standards, each tailored to fit a specific age category or procedure:
1. Quality standards for adult cochlear implantation

2. Quality standards for cochlear implantation in children and young adults
3. Quality standards for combined electric and acoustic stimulation (EAS)
4. Quality standards for middle ear implantation (MEI)
5. Quality standards for rehabilitation
6. Quality standards for minimal outcome measurements in adults and children.

With some slight variation (see Table 1), each set of standards has the same basic structure which can be divided into two subsections: (1) resources and (2) processes.

Resources: The Resources section is made up of three
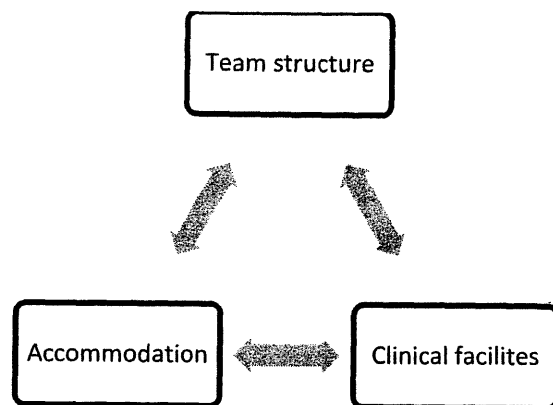
parts: team structure, accomodation, and clinical facilities.

Team structure outlines who every cochlear implant team should include and the minimum training and/ or experience each member should have. It also describes the importance of establishing and maintaining a program of continued professional development: with national or international courses, conferences, and meetings each team member should be up to date with the latest cochlear implantation-related developments. Extending beyond the core team, this section also provides a list of 'additional support' professionals whose expertize need not be part of a core team but whom the core team should have ready access to if necessary.

Accommodation is about the provision and differentiation of the clinic's physical space: the size, suitability, comfort, and privacy of areas designated for staff, present or potential implant users, and waiting relatives. As different cultures have different spatial expectations and comforts, the HEARRING standards do not prescribe specific sizes but rather those that are 'suitable', 'sufficient', and 'large enough to comfortable accommodate'. Accomodation is also about access and communication. It covers providing the present or potential implant user with suitable

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Table 1 The structural variations by Quality Standard

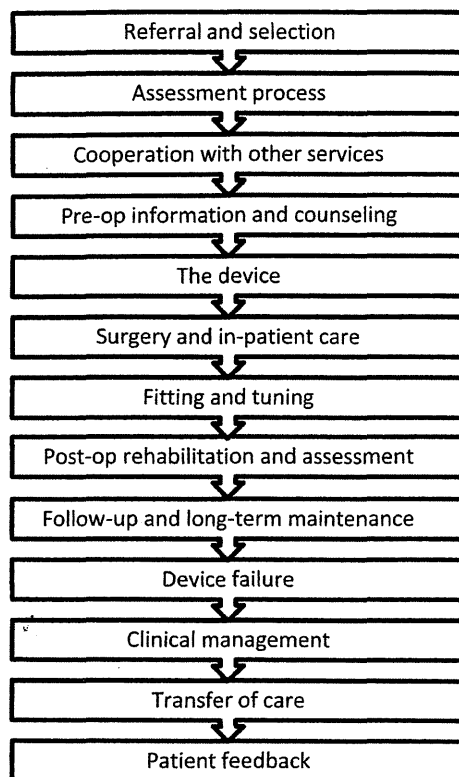|	Quality Standards for					
	Adult Cochlear Implantation	Cochlear Implantation in Children and Young Adults	Combined Electric and Acoustic Stimulation	Middle Ear Implantation	(Re)habilitation	Minimal Outcome Measurements
		Symbols: = equal ≠ differs + in addition − without (compared to basic document)				
Introduction Structure	Individualized Basic document	= + min of two surgeons, audiovestibular physician/ pediatrician, key worker, education, pediatrics	Individualized + hearing aid acoustician − audiological medicine	Individualized − clinical scientists, physiologists, rehab therapists, speech and language therapists, clinical physiologists, engineers, tinnitus, balance, medical physics, genetic counseling, interpreter services, social services for the deaf, deaf advocacy	Individualized + teacher of the deaf, key worker, parents, hearing aid acoustician, audiovestibular physician, cooperation with other services − otologist, audiologists, physiologists	Individualized NO
Accommodation	Basic document	+ suitable and family-friendly facilities	=	=	=	NO
Clinical Facilities	Basic document	+ spatial awareness	=	− OAE, electrically evoked potentials, balance function testing	NO	NO
Referral and Selection Criteria	CI selection criteria	CI in children/young adults selection criteria	EAS selection criteria	MEI selection criteria	NO	NO
Assessment Process	Basic document	+ ophthalmic assessment, family support and education, associated organizations, final outcome ≠ receptive skills assessment	+ APHAB test	12 weeks − referral for balance testing and genetic counseling, necessity for vaccination (meningitis), determination of UCL, hearing aid testing, electrically evoked response audiometry, promontory stimulation testing, OAE, details for communication, bilateral candidate assessment	≠ structure and content, children and adults are discussed separately − includes pre-op counseling	≠ describes basic sets of outcome measures to be used at routine visits for adults and children
Cooperation with Other Services	Basic document	+ newborn hearing screening	=	NO	NO (included in previous chapter)	NO
Pre-op Information and Counseling	Basic document	+ involvement of child, device	=	=	NO (included in previous chapter)	NO
Device	CI	NO (included in previous chapter)	EAS	MEI	NO	CI, but also applicable to other hearing implants
Surgery and In-patient Care	Basic document	+ monitoring of anesthetics and facial nerve − discussion of surgical procedure	=	− preservation of hearing, radiological examination	NO	NO
Fitting and Tuning	Basic document	+ electrophysiological measurements in the very young	=	+ rehabilitation	NO	NO

Continued

Table 1 *Continued*

	Quality Standards for					
	Adult Cochlear Implantation	**Cochlear Implantation in Children and Young Adults**	**Combined Electric and Acoustic Stimulation**	**Middle Ear Implantation**	**(Re)habilitation**	**Minimal Outcome Measurements**
			Symbols: = equal *≠ differs* *+ in addition* *– without (compared to basic document)*			
Post-op Rehabilitation and Assessment	Basic document	– lip reading, hearing tactics	=	– rehabilitation (included in previous chapter) ≠ post-op assessment	≠ structure and content, *children and adults are discussed separately*	NO
Follow-up and Long-term Maintenance	Basic document	+ assessment of FM systems	=	=	NO	NO
Device Failure	Basic document	=	+ detailed audiological reevaluation, consideration of a CI	=	=	NO
Clinical Management	Basic document	=	=	=	NO	NO
Transfer of Care	Basic document	=	NO	=	=	NO
Patient Feedback	Basic document	=	=	=	NO	NO

[1]The Quality Standards for Minimal Outcome Measurements in Adults and Children were based on the core elements of the other standards, and in itself describes procedural elements for routine assessment and reporting.

telecommuncations access to the clinic and, while in the clinic, with assistive listening devices and alerts.

As the name would suggest, the clinical facilities section outlines which technology should be available to be able to perform a variety of tests. Further, this section highlights the need to regularly calibrate instruments to nationally recognized standards.

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┌─────────────────────────────────────┐
│        Referral and selection       │
└─────────────────────────────────────┘
               ⬇
┌─────────────────────────────────────┐
│         Assessment process          │
└─────────────────────────────────────┘
               ⬇
┌─────────────────────────────────────┐
│     Cooperation with other services │
└─────────────────────────────────────┘
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┌─────────────────────────────────────┐
│    Pre-op information and counseling │
└─────────────────────────────────────┘
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│             The device              │
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│      Surgery and in-patient care    │
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│          Fitting and tuning         │
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│           Device failure            │
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│          Transfer of care           │
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               ⬇
┌─────────────────────────────────────┐
│          Patient feedback           │
└─────────────────────────────────────┘
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Processes:

The clinics and professionals of the HEARRING network believe that providing users with individualized hearing solutions is a careful and detailed process that does not start and stop at surgical implantation. Each of the individual 13 steps is subdivided to provide more specific and in-depth guidelines. Taken together, the cumulative effect is a wealth of best-practice detail which covers every step of the implant experience from selection criteria to long-term maintenance.

The aforementioned six quality standards are published in full on the forthcoming pages followed by a table highlighting the key differences between the standards. It is the HEARRING group's hope that a wide adoption and implantation of these standards will lead to still a greater delivery of the highest quality comprehensive care and thus happier, better hearing implant users.

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残存聴力活用型人工内耳（EAS：electric acoustic stimulation）

～低侵襲手術，聴力保存成績，術後聴取能，遺伝的背景について～

宇佐美　真　一

Our Experience with EAS (Electric Acoustic Stimulation) in Japan

—Atraumatic Surgery, Hearing Preservation, Outcome, and Genetic Background of the Patients—

Shin-ichi Usami

(Shinshu University School of Medicine)

Advances in developing new atraumatic concepts of electrode design as well as in the 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. Combined post-operative 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. Achievement of atraumaticity of round window insertion in the present cases has been confirmed from the viewpoint of minimal drilling time as well as preserved vestibular function. Post-operative evaluation after full insertion of the electrodes showed hearing at low frequencies was well preserved in all 16 cases (16 ears) who were followed up for more than one month. As for outcome of EAS, together with successful hearing preservation, all patients obtained 25-40dB in their average hearing threshold after implantation. The word recognition score significantly improved post-operatively. With regard to the genetic background of the patients, *CDH23* mutations and the 1555A>G mitochondrial mutation were identified among our series of EAS patients, confirming that these genes were the important genes responsible for high frequency involved hearing loss. Successful hearing preservation as well as good outcomes from EAS in these patients indicated that those with this combination of mutations are good candidates for EAS.

Keywords : EAS (electric acoustic stimulation), atraumatic surgery, hearing preservation, *CDH23*, gene, mitochondria

はじめに

高音急墜あるいは漸傾型の聴力像を呈する難聴患者は低音部に残存聴力を有するものの高音部の聴取能がきわめて悪く，補聴器のフィッティングが難しいために患者の望む補聴効果の得られない場合が多い．一方，低音部の聴力が残存しているために従来の人工内耳の適応に当てはまらず，有効な治療法がなかった．近年，残存聴力のある低音部は音響刺激で，重度難聴の高音部は電気刺激で音を送り込む「残存聴力活用型人工内耳（electric acoustic stimulation：EAS）」が開発され，人工内耳の適

応や可能性を広げるものとして注目されている（図 1, 2）．従来は内耳に電極を挿入することにより，もともとの内耳機能（基底板の振動による音響入力）は失われると考えられていたが，1999 年 von Ilberg ら[1]が低音部に残存聴力を有する高音急墜型の聴力像を呈する難聴患者に対して，低音部は音響刺激で，高音部は人工内耳で聞き取るいわゆる EAS を臨床的に応用し報告した．これは通常の音の振動による情報と，人工内耳により聴神経に入れた電気的刺激による情報が聴覚中枢で融合可能であることを初めて実証したきわめて画期的な報告である．

信州大学耳鼻咽喉科

その後，電極の改良，スピーチプロセッサの開発，および手術法の検討が進められ，欧米を中心に臨床研究が進められた．その結果，現在ヨーロッパではその有用性が認められて CE マークを取得し，高音急墜あるいは漸傾型の聴力像を呈する難聴患者の治療法として確立しつつあり，米国 FDA でも現在治験が進められている．日本でも 2010 年 8 月に厚生労働省から「残存聴力活用型人工内耳挿入術」が高度医療（第 3 項先進医療）として承認を受け，臨床研究が開始されている．

高度医療で認められた EAS の適応としては，ヨーロッパで使用されている基準をもとに下記の基準を用いて行われている（図 1，表 1）．有効性が確認されるに伴い，将来的にはさらに適応の拡大が行われていくと思われる．

当施設では現時点（2011 年 8 月）までに 18 例 19 耳（うち高度医療 9 例）の経験を重ね，手術法[2]，聴力保存成績[2][3]，前庭機能[2]，および術後聴取能[4]～[6]，日本語における有効性[4]～[6]，患者の遺伝的背景[7][8] などについて検討を重ねてきたが，本稿ではそれらの症例から明らかになった以下の5つのポイントを中心に解説を加えたい．

（1）低侵襲手術をすることにより残存聴力の保存が可能である．

（2）電極を挿入した部位でも基底板の可動性は保たれる．

（3）低侵襲手術は前庭機能の温存のためにも重要である．

（4）EAS は日本語においても有用である．

（5）患者の遺伝的背景が明らかになってきた．

低侵襲手術による聴力保存

EASは蝸牛への電極挿入と聴力温存という相反する目的を達成しなければならない点に医療技術の難しさがある．聴力温存を目的とした人工内耳手術の報告をレビューした総説によれば，24%の患者で術後聴力が悪化し，13%の患者では全聴力喪失したと報告されている[9]．人工内耳電極挿入による聴力低下に関しては，直接的な機械的障害，炎症性サイトカインによる遅発的障害，基底板の振動特性の変化などが関与していると考えられている．近年，内耳に対する障害を最小限にするために以下のような工夫がなされてきた．
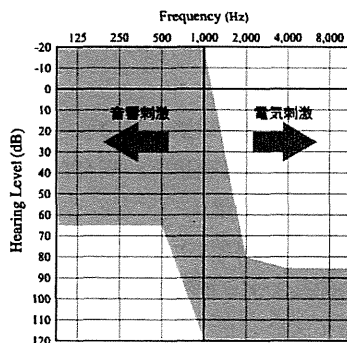
1）電極の改良

近年，先端を細くてしなやかな形状にし，直接的な機械的障害や基底板の振動に対する影響を少なくする電極が開発されている[10]．モデルを用いたシュミレーション実験では蝸牛外側壁に加わる圧力が従来の電極に比して有意に軽減されていることが証明されており[10][11]，側頭骨を用いた検討でも蝸牛への侵襲が少ないことが証明されている[11]．

2）低侵襲手術

手術法に関しても残存聴力を残すための低侵襲手術の試みがなされている．電極挿入のアプローチとして従来は鼓室岬角（蝸牛）の骨壁を削開し蝸牛鼓室階にアプローチする cochleostomy からの電極挿入が一般的であったが，近年，正円窓からのアプローチによる電極挿入がより低侵襲であり，残存聴力をより高い確率で保存できることが明らかになってきた[12][13]．従来 cochleostomy からの電極挿入の際にも可能な限り低侵襲の手術が望ましいとされ，soft surgery が推奨されてきた[14]．しかしながら挿入電極の位置について，CT を用いて retrospective に検証した研究によれば，電極が鼓室階ではなく，前庭階に挿入された例，あるいは鼓室階から基底板を貫き前庭階に挿入されている例が報告されている[15]．このような場合には当然のことながら聴力の温存は不可能であ

図 1 EAS の適応となる聴力像

表 1 EAS の適応基準（高度医療）

両耳とも以下の条件を満たす感音難聴患者
1）純音聴力検査
　・125 Hz，250 Hz，500 Hz の純音聴力閾値が 65 dB 以内
　・2000 Hz の純音聴力閾値が 80 dB 以上
　・4000 Hz，8000 Hz の純音聴力閾値が 85 dB 以上
　ただし，上記に示す周波数のうち 1ヵ所が 10 dB 以内の幅で外れる場合には対象とする．
2）補聴器装用下において静寂下での語音弁別能が 65 dBSPL で 60％未満であること．

る．近年の総説でEASを目的とした人工内耳の手術法の変遷についてレビューされているが，正円窓アプローチによる手術法が導入されてから聴力保存率が改善して

いることが記載されている[16]．Cochleostomyアプローチでよい保存成績をあげている施設もあり[17]，いずれのアプローチでも残存聴力を温存させる低侵襲手術を行うこ
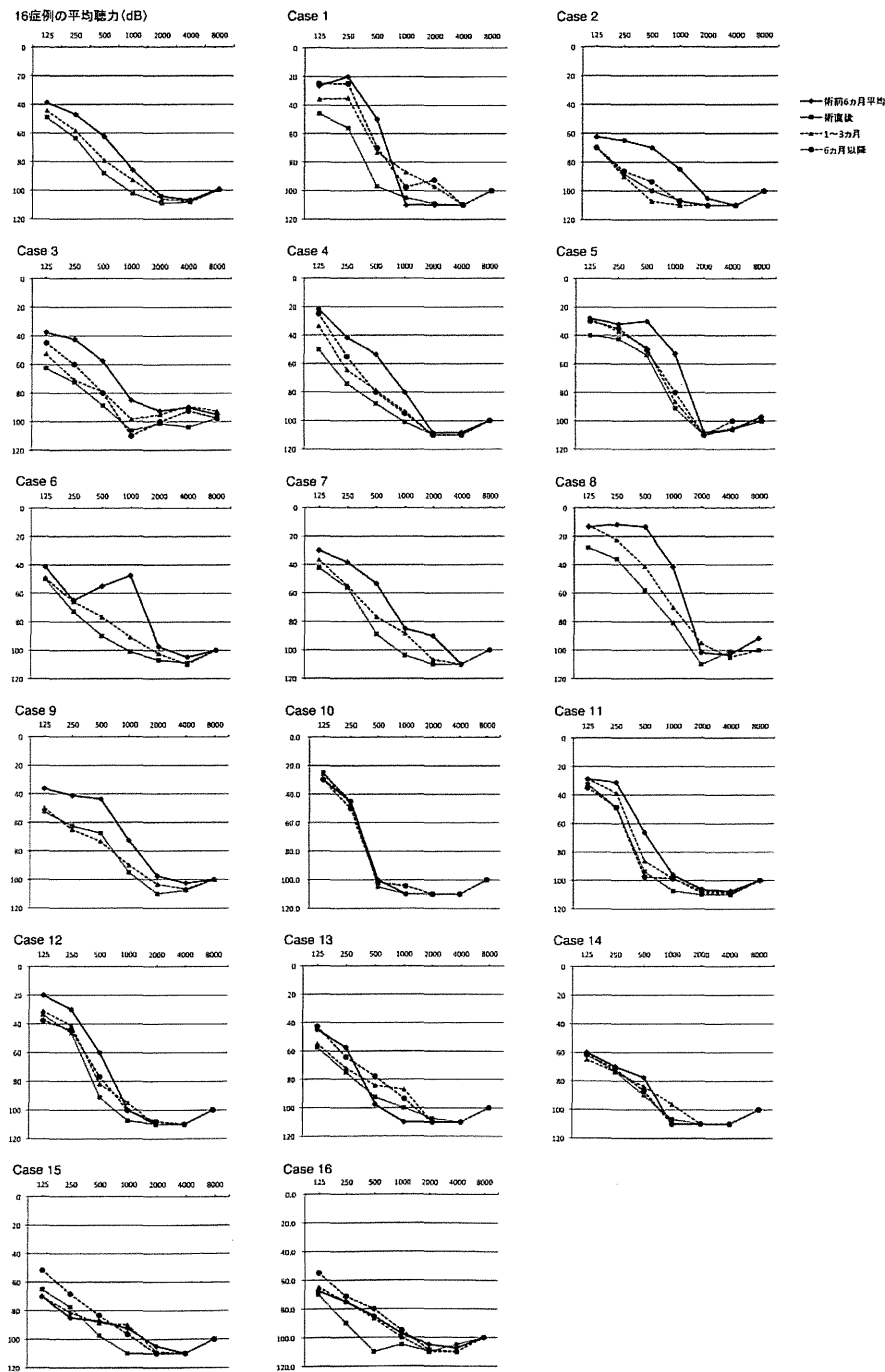

図2　人工内耳手術前後の聴力変化（文献3より引用）
　　（術後6カ月平均，術直後，術後1〜6カ月平均，術後6カ月以上平均の比較）
　　低音部の残存聴力は術後もよく保たれている．
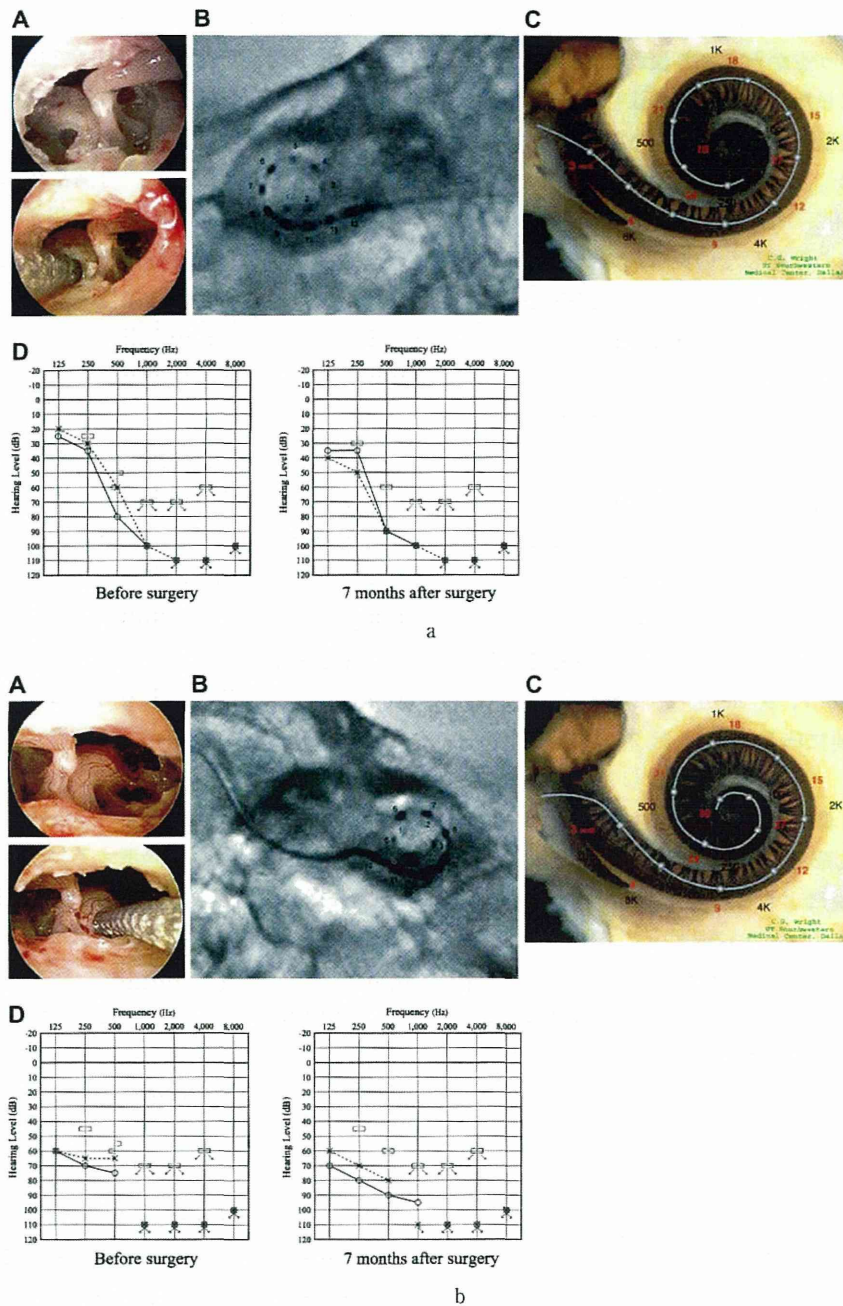
図3　電極挿入深度（a：24 mm，b：31.5 mm）と聴力保存（文献2より引用）
　　　24 mm（a）あるいは31.5 mm（b）の長さの電極を full insertion した場合でも低音部の残存聴力が保存でき，電極の存在している周波数帯でも基底板が機能する（聴力が保存可能である）.

とが必要である.

　現在われわれの施設では鼓室階に確実に挿入できる利点に加え，音響外傷のリスクおよび前庭機能温存の面から，人工内耳手術はすべて正円窓アプローチで行っている. 蝸牛骨壁削開の際の音響レベルに関して実際に測定した報告によればその音響レベルは114～128 dB SPLとされ，音響外傷を起こすのに十分なレベルに達していることが報告されている[18]. われわれ[2] は正円窓アプローチがより低侵襲であることを音響外傷の面から検証し，正円窓アプローチではcochleostomyからの電極挿入に比

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較し，骨削開時間が1/5以下の時間で終了しており音響外傷のリスク軽減という点からもより優れた低侵襲手術であることを明らかにした．また後述のように正円窓アプローチでは前庭機能温存という点からもより優れた低侵襲手術といえる．

　3）ステロイドの使用

　①浅い挿入でも電極の存在しない低音部の聴力低下が認められる症例があること，②遅発性の障害が認められる症例があることから，電極挿入に伴う炎症性サイトカインの誘導が起こることが推測されている．したがって聴力温存のためには電極挿入による直接的な影響とともに電極挿入に伴う炎症性サイトカインの誘導を抑制することが重要になる．遅発性聴力障害の予防に関してはステロイドの使用が有効であることが動物実験でも実証されており[19]，臨床例でも局所あるいは全身投与されることが多い．現在，高度医療で行われているプロトコールではステロイドの全身投与を6日間（術中から術後5日目まで，デキサメタゾン8，8，4，4，2，2mg）を1クールとして，さらに必要に応じてもう1クール行っている[2].

　これら電極の改良，低侵襲手術，ステロイドの使用などに伴い聴力の温存成績が上がってきており，EASに関する近年の報告や総説によれば，聴力保存成績は90〜100%とするものが多くなっている[3][16][17][20]〜[23].

　信州大学において2008年11月から2011年8月までに行われたEAS患者18例19耳を対象とし，術後1ヵ月以上経過し純音聴力検査のデータが得られている16例16耳についての聴力温存について詳細な検討を行ったところ，すべての症例で残存聴力の保存が可能であった[3]（図2）.

電極挿入と蝸牛基底板の可動性

　挿入深度に関しては，EASの開発当初は電極挿入により基底板の可動性が障害されると考えられており，6〜10mmの短い電極を用いて基底回転のみ（高音部）に電極を挿入する方法[24]や，長い電極を途中まで挿入する方法[25]が試みられてきた．われわれ[2]は24mmあるいは31.5mmの長さの電極をfull insertionした場合でも低音部の残存聴力が保存でき，電極の存在している周波数帯でも基底板が機能する（聴力が保存可能である）ことを明らかにし，報告した（図3）．これまでにわれわれ[3]が経験した18例19耳（FLEXeas電極13例，FLEXsoft電

極5例，COMBI40＋standard電極1例）ではすべてfull insertionが行われたが，全症例で聴力が温存でき，電極を深く挿入しても残存聴力の保存は可能であることを再確認できた．電極の挿入深度についてはまだ結論は出ていないが，Skarzynskiら[26]も同様に低侵襲電極をより深く挿入し聴力を保存しえたとの報告を行っている．EASの適応になる患者は進行性の難聴を呈することが多いこと，手術に伴う急性，遅発性の聴力障害へのレスキューを考えると，より長い電極を安全に挿入するのが，今後最良の方法になると考えられる．

低侵襲手術による前庭機能温存

　人工内耳手術の際に忘れがちになるのが前庭機能である．従来から人工内耳の術後にめまい，前庭機能の低下が起きる場合があることが報告されてきたが，前庭には代償作用があるため一側の手術の際には日常生活上問題とならない場合が多い．しかしながら今後人工内耳が普及するにつれ両側例が増えて行くことを考えると，今後聴力の残存とともに前庭機能の温存が重要となることが予想される．前庭機能に関しては，cochleostomyアプローチ症例でVEMP（vestibular evoked myogenic potential）およびカロリック反応が低下する例が多く認められたことから，正円窓アプローチの方が前庭機能の低下およびめまいのリスクを軽減するとされている[27]．われわれ[2]も手術アプローチを前庭機能温存の面から検討した結果，温度眼振検査では両アプローチで差がないものの，cochleostomyアプローチ症例ではVEMPの反応低下が認められた（図4）．前庭機能の温存という点からも正円窓アプローチは優れた低侵襲手術であるといえる．

術後聴取能と日本語における有用性

　術後聴取能および言語成績に関して，高音急墜あるいは漸傾型聴力像を示す難聴患者を対象にヨーロッパを中心に行われたEASの臨床研究では，EAS装用での聴取能が大幅に改善しており（単音節の正答率平均が50%以上改善），その有効性が確かめられている[28]〜[31]．使用された電極，挿入深度，施設，術後治療などがさまざまであり一概に比較は困難であるが，複数の関連論文の成績をCenter for Evidence Based Medicineのgrading systemを用いたエビデンスのレベル付けに基づいて検討したレビューでも，周波数弁別に関して通常の人工内耳と比較し92%の有用性が認められている[9]．多施設研究でも術
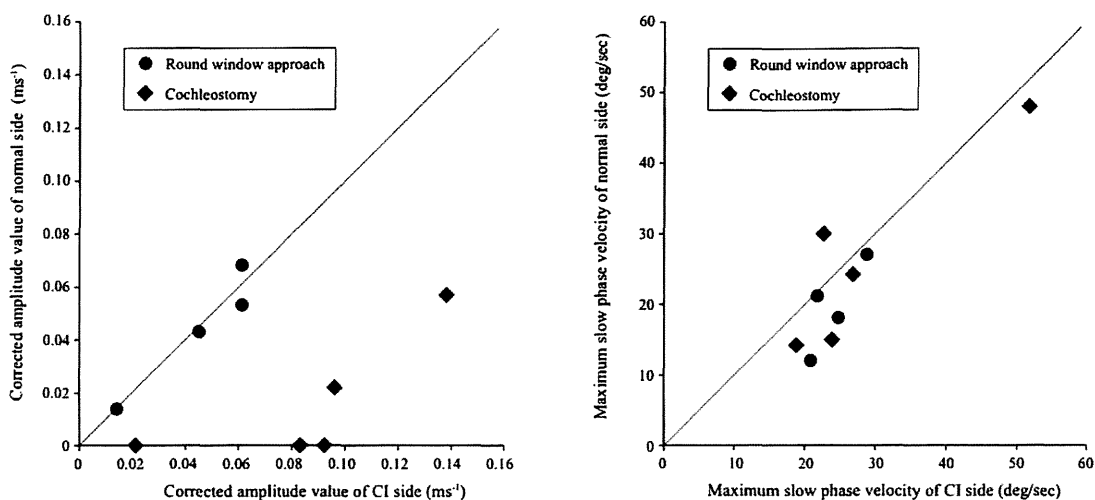
図 4　人工内耳後の VEMP および温度眼振検査（文献 2 より引用）

cochleostomy 症例で VEMP（vestibular evoked myogenic potential）の反応低下が認められた．温度眼振検査については cochleostomy 症例，正円窓アプローチ症例とも反応は保たれている．
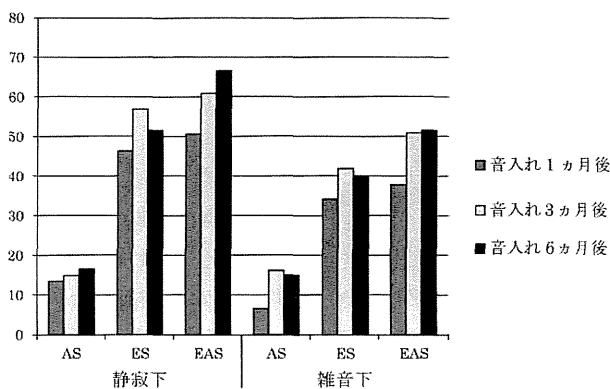

図 5　67-S 語表を用いた静寂下と雑音下での聴取能（n＝ 8）
（文献 6 より引用）
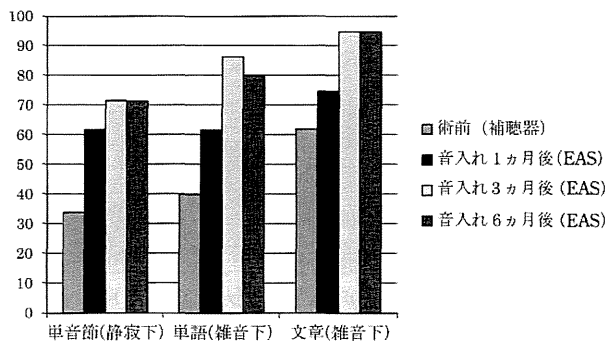音響刺激（AS），電気刺激（ES），残存聴力活用型人工内
耳（EAS）

図 6　CI2004 の各検査項目における聴取能（n＝8）
（文献 6 より引用）

後の聴取成績は個人差があるものの，おおよそ術後 6ヵ
月まで改善し，とくに騒音下の聴取成績で優れた成績を
示すことが報告されている．またアンケート調査でも良
好な成績が得られている[30]．

現在，日本語における有用性をさまざまな患者につい
て検証しているが，自験例でも，音入れ後 6ヵ月で単音
節で 50%の聴取能を獲得でき，日本語の聴取にも大きな
メリットがあることが確認できている[4]．高度医療で行
われた EAS 患者 8 例について検討した結果では，装用後
の閾値は音入れ後 1ヵ月で低音部から高音部までほぼ

40 dB SPL 以下となり十分な装用閾値を認めた[6]．67-S 語
表あるは CI2004 を用いた，静寂下と雑音下での AS，ES，
EAS 入力条件での聴取能の結果では，EAS 条件が ES に対
して優れている傾向がみられた[6]（図 5, 6）．この傾向は
静寂下よりも雑音下で顕著に認められた．全体的な聴取
能としては音入れ後，比較的早期である 3ヵ月目ですで
に大きく改善していた．また高度医療の適応外ではある
が，低音部に残存聴力を有する 3 例についての長期聴取
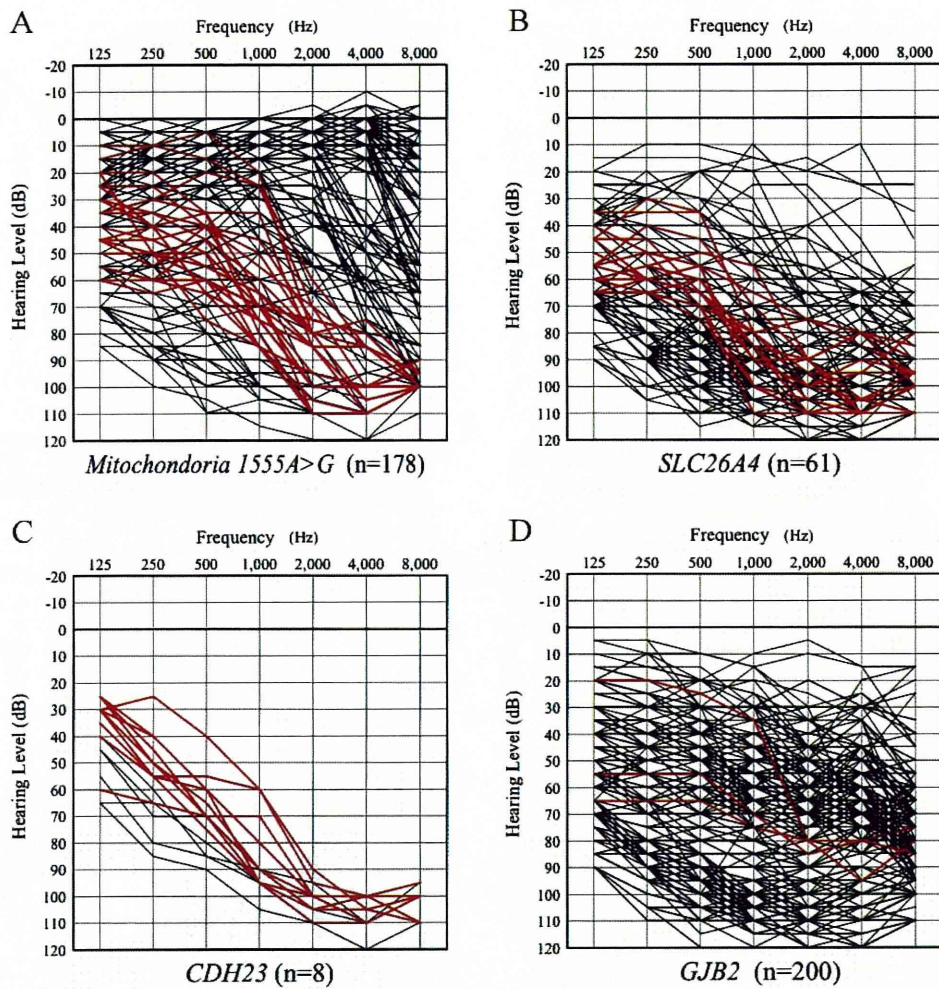能成績の検討でも EAS による聴取能の改善が認められて
おり，EAS がより幅広い難聴患者に有用である可能性を
示唆している[5]．

図7　難聴原因遺伝子の聴力像（重ね合わせオージオグラム）（文献7より引用）
　　ミトコンドリア遺伝子1555変異，*SLC26A4* 遺伝子，*CDH23* 遺伝子，*GJB2* 遺伝子に変異を持つ患者の中に EAS 人工内耳の
　　適応患者が含まれる．*CDH23* はほぼすべての患者で残存聴力を認め，EAS のよい適応になると考えられる．

患者の遺伝的背景

　EASの適応になる難聴患者は先天性進行性難聴患者あるいは後天性の難聴患者の中に見出されるが，両側対称性のオージオグラムを呈すること，ほぼ同じような経過で進行することから病因として遺伝的な背景が考えられている．われわれは信州大学耳鼻咽喉科の難聴遺伝子データベース（発端者 1520 例）のうち，EAS の適応基準を満たすオージオグラムを呈する患者（139 例）の臨床像の特徴と遺伝的背景を検討した[7]．その結果，53%が常染色体劣性遺伝形式（孤発例も含む），28%が常染色体優性遺伝形式／ミトコンドリア遺伝形式を示しており，単一の原因ではなく種々の遺伝子が関与していることが推測された[7]．発症年齢については常染色体劣性遺

伝形式（孤発例も含む）では常染色体優性遺伝形式／ミトコンドリア遺伝形式を示す症例に比して発症年齢が低い傾向が認められた．また全体で 56% の症例が進行性であった．このうち 27% の患者で原因遺伝子変異が特定可能であり，少なくとも 4 種類の原因遺伝子が EAS の適応となる聴力像を示すことが明らかになった（図7）．すなわち，ミトコンドリア遺伝子1555変異（12.9%），*SLC26A4* 遺伝子（7.2%），*CDH23* 遺伝子（4.3%），*GJB2* 遺伝子（2.2%）である．図7に遺伝子ごとの重ね合わせオージオグラムを示すが，これらの遺伝子のうち *CDH23* はほぼすべての患者で残存聴力を認め，EAS のよい適応になると考えられている[7]．EAS 手術を行った 18 例の遺伝子解析を行ったところ，言語習得前難聴患者 3 例に *CDH23*