as can be seen with subject 46, this formula is not a true reflection of a user's available post-operative hearing, and therefore, it is not a true measure of hearing preservation.

(1) This classification is not suitable for the range of standard cochlear implant users: the worse a user's pre-operative hearing is, the better his/her general results may seem. For example, for users with a pre-operative Pure Tone Average (PTA) worse than 90 dB there is no minimal hearing loss, and for users with a PTA worse than 110 dB there is no minimal and no partial hearing loss, both due to the floor-effect of the audiogram.

Lastly, the existing classification systems measure and discuss how much hearing is *lost*. A more patient-centric classification system which focuses on the extent of CI users' post-operative residual hearing, i.e. what they can hear, would be preferable.

The presence of these multiple systems has made it difficult to compare different studies' results. If, however, a standard system is used, there will be better reporting of surgical and device intervention. This, in turn, will allow to increase greatly the ease of study comparison and meta-analysis of data. Meta-analysis of data is particularly important in the hearing implant field, where conducting randomized, controlled double-blinded studies is impossible; sample sizes are often small (usually ranging from case studies to small groups of 10–20 subjects); and the use of different HP classification systems is a handicap for meta-analysis with their combined data. Meta-analysis of data using the same HP classification system would allow us to pool data for stronger evidence-based medicine e.g. [16]., and consequently, we would be better able to support health technology assessment for reimbursement.

Method

The HEARRING group proposes the following formula for qualitative HP classification:

$$\text{Relative change} = \frac{(\text{PTApost-PTApre})}{(\text{PTAmax-PTApre})}$$

where PTApost is pure tone average measured post-operatively, PTApre is pure tone average measured pre-operatively, and PTAmax is the limits of the audiometer.

Firstly, classification based on this equation is independent of initial hearing and can be used for all CI users with measurable pre-operative residual hearing (PTA: 0–120 dB). Because the classification is scaled to the pre-operative audiogram, we eliminate the effect of worse pre-operative hearing tending to produce misleadingly better post-operative HP results.

Table III. Scale for proposed HP classification system.

Percent of residual hearing preserved	Classification
>75%	Complete HP
>25–75%	Partial HP
0–25%	Minimal HP
No measurable hearing	Loss of hearing/No hearing

Secondly, the equation presents the relative change as a percentage of hearing loss, a user-friendly concept. The hearing loss is converted to preservation by calculating 100% - relative change in %:

$$S = \left[1 - \left(\frac{(\text{PTApost} - \text{PTApre})}{(\text{PTAmax} - \text{PTApre})} \right) * 100 \right] [\%]$$

where S is preservation numerical scale.

Thirdly, the numerical scale is converted to a categorical scale for ease of reporting. The categorization is defined in Table III.

The HP Classification System is based on a routine audiogram. The selection of frequency for pure tone average determination is based on ASHA guidelines as they, among the several audiometric procedure standards, are the most commonly used [17]. Hearing threshold levels should be obtained at octave intervals from 125 Hz to 8000 Hz. In addition, implementation of inter-octave frequencies is recommended and provides a more complete and accurate hearing profile. Missing inter-octaves are automatically interpolated in the formula sheet (see: www.hearring.com/HEARRING_HP_Calculation.xlsx).

The hearing threshold levels range from -10 dB HL to 120 dB HL, again based on the ASHA recommendation. However, one must consider the maximum output levels of the audiometer in the equation. The levels selected to fit the equation for all clinically available audiometers can be seen in Table IV.

So the maximum level was set to the most conservative minimal output of all available maximum

Table IV. Maximum detectable hearing (mdh) measurable for each frequency.

[Hz]	125	250	500	750	1k	1.5k	2k	3k	4k	6k	8k
mdh	90	105	110	120	120	120	120	120	115	100	95

Table V. Subject 13.

Preservation numerical scale PS (%)	Kiefer et al. 2004	Balkany et al. 2006	Skarzynski et al. 2007	Gstoettner et al. 2009	Gantz et al. 2009	Rajan et al. 2012
55.1% = Partial HP	PTA_{PRE} = 42 dB HL	PTA_{PRE} = 70 dB HL	PTA_{PRE} = 74 dB HL	PTA_{PRE} = 53 dB HL	PTA_{PRE} = 86 dB HL	PTA_{PRE} = 42 dB HL
	PTA_{POST} = 68 dB HL	PTA_{POST} = 87 dB HL	PTA_{POST} = 90 dB HL	PTA_{POST} = 76 dB HL	PTA_{POST} = 99 dB HL	PTA_{POST} = 68 dB HL
	Not classified	Partial HP	Not classified	Partial HP	Not classified	Partial HP

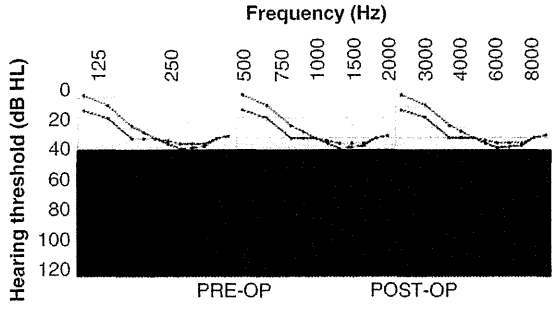


Figure 4. Subject 13 pre- and post-op scores.

output levels for each particular frequency, according to the literature and technical specifications of the most common audiometers.

The HEARRING group recommends using insert earphones when testing hearing for the preservation scale. Supra-aural headphones underestimate hearing loss as they may results in vibrotactile responses at higher intensity levels in the low frequency range [18]. Insert earphones have minimal contact between the earphone and skin leading to a reduction in vibration responses and a more accurate measurement of (low frequency) hearing thresholds.

Result

HEARRING's proposed HP classification system in use

From the 48 subjects in the Table II, we selected 3 as case studies to illustrate the results of our HP formula and to compare these results to how they would have been reported by previously published classification systems [2,3,6,13,14,19]. Key to the other systems is that they all calculate a pure tone average (PTA) using low frequency thresholds in four cases and two also include 4000 Hz [3,19]. There are also variations in which low frequencies are used in PTA calculations, e.g. [13,20] use 125 Hz whereas [14,19] do not. Our formula looks beyond the traditional EAS low frequency perspective by calculating up to 8000 Hz, thus taking high frequency hearing preservation into consideration (an important aspect in the future). It also calculates remaining low frequency hearing using all test frequencies.

Subject 13, a typical EAS case, was deemed by four classification systems to have partial post-operative residual hearing loss, however, three of the systems have no procedure for classifying hearing loss beyond either 10 [3,19] or 20 dB [13]. The system from [14] is also interesting in that all hearing loss beyond 11 dBHL is considered partial – which is a rather broad range (Table V, Figure 4).

Subject 35 shows that preservation is deemed to be complete across all schemes. However, by considering area, we can see the preservation is greater than 100%, this is because, instead of losing residual hearing area, this has actually increased and the formula shows this gain (Table VI, Figure 5).

Subject 45 is a perfect example of the increased descriptive accuracy of our formula. Other classification systems, e.g. [3,19] would consider a hearing loss of less than 10 dB to be hearing preservation, whilst the others call this complete preservation. We call this minimal hearing preservation. This is where the essence lies. The other systems only consider the pure tone average and thus one audiogram compared to the other. Our system looks at the remaining hearing and the value of that preservation to the user. In many cases, this value is of clinical importance, however, here, where there is limited hearing to start with, we are in some way able to also show structural preservation. Structural preservation is a key surgical goal, important for caring for the anatomy of the cochlear now, and for treatment modalities that may be available in the future. So, although the hearing loss was minimal – the comparison is of one area of remaining hearing relative to a later area of remaining hearing. In this case, the area was minimal to begin with, and because most of this area was lost, the preservation is deemed minimal, showing some structural damage (Table VII, Figure 6).

Table VI. Subject 35.

Preservation numerical scale PS (%)	Kiefer et al. 2004	Balkany et al. 2006	Skarzynski et al. 2007	Gstoettner et al. 2009	Gantz et al. 2009	Rajan et al. 2012
101.1% = Complete HP	PTA_{PRE} = 79 dB HL	PTA_{PRE} = 80 dB HL	PTA_{PRE} = 91 dB HL	PTA_{PRE} = 76 dB HL	PTA_{PRE} = 94 dB HL	PTA_{PRE} = 73 dB HL
	PTA_{POST} = 80 dB HL	PTA_{POST} = 80 dB HL	PTA_{POST} = 92 dB HL	PTA_{POST} = 79 dB HL	PTA_{POST} = 94 dB HL	PTA_{POST} = 78 dB HL
	Complete HP	Complete HP	Complete HP	Complete HP	Complete HP	Complete HP

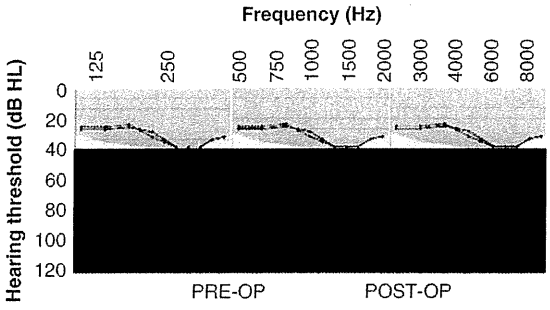


Figure 5. Subject 35 pre- and post-op scores.

The value of a percentage – some useful applications of the formula

The value of calculating a percentage and showing its uses can be demonstrated via a few examples, which are demonstrated here.

Example one

Individual clinics can obtain an overview about hearing preservation surgery outcomes. By calculating this formula, a clinic can see how many cases of complete preservation they have, how many losses etc. A clinic could then review how measured HP changes over time by looking at reduction in area.

Example two

Having a sufficient sample size to demonstrate statistical and clinical significance is key to proving outcomes of a methodology. One way to do this is to pool clinics' data to allow for a greater sample size, and to support multi-center studies. The formula data can be calculated to prove that preservation rates are the same, thus justifying pooling of the data. Using the cases from the Table II, we are able to compare outcomes from two centers and show that preservation is the same and thus data may be pooled.

We found no significant difference in percent of hearing preservation between Warsaw (n = 32) and Antwerp (n = 16) according to the results of the non-parametric Mann-Whitney U-test (p = 0.279).

Furthermore, no significant difference between the 2 centers in Hearing Preservation was reached for subjects with

- Complete HP (Warsaw: n = 15; Antwerp: n = 5; Mann-Whitney U-test: p = 0.896),
- Partial HP (Warsaw: n = 12; Antwerp: n = 8; Mann-Whitney U-test: p = 0.616), and
- Minimal HP (Warsaw: n = 5; Antwerp: n = 3; Mann-Whitney U-test: p = 0.655).

As no significant difference between the Warsaw and Antwerp data in Hearing Preservation was reached, their data can be pooled.

Example three

The data could be used for correlation analysis to see, for example, if the degree of hearing preservation is correlated to age at implantation. Using the subjects' percent of hearing preservation we found that:

(1) The correlation between the degree of hearing preservation and age at implantation was small and negative (r = -0.101) and not significant (p = 0.496)
(2) The correlation between age at implantation and Hearing Preservation when stratified for extent of Hearing Preservation did not show a significant correlation in cases of complete (r = 0.137; p = 0.565), partial (r = 0.042; p = 0.860), or minimal (r = 0.452; p = 0.260) hearing preservation.

Example four

The data could be used for comparison; for example, the outcomes of two different electrode array lengths. In this case, we can compare hearing preservation outcomes with two electrodes. In the earlier days of

Table VII. Subject 45.

Preservation numerical scale PS (%)	Kiefer et al. 2004	Balkany et al. 2006	Skarzynski et al. 2007	Gstoettner et al. 2009	Gantz et al. 2009	Rajan et al. 2012
20.0% = Minimal HP	PTA_{PRE} = 93 dB HL	PTA_{PRE} = 108 dB HL	PTA_{PRE} = 108 dB HL	PTA_{PRE} = 100 dB HL	PTA_{PRE} = 112 dB HL	PTA_{PRE} = 98 dB HL
	PTA_{POST} = 102 dB HL	PTA_{POST} = 112 dB HL	PTA_{POST} = 110 dB HL	PTA_{POST} = 103 dB HL	PTA_{POST} = 114 dB HL	PTA_{POST} = 102 dB HL
	Complete HP	Complete HP	HP	Complete HP	HP	Complete HP

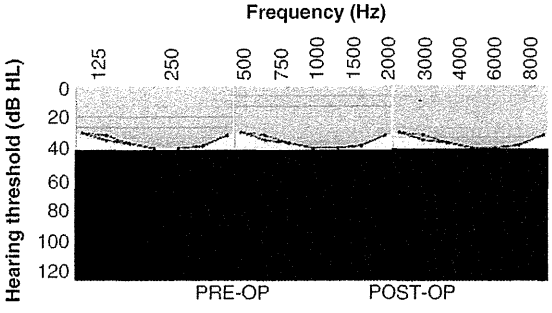


Figure 6. Subject 45 pre- and post-op scores.

EAS surgery, Warsaw used the MED-EL Standard electrode, which they only partially inserted, until the MED-EL Medium electrode was made available. We found that the electrode array length didn't have a significant difference on percent of hearing preserved for any class of hearing preservation: complete (Standard: n = 12; Medium: n = 3; Mann-Whitney U-test: p = 0.248), partial (Standard: n = 7; Medium: n = 7; Mann-Whitney U-test: p = 0.654) or minimal (Standard: n = 4; Medium: n = 1; Mann-Whitney U-test: p = 0.480) hearing preservation.

Discussion

To remedy the current lack of an accepted HP classification standard, the HEARRING group hereby proposes a comprehensive HP Classification System that 1) is suitable for reporting the hearing preservation results of all hearing preservation surgery cases, 2) is independent from the user's pre-operative hearing levels, and 3) considers the relative change of hearing thresholds. The system classifies HP when using an intervention system which comprises all elements of surgery (round window, cochleostomy, drugs used, blood contamination, etc.), the electrode itself (contacts, atraumaticity, length, coated or not), trauma due to the electrode and the surgery, as well as the fact that the electrode is a space filler.

The HEARRING group hopes clinicians put this system into practice not only because it clearly and accurately describes hearing preservation results, but because the system will enable a larger overview of hearing and structural preservation. By making the results of different HP studies more comparable, the application of our standard will allow better meta-analysis of data, thereby resulting in better evidence-based practice in the field of cochlear implantation.

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

[2] Gstoettner W, Helbig S, Settevendemie C, Baumann U, Wagenblast J, Arndoldner C. A new electrode for residual hearing preservation in cochlear implantation: first clinical results. Acta Otolaryngol 2009;129:372–9.

[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] Helbig S, Baumann U, Hey C, Helbig M. Hearing Preservation after complete cochlear coverage in cochlear implantation with the free-fitting FLEX^{SOFT} electrode carrier. Otol Neurotol 2011;32:973–9.

[5] Bruce IA, Bates JE, Melling C, Mawman D, Green KM. Hearing preservation via a cochleostomy approach and deep insertion of a standard length cochlear implant electrode. Otol Neurotol 2011;32:1444–7.

[6] Rajan GP, Kuthubutheen J, Hedne N, Krishnaswamy J. The Role of Preoperative, Intratympanic Glucocorticoids for Hearing . Preservation in Cochlear Implantation: A Prospective Clinical Study. Laryngoscope 2012;122:190–5.

[7] van de Heyning P, Mertens G, Kleine Punte A. Electric-Acoustic stimulation and hearing preservation. In Anil K, Lalwani MD, Markus HF, Pfister MD, eds. Recent advances in otolaryngology: head and neck surgery. India: Jaypee. 2012. 68–87.

[8] James C, Albegger K, Battmer R, Burdo S, Deggouj N, Deguine O, et al. Preservation of residual hearing with cochlear implantation: how and why. Acta Otolaryngol 2005;125:481–91.

[9] Derinsu U, Serin GM, Akdaz F, Batman C. Cochlear implantation: is hearing preservation necessary in severe to profound hearing loss? J Craniofac Surg 2011;22:520–2.
[10] Gstoettner W, Kiefer J, Baumgartner W, Pok S, Peters S, Adunka O. Hearing preservation in cochlear implantation for electric acoustic stimulation. Acta Otolaryngol 2004;124: 348–52.
[11] Skarzynski H, van de Heyning P, DeMin H, Li Y, Bo L, Caversaccio M, et al. Hearing preservation classification. J Hear Sci 2012;2:95–6.
[12] Skarzynski H, Lorens A, Piotrowska A, Podskarbi-Fayette R. Results of partial deafness cochlear implantation using various electrode designs. Audiol Neurootol 2009;14:39–45.
[13] Kiefer J, Gstoettner W, Baumgartner W, Pok SM, Tillein J, Ye Q, et al. Conservation of low-frequency hearing in cochlear implantation. Acta Otolaryngol 2004;124:272–80.
[14] Balkany TJ, Connell SS, Hodges AV, Payne SL, Telischi FF, Eshraghi AA, et al. Conservation of Residual Acoustic Hearing After Cochlear Implantation. Otol Neurotol 2006; 27:1083–8.
[15] Harris JD. Proem to a quantum leap in audiometric data collection and management. J Aud Res 1978;18:1–29.
[16] University of Oxford. CEBM: Centre for Evidence Based Medicine. http://www.cebm.net/index.aspx?o=1025.last accessed 22 January 2013.
[17] Guidelines for manual pure-tone threshold audiometry. ASHA 1978;20:297–301.
[18] Marangoni AT, Gil D. Influence of the type of transducer in profound hearing loss. Pro Fono 2009;21:195–200.
[19] Gantz BJ, Hansen MR, Turner CW, Oleson JJ, Reiss LA, Parkinson AJ. Hybrid 10 clinical trial: preliminary results. Audiol Neurootol 2009;14:32–8.
[20] Fraysse B, Macias AR, Sterkers O, Burdo S, Ramsden R, Deguine et al. Residual hearing conservation and electro-acoustic stimulation with the nucleus 24 contour advance cochlear implant. Otol Neurotol 2006;27:624–33.

7 診療科別先進医療

耳鼻科

信州大学医学部耳鼻咽喉科 教授　宇佐美真一
信州大学医学部耳鼻咽喉科 助教　西尾　信哉

耳鼻咽喉科領域における先進医療

先進医療は，将来的な保険導入のための評価を行うことを目的として実施されている保険外併用療法であり，2012年9月末現在耳鼻咽喉科領域の先進医療としては，第2項先進医療，「三次元形状解析による体表の形態的診断」，「RET遺伝子診断」，「MEN1遺伝子診断」の3技術が，また第3項先進医療「残存聴力活用型人工内耳挿入術　両側性感音難聴（高音障害急墜型または高音障害漸傾型の聴力像を呈するものに限る。）」の1技術が承認されている。2012年4月まで第2項先進医療で実施されていた「先天性難聴の遺伝子診断」は先進医療での有効性が認められ，2012年度の診療報酬改定で保険収載された。現在実施されている技術のうち，第2項先進医療の3技術に関しては，形成外科，脳神経外科，内科，小児科，内分泌代謝科，外科で実施されているため，本稿では耳鼻咽喉科のみで実施されている「残存聴力活用型人工内耳挿入術　両側性感音難聴（高音障害急墜型または高音障害漸傾型の聴力像を呈するものに限る。）」の1技術について詳しく解説を行う。

残存聴力活用型人工内耳挿入術の概要

難聴はコミュニケーションの大きな障害となるため，それに伴い日常生活や社会生活の質（クオリティ・オブ・ライフ：QOL）の低下を引き起こす。現在，保険診療として実施されている人工内耳の適応は，全周波数が90dB以上の重度難聴患者に限られており，高音急墜あるいは漸傾型の聴力を示す難聴患者は適応外となっている。しかし，高音急墜あるいは漸傾型の難聴患者に対して従来型の補聴器では十分な補聴をすることはできず，コミュニケーションに必要な聴力閾値までの補聴は困難な場合がほとんどであるため，現在の保険診療の範囲内に高音急墜あるいは漸傾型の聴力を示す難聴患者に対する有効な治療法は無いのが現状であった。

近年，高音急墜あるいは漸傾型の聴力を示す難聴患者に対する新しい治療法として，低音部は音響刺激，高音部は電気刺激を組み合わせることにより聴神経を刺激する「残存聴力活用型人工内耳」が登場し，欧米を中心に臨床研究が進められ欧州では臨床応用が認められている。(Kiefer et al., 2005；Gstoettner et al., 2008；Skarzynski et al., 2007)。

残存聴力活用型人工内耳は，体内に埋め込むインプラントと，体外に装着するスピーチプロセッサ（体外機）の2部分により構成されている。体外機のマイクロフォンより拾った音声情報を，周波数帯域に応じて音響刺激回路と電気刺激回路にそれぞれ分離し，低音部分はアンプにより増幅された音響刺激として外耳道経由で音声情報を内耳に伝える。一方，高音部分の音声情報はスピーチプロセッサで最適なパルスへと変換（コード化）された後に，体外機の送信コイルを経由して，体内に埋め込まれたインプラントの受診コイルに電磁誘導で信号を送信する。インプラントの先端は蝸牛に挿入されており，蝸牛内の電極アレイ間に電気パルスを送ることで，直接聴神経を電気的に刺激する（図1）。このように，音響刺激と電気刺激を組み合わせることで，従来の補聴器では聴取困難であった高音

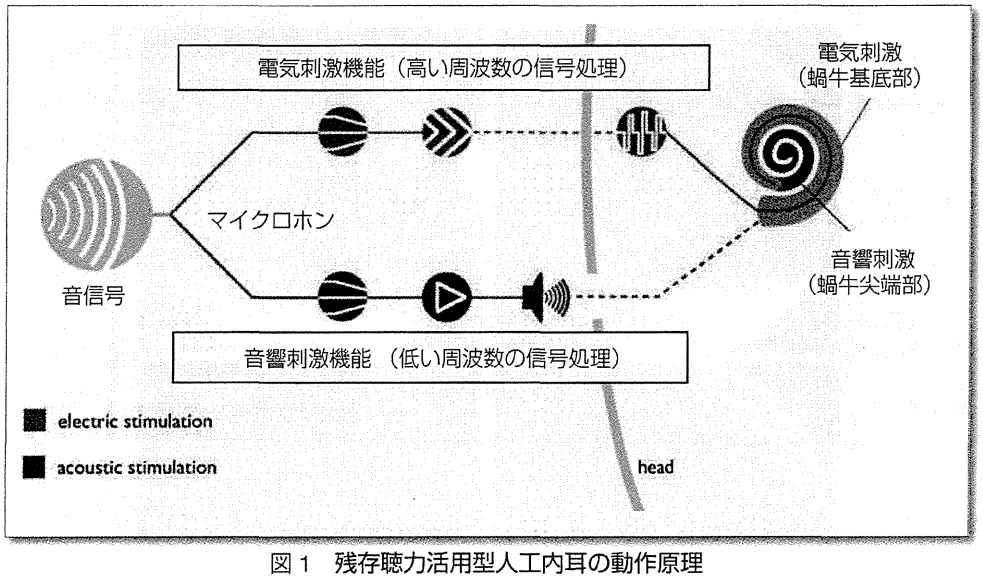


図1　残存聴力活用型人工内耳の動作原理

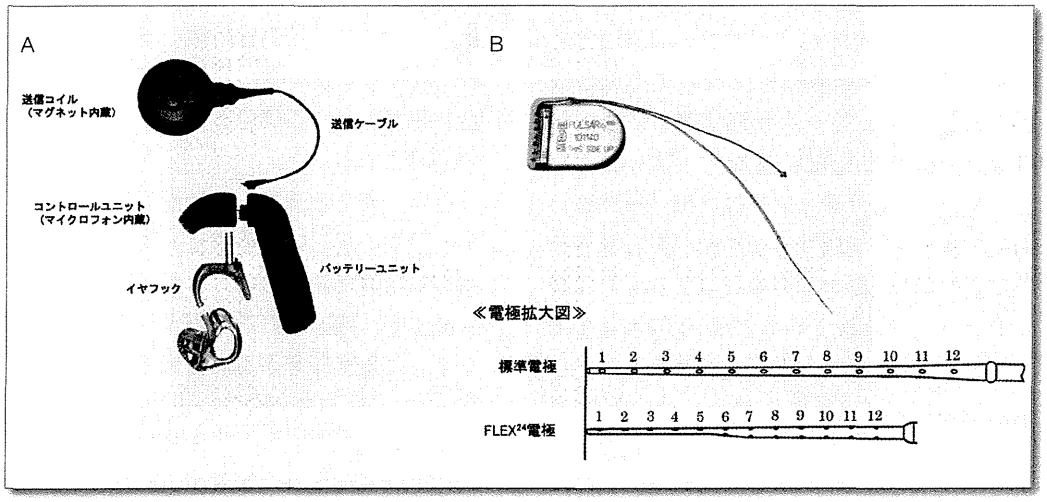


図2　残存聴力活用型人工内耳

A：スピーチプロセッサ（体外機）の形状を示す。コントロールユニットに内蔵されたマイクロフォンにより拾った音声情報を，周波数帯域に応じて音響刺激回路と電気刺激回路にそれぞれ分離し，低音部分はアンプにより増幅された音響刺激として，高音部分の音声情報は送信コイルを経由して，体内に埋め込まれたインプラントの受診コイルに電磁誘導で信号を送信する。

B：インプラントの形状を示す。従来の標準電極と比較して先端形状がより細く，柔軟性に富んだ形状に変更されており，低音部の残存聴力の保持（電極挿入に伴う蝸牛内の障害の軽減）に非常に優れている。

急墜あるいは漸傾型の聴力を示す難聴に対して効果的に補聴することが可能となっている。

従来，蝸牛に人工内耳電極を挿入することで，蝸牛の内部構造が障害され聴力はすべて失われると考えられていたが，インプラントの改良および手術手技の改良により低音部の残存聴力を温存したまま人工内耳電極を挿入することが可能となった点が本先進医療のポイントである。

残存聴力活用型人工内耳挿入術に用いるインプラント（PULSAR FLEX^{24}）は，人工内耳電極を蝸牛内に挿入する際に，低音部の残存聴力の障害を軽減することを目的に，電極の先端形状がより細く，柔軟性に富んだ形状に変更されており，従来の人工内耳を挿入する場合と比較して，低音部の残存聴力の保持（電極挿入に伴う蝸牛内の障害の軽減）に非常に優れている（図2：Adunka et al., 2004）。

また，手術手技に関しては，低音部の残存聴力を維持するため，round window アプローチという新しい

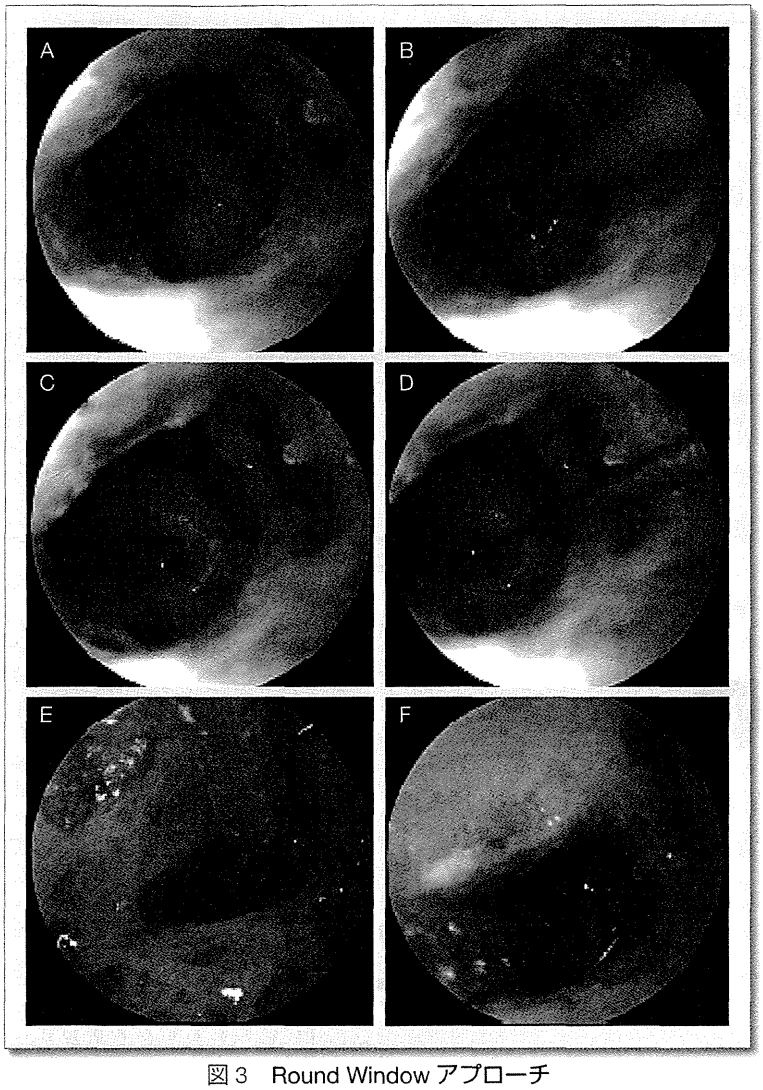


図3　Round Window アプローチ
A：通常の人工内耳挿入術と同様の手法で後鼓室解放を行う。B：正円窓の上部にある骨性のオーバーハングをドリルで切削する。C：切削後には正円窓が直視できる。D：正円窓膜をピックを用いて切開する。E・F：切開部より人工内耳電極を挿入する。（文献6より引用）

手術手技を用いる（図3：Adunka et al.,2004；Skarzynski et al.,2007；Usami et al., 2011）。round window アプローチは，蝸牛の回転軸に沿った方向から電極を挿入することで，挿入電極による蝸牛の内部構造の破壊を軽減する手術法であり，従来の人工内耳挿入術と比較して，低音部の残存聴力の維持に優れている。また，手術の安全性に関しては，電極挿入以外の部分は現在保険で承認されている通常の人工内耳手術とほぼ同様の手法を用いるため有害事象が起こる確率はきわめて低いと考えられる。

このように，本高度医療　残存聴力活用型人工内耳埋込は，低音部に残存聴力を有するため通常の人工内耳の適応（全周波数にわたり高度難聴）には該当しないが，補聴器での聞き取りは困難であり，従来治療法のなかった高音急墜あるいは漸傾型の聴力像を示す難聴患者に対して，聴取能の改善をもたらすことが可能であり，QOL の大幅な向上に寄与することが可能である先進性の高い医療である。

残存聴力活用型人工内耳挿入術の実際

残存聴力活用型人工内耳挿入術は，国立大学法人信州大学医学部附属病院，国家公務員共済組合虎の門病院，地方独立行政法人神戸市民病院機構神戸市立医療センター中央市民病院，国立大学法人長崎大学医学部

附属病院，国立大学法人宮崎大学医学部附属病院の5施設での実施が承認されている。

第3項先進医療「残存聴力活用型人工内耳挿入術」の適応は，気導聴力閾値が，125Hz，250Hz，500Hzが65dB以下，2000Hzが80dB以上，4000Hz，8000Hzが85dB以上（※ただし，上記に示す周波数のうち1箇所が10dB以内の幅で外れる場合には対象とする。）を満たし，かつ，補聴器装用下において静寂下での語音弁別能が65dBで60％未満である者となっている。

先進医療では，術前の検査として純音聴力検査を実施し適応聴力を満たしていることを確認するとともに，静寂下での語音弁別検査を実施して日本語単音節の聴取においても適応基準を満たすことを確認する。その後，麻酔等の手術適応のための各種検査を行った後に手術を実施する。手術後1ヵ月より体外機の装用を開始し，機械の調整を繰り返すとともに，12ヵ月後まで継続的に聴取成績の検討を実施している。

2010年7月に承認を受けて以降，現在までに24例の予定症例のうち23例の手術が完了しており，また，術後6ヵ月の有効性評価が終了した症例が14症例，12ヵ月のフォロー期間が完了した症例が9症例という状況である。術後6ヵ月時の有効性評価が終了した14例を対象に有効性に関する検討を行った結果，全例で装用下聴力閾値の大幅な改善を認めた。また，日本語単音節の聴取に関しても13例で改善を認めており，残存聴力活用型人工内耳の日本語話者に対する有効性が確認できつつある。このように残存聴力活用型人工内耳挿入術は，現在の保険診療の範囲内に治療法のない高音急墜型あるいは漸傾型難聴に対する治療法として非常に有効な治療法であり，早期に保険導入されることが適当であると考えられる。

参考文献

1) Kiefer J. Pok M., Adunka O., Sturzebecher E., Baumgartner W., Schmidt M., Tillein J., Ye Q and Gstoettner W. Combined electric and acoustic stimulation of the auditory system：Results of clinical study. Audiology and Neurotology 2005；10：134-144
2) Gstoettner W K., Heyning P V D., O'Connor A F., Morera C., Ainz M., Vermeire K., McDonald S., Cavalle L., Helbig S., Valdecasas J G., Anderson I and Adunka O F. Electric acoustic stimulation of the auditory system：results of a multi-centre investigation. Acta Oto-Laryngologica 2008 1-8
3) Adunka O., Kiefer J., Unkelbach M. H. Lehnert T and Gstoettner W. Development and evaluaton of an improved cochlear implant electrode design for electric acoustic stimulation. The Laryngoscope 2004；114：1237-1241
4) Skarzynski H., Lorens A., Piotrowska A and Anderson I. Preservation of low frequency hearing in partial deafness cochlear implantation (PDCI) using the round window surgical approach. Acta Oto-Laryngologica, 2007；127：41-48
5) Usami S, Moteki H, Suzuki N, Fukuoka H, Miyagawa M, Nishio S Y, Takumi Y, Iwasaki S, Jolly C. Achievement of hearing preservation in the presence of an electrode covering the residual hearing region. Acta Otolaryngol 131：405-412, 2011
6) 宇佐美真一，茂木英明，宮川麻衣子，内藤武彦，西尾信哉，工穣，岩崎　聡：残存聴力活用型人工内耳（EAS：electrical acoustic stimulation）～手術法と聴力保存成績について～．Otol Jpn　21：763-770，2011

Auris Nasus Larynx 39 (2012) 638–640

Contents lists available at SciVerse ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

A postmeningitic cochlear implant patient who was postoperatively diagnosed as having X-linked agammaglobulinemia

Ryosei Minoda [a,*], Haruo Takahashi [b], Satoru Miyamaru [a], Masako Masuda [a], Toru Miwa [a], Tetsuji Sanuki [a], Toshinori Hirai [c], Eiji Yumoto [a]

[a] Department of Otolaryngology Head and Neck Surgery, Graduate School of Medicine, Kumamoto University, 1-1-1 Honjo Kumamoto 860-8556, Japan
[b] Division of Otorhinolaryngology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Sakamoto 171, Nagasaki 852-8501, Japan
[c] Departments of Diagnostic Radiology, Graduate School of Medicine, Kumamoto University, 1-1-1 Honjo Kumamoto 860-8556, Japan

ARTICLE INFO

Article history:
Received 17 October 2011
Accepted 20 January 2012
Available online 16 February 2012

Keywords:
X-linked agammaglobulinemia
Primary immunodeficiency
Cochlear implant

ABSTRACT

X-linked agammaglobulinemia (XLA) is caused by a mutation in the Bruton tyrosine kinase, leading to an arrest in B cell development. Consequently, patients with XLA show significant decreases in gammaglobulin. Here, we describe a child with postmeningitic deafness and XLA who underwent a cochlear implantation. His psychomotor development had been normal and his congenital immunodeficiency was noticed only postoperatively. Immunoglobulin replacement treatment was started, but he still suffered repeated infections. Eventually, his cochlear implant was removed. A preoperative check of immunological status might be advisable in postmeningitic patients undergoing cochlear implantation to reduce the risk of postoperative infectious complications.

1. Introduction

Cochlear implantation is generally accepted as a safe and effective treatment to rehabilitate patients with bilateral severe-to-profound hearing loss. The complication rate is relatively low. The most common non-device-related complications occur around the skin flap, and the incidence of infectious complications has been reported as 12.9% [1].

Primary immunodeficiency affects as many as 10 million people worldwide. More than 150 primary immunodeficiency diseases have been identified, and they range widely in severity. Immunodeficient conditions likely increase the risk of postoperative infectious complications even in cochlear implant patients.

To the best of our knowledge, only five patients with cochlear implants who had primary immunodeficiencies have been reported to date. Hopfenspirger et al. [2] described two patients with primary immunodeficiency: one with neutropenia/chemotactic neutrophil dysfunction and one with IgA deficiency. Although they had been diagnosed with primary immunodeficiencies preoperatively, they suffered postoperative infections at the surgical sites. Eventually, the cochlear implants in both patients were removed. Yu et al. [3] reported two patients with immunodeficiency who also suffered postoperative infections after cochlear implant surgeries and were then diagnosed with primary immunodeficiencies based on results of their IgG isohemagglutinin titers decreasing postoperatively. They reported that the cochlear implant in one of the two patients was preserved with daily low-dose oral antibiotic administration, without intravenous immunoglobulin therapy [3]. More recently, Brookes et al. [4] reported on a patient who was diagnosed with deafness-dystonia-optic neuronopathy (DDON) syndrome and X-linked agammaglobulinemia (XLA). His XLA was preoperatively diagnosed and antibody replacement therapy was initiated. He did not appear to have any wound troubles after cochlear implantation.

Here, we report on the clinical course of a child with a cochlear implant who was diagnosed with XLA postoperatively. To the best of our knowledge, this is the second report of a patient with XLA who underwent cochlear implantation.

2. Case report

A 3-year-old boy with a postmeningitic profound sensorineural hearing loss (SNHL) was referred to our department in May 2006, to obtain an evaluation for cochlear implantation. A physical examination at the first visit to our department revealed that he had a partial severe retraction of tympanic membrane pars tensa in the right ear and accumulated effusions in the left ear, with purulent rhinorrhea in his nasal cavities. Play audiometry and an auditory brainstem response examination revealed bilateral profound SNHL. A CT scan and MRI examinations revealed

* Corresponding author. Tel.: +81 96 373 5255; fax: +81 96 373 5256.
E-mail address: minoda@gpo.kumamoto-u.ac.jp (R. Minoda).

0385-8146/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.anl.2011.12.005

ossification of the basal turn of the scala tympani of the bilateral cochleae.

In June 2006, we performed cochlear implantation surgery on the left ear. Although ossification was observed in the basal turn of the scala tympani, all electrodes (CI24RE (CA); Cochlear, Ltd., Cove, NSW, Australia) were inserted into the scala tympani. He received ceftriaxone for 10 days postoperatively. His postoperative clinical course and postoperative speech recognition ability were good.

However, in December 2007, he complained of pain where the device had been implanted, and his mother noticed swelling at the site. The swelling and his symptoms became worse (Fig. 1), although he was receiving an oral antibiotic. We then performed surgical drainage, revealing that the content of the swelling was a purulent secretion. Drain tubes were placed during the surgery. Bacteriological examination of the purulent secretion revealed *Streptococcus pneumoniae* (PISP). The local condition improved with daily postoperative lavage through the drain tubes and antibiotic administration.

In April and July 2008, the localized swelling and pain re-appeared again twice. We performed surgical drainage. The content of the swelling revealed a blood clot, and bacteriological examinations of the contents were negative. The local condition again improved with the same treatment as before. During his hospital stay, he underwent patch tests against the materials used in the cochlear implant, provided by the implant company; all the tests were negative. In June 2008, he was treated at a hospital for pneumonia. In September 2008, he underwent an immunological evaluation. His peripheral blood B cell subset was less than 1%, and his serum IgG, IgA, and IgM were 7 mg/dL, 3 mg/dL, and 30 mg/dL, respectively. Gene analysis revealed a mutation in the Bruton tyrosine kinase gene.

He was finally diagnosed with XLA. He started to undergo antibody replacement therapy every 3 weeks: his physical activity level improved significantly; and, his repeated purulent nasal discharges stopped spontaneously without usage of antibiotics,

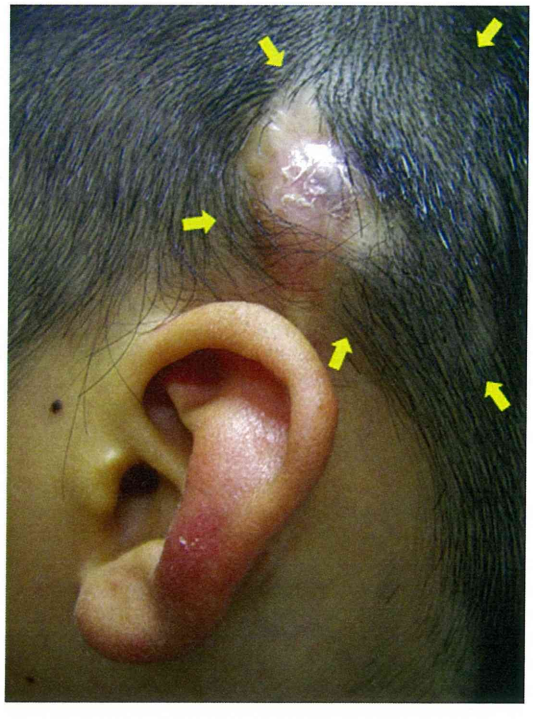


Fig. 1. Swelling at the site where the cochlear implant was implanted.

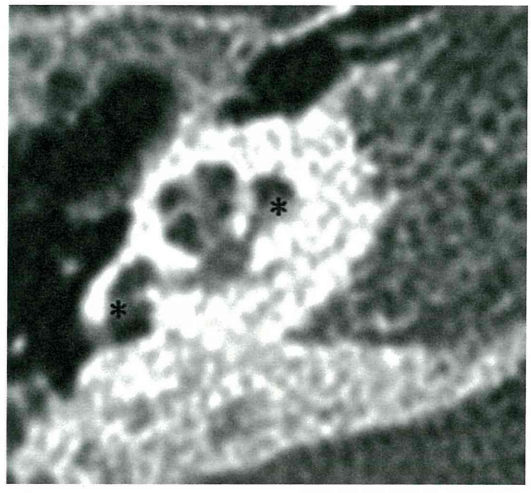


Fig. 2. A CT scan image of right ear at the second cochlear implantation. The asterisks indicate ossification of the scala tympani in the basal turn of the cochlea.

after this treatment. Despite the antibody replacement therapy, subsequently, local swelling around the implant recurred twice more. On the second occurrence, we removed granulation tissue surrounding the cochlear implant in addition to surgical drainage under general anesthesia. During the surgery, we held electrode bundle near the implant, turned it over, removed all granulation tissue surrounding the cochlear implant, to the extent possible, and washed the wound gently with saline many times, after which the cochlear implant was covered with the temporal muscle. Nevertheless, he experienced local swelling and pain again, and self-destruction of wound skin was observed. Finally, we decided to remove the cochlear implant. In February 2010, we performed cochlear implant surgery on the right ear (PULSAR; Med-El, Innsbruck, Austria) and subsequently removed the cochlear implant from the left ear. We inserted the electrode into the scala vestibule because a preoperative CT scan study revealed ossification of the scala tympani in the right ear (Fig. 2). We successfully inserted all except one electrode. Postoperatively, he received flomoxef and clindamycin for 12 days and his serum IgG level was maintained at 1000–1700 mg/dL by intravenous administration of γ-globulin perioperatively. His postoperative clinical course was good. For 22 months, no recurrence of local swelling occurred since the surgery. Postoperative speech recognition ability testing revealed 56% (words) by the Japanese speech recognition test battery, "CI–2004" under the auditory-only listening condition.

3. Discussion

XLA is caused by mutations in the Bruton tyrosine kinase, located at chromosome Xq22, leading to arrested B cell development at a pre-B cell stage. As a result, patients have no mature B cells, and IgG is less that 200 mg/dL. XLA accounted for 7.3% of primary immunodeficiency conditions in a 2007 survey in the United States. The immunodeficient condition allows bacterial meningitis, although most patients who present with bacterial meningitis do not have XLA or any other obvious deficiency in immune function [5]. Additionally, only 7.1% of child patients experience bilateral profound hearing (>90 dBSPL) after childhood bacterial meningitis [6]. Given these numbers, very rarely will a patient with postmeningitis who is a candidate for cochlear implant surgery have an immunodeficiency condition.

The most reliable strategy for the management of postoperative wound infections after cochlear implantation may be to explant

the device. Tambyraja et al. [1] summarized data from the Manufacturer User Facility and Distributor Experience (MAUDE) database, which is maintained by the Food & Drug Administration and has mandatory reporting requirements. In the pre-2002 period, 102 cases of flap problems were reported, which included flap necrosis, flap infection, flap dehiscence, and device extrusion. Approximately 70% of cochlear implants were explanted in those patients. However, current recommendations call for conservative measures [7]. Yu et al. [3] reported four patients with postoperative infections including two primary immunodeficiency patients, who showed decreased IgG isohemagglutinin titers. The postoperative cochlear implant infections in three of the four were controlled effectively with limited surgical approaches and prolonged postoperative antibiotic administration [3]. The cochlear implant was explanted due to failure of infection control in one patient with a primary immunodeficiency although antibody replacement therapy and intravenous antibiotics administration were continued [3]. Considering these reports, prolonged medical management may be effective. However, in the patient with primary immunodeficiency who did not need device removal, the report did not provide detailed levels of immunoglobulin, and her infection was successfully controlled using only a daily low-dose oral antibiotic (cephalexin) with no antibody replacement therapy; her immunodeficiency thus may not have been severe. Taken together, the conservative approach probably has limited efficacy in patients who are immunodeficient.

Controlling infectious complications after cochlear implant surgery can be difficult even in healthy patients. Recently, biofilm formation on the surface of a cochlear implant receiver–stimulator device was suggested to probably contribute to persistent cochlear implant infection. Such a bacterial biofilm on the device is highly resistant to antibiotic therapy and to removal by direct washing of the device [8]. Moreover, Pawlowski et al. [8] reported that the biofilm on the device was most substantial in the depressions along the surface of the device that were created by the manufacturer. Considering these points, the first infection on our patient was likely due to his untreated immunodeficiency condition, and biofilm on the surface of the device probably contributed to the persistent local infection.

If the patient's immunodeficiency is diagnosed preoperatively, one can add supplemental treatments perioperatively to help avoid postoperative complications. Brookes et al. [4] reported on a patient who was diagnosed with DDON syndrome and XLA. His XLA was preoperatively diagnosed and antibody replacement therapy was initiated. He did not appear to have any wound troubles after cochlear implantation. However, if the patient has not been diagnosed preoperatively, like our patient, the immunodeficient condition probably tends to increase infectious complications, ultimately leading to extraction of the implant. Also, in patients who are postmeningitic, cochlear implant surgery on the opposite side probably becomes more formidable because of postmeningitic ossification in the cochlea. Thus, considering the presence of an immunodeficient condition in patients is important, especially from symptoms suggesting such conditions such as recurrent infections. In most patients with XLA, they typically present with recurrent pyogenic infections starting at 5–6 months of age when passively placentally transferred maternal antibodies have waned [9]. Our patient had repeated purulent rhinorrhea preoperatively, which continued postoperatively. He also suffered from pneumonia once postoperatively. With hindsight, these were likely signs of his immunodeficient condition. Physicians should pay attention to the possibility of an immunodeficient condition in a patient before and after surgery. To reduce the risk of complications after a cochlear implant, we think that in addition to obtaining a careful history about any repeated infections, preoperative checks of serum immunoglobulins (IgG, IgA, IgM) and IgG subclass analyses might be needed for the diagnosis of major primary immunodeficient deficits on cochlear implant candidates who have had repeated infectious episodes. Moreover, the prevalence of acquired immune-deficiency syndrome (AIDS) continues to increase, so a preoperative check of the CD4/CD8 ratio might also be useful.

4. Conclusion

An immunodeficient condition may allow bacterial meningitis. However, most patients who present with bacterial meningitis do not have an immunodeficiency [5] and less than 10% of children with meningitis experience bilateral profound hearing after bacterial meningitis [6]. Thus, the chance of seeing a patient with XLA as a candidate for cochlear implant surgery is very low. However, we should consider an immunodeficient condition as a possible cause of meningitis in patients who are candidates for cochlear implants in helping to avoid postoperative infectious complications.

Conflicts of interest

None.

References

[1] Tambyraja RR, Gutman MA, Megerian CA. Cochlear implant complications: utility of federal database in systematic analysis. Arch Otolaryngol Head Neck Surg 2005;131:245–50.
[2] Hopfenspirger MT, Levine SC, Rimell FL. Infectious complications in pediatric cochlear implants. Laryngoscope 2007;117:1825–9.
[3] Yu KC, Hegarty JL, Gantz BJ, Lalwani AK. Conservative management of infections in cochlear implant recipients. Otolaryngol Head Neck Surg 2001;125:66–70.
[4] Brookes JT, Kanis AB, Tan LY, Tranebjaerg L, Vore A, Smith RJ. Cochlear implantation in deafness-dystonia-optic neuronopathy (DDON) syndrome. Int J Pediatr Otorhinolaryngol 2008;72:121–6.
[5] Overturf GD. Indications for the immunological evaluation of patients with meningitis. Clin Infect Dis 2003;36:189–94.
[6] Adachi N, Ito K, Sakata H. Risk factors for hearing loss after pediatric meningitis in Japan. Ann Otol Rhinol Laryngol 2010;119:294–6.
[7] Cunningham 3rd CD, Slattery 3rd WH, Luxford WM. Postoperative infection in cochlear implant patients. Otolaryngol Head Neck Surg 2004;131:109–14.
[8] Pawlowski KS, Wawro D, Roland PS. Bacterial biofilm formation on a human cochlear implant. Otol Neurotol 2005;26:972–5.
[9] Mahmoudi M. Allergy and asthma: Practical diagnosis and management. McGraw-Hill Professional Publishing; 2007.

Auris Nasus Larynx 40 (2013) 435–439

Contents lists available at SciVerse ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Long term speech perception after cochlear implant in pediatric patients with *GJB2* mutations

Haruo Yoshida [a,b,*], Haruo Takahashi [b], Yukihiko Kanda [b,c], Shin-ichi Usami [d]

[a] Department of Otolaryngology-Head and Neck Surgery, National Hospital Organization Ureshino Medical Center, Saga, Japan
[b] Department of Otolaryngology-Head and Neck Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[c] Nagasaki Bell Hearing Center, Nagasaki, Japan
[d] Department of Otorhinolaryngology, Shinshu University School of Medicine, Asahi, Matsumoto, Japan

ARTICLE INFO

Article history:
Received 4 September 2012
Accepted 24 January 2013
Available online 9 March 2013

Keywords:
GJB2 hearing impairments
Cochlear implant
Genetic testing
Hereditary hearing loss

ABSTRACT

Objectives: To determine the long term effect of cochlear implant (CI) in children with *GJB2*-related deafness in Japan.
Methods: Genetic testing was performed on 29 children with CI. The speech perception in 9 children with *GJB2* gene-related deafness fitted with CI was compared with those in matched 10 children who were diagnosed as having no genetic loci. The average follow-up period after CI was 55.9 months and 54.6 months, respectively.
Results: A definitive inherited hearing impairment could be confirmed in 12 (41.4%) of the 29 CI children, including 10 with *GJB2*-related hearing impairment and 2 with SLC26A4-related hearing impairment. The results of IT-MAIS, word or speech perception testing under the noise, and development of speech perception and production testing using the Enjoji scale were slightly better for the *GJB2* group after CI than for the control group without statistical significant difference.
Conclusion: The long-term results of this study show that CI is also effective in the development of speech performance after CI in Japanese children with *GJB2*-related hearing impairments as HL due to other etiologies.

1. Introduction

Recent progress in the research on hereditary hearing loss is remarkable. Since 1992, more than 125 genetic loci have been reported to be involved in nonsyndromic hearing loss (HL) [1], and over 67 of those loci are involved in autosomal recessive nonsyndromic HL [2]. Among these, the *GJB2* gene encoding the connexin (Cx) 26 protein (chromosomal 13q11-12) is the most common, of which about 100 different *GJB2* mutations have been reported globally [3]. It is reported to account for between 20 and 50% of all recessive nonsyndromic cases [4].

On the other hand, the benefits of cochlear implantation (CI) for spoken language, reading skills, and cognitive development have been clearly demonstrated [5,6]. Recently, the outcomes of CIs in patients with *GJB2* mutations have also been reported. Several studies have shown that patients with *GJB2* mutations (OMIM 121011) usually exhibit excellent speech perception and language performance after CI, when compared with those without identifiable *GJB2* mutations [7–11]. However, other studies have demonstrated that when the control group is appropriately matched with regard to age at implantation and length of post CI, there is no significant difference when comparing those with *GJB2*-related deafness to those without it [12–15]. Results analyzing post-CI speech performance in patients with *GJB2* mutations are still controversial.

In this study, in order to know whether the long term effect of CI is better in children with *GJB2*-related deafness or not, we have studied the speech perception outcome of CI in children with *GJB2* gene mutations, and compared them to those in matched children without inherited hearing loss.

2. Materials and methods

2.1. Subjects

We have performed CI in 301 cases in our clinic since 1997. Genetic testing was performed in 29 children with CI, and definitive *GJB2*- and *SLC26A4*-related hearing impairment was confirmed in 10 (34.5%) and 2 (6.9%) children with CI, respectively.

* Corresponding author at: Department of Otolaryngology-Head and Neck Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. Tel.: +81 95 849 7349; fax: +81 95 849 7352.
E-mail address: y-haruo@f6.dion.ne.jp (H. Yoshida).

0385-8146/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.anl.2013.01.006

Table 1
Clinical information of cases in the 2 groups.

Group	Control	GJB2	*P* value
Number of cases	10	9	
Sex (male:female)	3:7	2:7	
Age at CI (months)	36.7	37.4	0.5996
Post CI (months)	54.6	55.9	0.6736
Pre-CI education	Auditory-verbal/oral	Auditory-verbal/oral	

CI: cochlear implantation.

Finally, 19 children whose selection criteria were as follows were enrolled for this study.

1. Their age at CI was 6 years or less
2. Their guardian accepted gene mutation analysis
3. There was no any other apparent cause of deafness such as inner ear anomaly, central disorders/learning difficulties, or cytomegalovirus (CMV) infection

We divided them into two groups: the first, a control group consisting of 10 children who were diagnosed as having no genetic loci, while the second was the actual *GJB2* study group consisting of 9 children with *GJB2* gene-related deafness. Detail of their clinical information is shown in Table 1. HL was diagnosed at a different age in each child, but showed 90 dB or more severe HL before the age of 6 on auditory brainstem response (ABR) test. Preoperative imaging studies (CT and MR) showed no abnormal findings in any of the children in each group. None of the children showed any cognitive delay. The average age at CI in the two groups was 36.7 months (ranging from 21 to 67 months old; 3 male and 7 female) and 37.4 months (ranging from 22 to 63 months old; 2 male and 7 female), respectively. Thus, there is no significant difference between the two groups (Student's *t*-test, $t = -0.5339$, $P = 0.5996$). Their average follow-up period after CI was 54.6 months (ranging from 24 to 110 months) and 55.9 months (ranging from 47 to 62 months), respectively (Student's *t*-test, $t = -0.4278$, $P = 0.6736$). All the cases in this study had an intensive auditory-verbal education without visual information since childhood. Both the CI operation and the (re)habilitation after CI took place in the same clinic.

All patients were fitted with a CI system from either nucleus multichannel cochlear implant system (Cochlear Corporation, Englewood, CO, U.S.A.) or Combi40+ cochlear implant system (MED-EL, Innsbruck, Austria). All electrode arrays were inserted in all patients. There were no perioperative complications in any of the patients.

We examined the hearing level (both with CI and with hearing aids), the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS), speech perception skills, and development of articulation in the two groups before and after CI several times in the postoperative period ranging from 6 months to 4 years. The best results from this period were used in evaluating the hearing level and the speech perception skills in the two groups. The speech perception skills were evaluated using CI 2004, SDS-67S, and Japanese CD SDS system (TY-89) tested at 70 dB SPL (sound pressure level) using an open-set questionnaire. We also examined the development of speech perception and production by using the Enjoji Scale of Infant Analytical Development (Enjoji Scale), which was developed in Japan and is now established as one of the standard developmental examinations for evaluating the development of children from birth to about the age of 6 [16]. In this examination, the development of a child can be assessed by checking his or her performance on the chart, in which standard developmental items at each month are described in the three fields including motor, social and language skills. The results allow us to clearly assess to what extent a child is successfully developing in each of the three fields and the six subdivided categories. These tests were conducted up to 2 years after CI.

2.2. Mutation detection

15 ml peripheral venous blood using standard procedure was sent to the Institute of Otorhinolaryngology, Shinshu University School of Medicine, Matsumoto, Japan for Genomic DNA extraction. All subjects underwent mutation screening for 47 common mutations of 10 hearing loss related genes in Japan by using invader assay [17,18].

Written informed consent was obtained from the guardians of all the subjects and the study was approved by the ethical committee of our institute (approval number: 07122106). The differences between in the two groups were analyzed statistically using the paired *t*-test and the unpaired Student's *t*-test. All the acceptance criterion for a significant addition to the explained variance was set at *P* values under 0.05.

3. Results

A definitive *GJB2*-related hearing impairment was confirmed in 9 (32.2%) of the 29 children with CI. Table 2 shows the details of detected *GJB2* gene-mutations. *GJB2 c.*235delC was observed in 3 cases, while six children each had one distinct mutation as listed in the table.

Fig. 1 shows the preoperative aided hearing thresholds. The preoperative hearing level was over 90 dB in all the cases, and the average level of preoperative aided hearing thresholds was nearly 60 dB in the two groups presenting no significant difference between the two groups.

Fig. 2 shows the postoperative hearing thresholds with CI. After CI, the hearing level improved to 25–30 dB in both groups, thus there was no significant difference between the groups.

Fig. 3 shows the results of the IT-MAIS for the two groups. Preoperative scores were worse in the *GJB2* group than in the control group, however, these improved from 1 year to 3 years after CI. The averaged IT-MAIS score in the GJB2 group was 9.8 ± 12.9 (range, 0–31) preoperatively. The averaged IT-MAIS score at 2 years after CI increased up to 33.6 ± 7.8 (range, 20–39), and this improvement was statistically significant (paired *t*-test, $P = 0.017$). The averaged IT-MAIS score in the control group at 2 years after CI

Table 2
Mutations with GJB2 gene in 9 cases.

Mutation	Number of cases
GJB2 c.[235delC];[235delC]	3
GJB2 c.[511insAACG];p.[T86R]	1
GJB2 c.[235delC];[299-300delAT]	1
GJB2 p.[G45E;Y136X];[R143W]	1
GJB2 c.[176-191del16];[299-300delAT]	1
GJB2 c.[235delC];p.[G45E;Y136X]	1
GJB2 c.[235delC];p.[R143W]	1

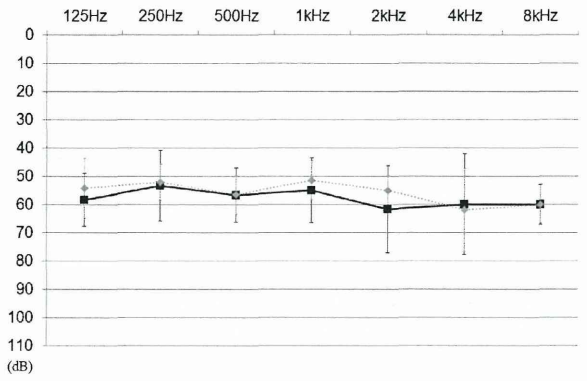


Fig. 1. Results of the average level of preoperative aided hearing thresholds at each frequency. Diamond dots and solid line: control group; square dots and solid line: *GJB2* group; bars: indicate two standard deviations.

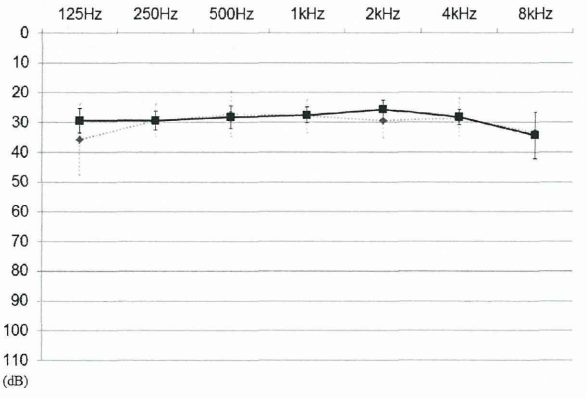


Fig. 2. Results of the average level of postoperative hearing thresholds with CI at each frequency. Diamond dots and solid line: control group; square dots and solid line: *GJB2* group; bars: indicate two standard deviations.

was 30.4 ± 7.6 (range, 19–38). There was no significant difference in the scores between the two groups at 4 years after CI.

Fig. 4 shows the results of speech perception skills in the two groups after CI. Longitudinal axis indicates the results (%) when tested at 70 dB SPL using CI 2004, SDS-67S, and Japanese CD SDS system (TY-89) in the two groups. There was no significant difference between the two groups, but the percentage of correct answers (%) examined under the noise tended to be better in the *GJB2* group.

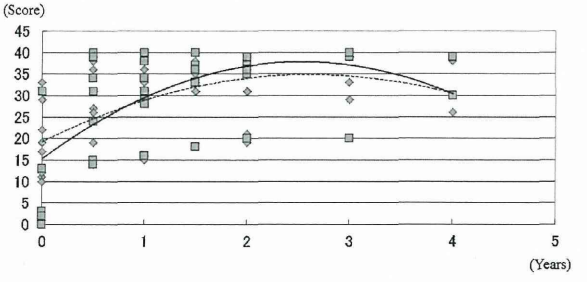


Fig. 3. Results of the difference of IT-MAIS scores from 0 years (=preoperative) to 4 years after CI. Diamond dots: scores in the control group; square dots: scores in the *GJB2* group; dotted line: trend line in the control group; solid line: trend line in the *GJB2* group.

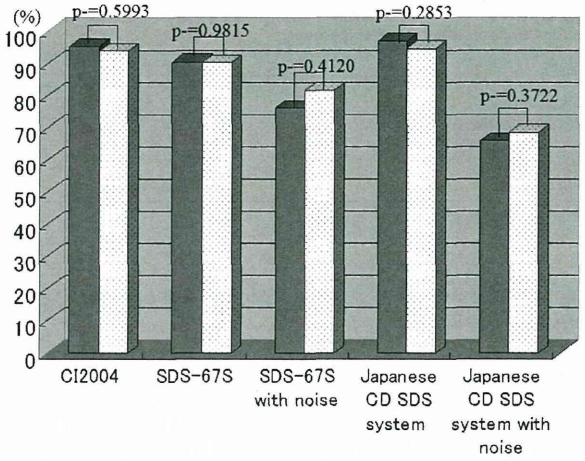


Fig. 4. Results of speech perception skills examined by using CI 2004, SDS-67S, and Japanese CD SDS system (TY-89). Longitudinal axis indicates the correct answer rate (%). Gray bars: control group; dotted bars: *GJB2* group.

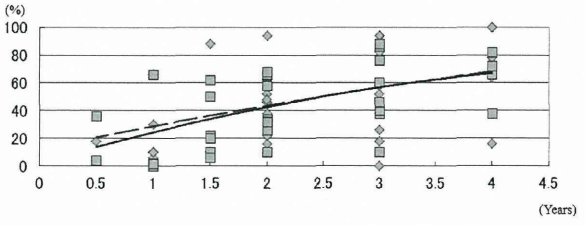


Fig. 5. Results of the development of articulation from 0.5 to 4 years after CI. Diamond dots: accuracy rates in the control group; square dots: accuracy rates in the *GJB2* group.

Fig. 5 shows the results of development of articulation in the two groups after CI. There was no significant difference in the scores between the two groups.

Fig. 6 shows the results in the development of speech perception (Fig. 6a) and production (Fig. 6b) in the two groups after CI. Values of month in the ordinate were calculated by subtracting the developmental months assessed by the Enjoji Scale from the actual age at each period, thus, smaller values indicate better development of speech perception and production. Postoperative language perception and production in the *GJB2* group tended to be slightly better, especially at one and half years after surgery, but there was no significant difference in these scores.

4. Discussion

The incidence of HL is approximately 0.1% among newborns, and hereditary HL is identified in at least 60% of patients with congenital HL, for whom the proportion of syndromic and non-syndromic is 30% and 70%, respectively [19]. The most common trait of nonsyndromic HL is autosomal recessive, which accounts for about 80% of cases [20], and *GJB2* is the gene most frequently associated with hereditary HL. The incidence of *GJB2* mutations in the Japanese population with HL is 14.2% overall and 25.2% in patients with congenital hearing loss [21], and 35 of the 119 cases (29.4%) with non-syndromic deafness [22]. In children with CI, 135 hearing-impaired patients (270 alleles) were tested, and *GJB2* mutations for the c.235delC were found in 39 alleles of 270 alleles (14%). Especially the homozygous of c.235delC was detected in 26

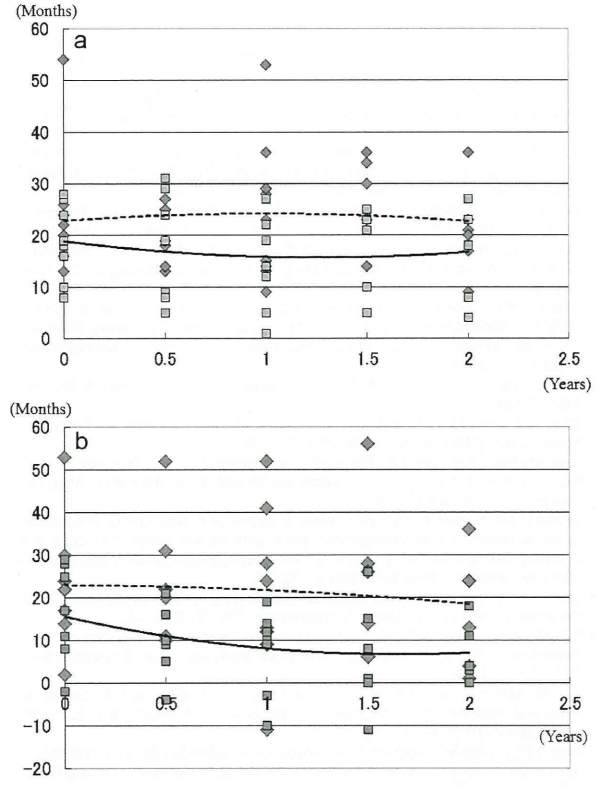


Fig. 6. Results of the developmental course of language perception (a) and production (b) in the control and *GJB2* groups examined by Enjoji Scale of Infant Analytical Development test. Diamond dots: scores in the control group; square dots: scores in the *GJB2* group; dotted line: trend line in the control group; solid line: trend line in the *GJB2* group.

alleles (9.6%), single heterozygous of c.235delC was detected in 1 allele (0.4%) and compound heterozygous of c.235delC was found in 12 alleles (4.4%) [23].

In this study, a definitive inherited hearing impairment could be confirmed in 11 (37.9%) of the 29 CI children, including 9 with *GJB2*-related hearing impairment, 2 with *SLC26A4*-related hearing impairment. These percentages are quite high and remind us of the importance of performing the mutation detection for CI patients.

The *GJB2* group underwent the IT-MAIS, word or speech perception testing under the noise, and development of speech perception and production testing using the Enjoji scale. The finally achieved performances in the two groups were not significantly different, but the averaged IT-MAIS score at 2 years after CI was significantly better in the GJB2 group than in the control group. This result may indicate that the necessary period to achieve the actual age development was shorter in the *GJB2* group than in the control group, and the difference may become smaller as they acquire language through CI in longer term. Matsushiro evaluated 4 CI children with GJB2 gene mutation and reported that the postoperative IT-MAIS score at 6 months was significantly higher in comparison with that of other prelingual CI patients [24]. In this study, children such as those having inner ear anomaly or cytomegalovirus infection, whose postoperative performance after CI is not necessarily good, were excluded from the control group. Considering that these children may also be candidates for CI in general, we can expect CI is efficient for Japanese children with *GJB2* gene mutation as well as for those reported previously [8,23,24].

GJB2 and *GJB6*, mapping to the DFNB1 locus and encoding the gap-junctions Cx 26 and 30, respectively [25]. Cx 26 and 30 are widely expressed in the cochlea at the level of the organ of Corti's supporting cells and connective tissues, and have an important role in forming homomeric or heteromeric hemichannels [26,27]. Mutations in Cx26 are presumed to result in altered potassium recirculation, leading to an accumulation of potassium in the cochlear endolymph and causing hair cell dysfunction and deafness [28]. In other words, mutations in the Cx26 protein mainly lead to the impairment of the endolymph potassium concentrations, which are required for auditory signal transduction, but may not lead to severe damage or decreasing the number of hair cells. It is generally assumed that the results of CI are poorer for inner ear malformation and in cases with neural and/or central damage than in cases with disorders within the inner ear causing the hair cells damage because the auditory pathway including the first neuron, spiral ganglion cells, may well be preserved in the latter. We speculate that the reason why the *GJB2* group had better results in this study is perhaps due to a comparatively good survival and preservation of electrical excitability of the cochlear spiral ganglion cells and the auditory nerve, which is important in the successful CI results [29].

There are some specific reports which support the present results and our speculations. In a rat model, Cx26 was shown to be expressed in nonsensory epithelial and connective tissue cells, but not in the inner or outer hair cells or cochlear nerve fibers [30]. Anatomically, Cx26 mutations result in a dysgenesis of the stria vascularis and hair cells in the organ of Corti, but with minimal neural degeneration and a normal population of spiral ganglion cells in both the apical and basal turns of the cochlea. [31] In the electrophysiological study, children with *GJB2*-related HL had greater similarities between low- and high-frequency residual hearing and between neural activity electrically evoked at apical and basal regions of the cochlea than children with non-*GJB2*-related HL [32]. These results may suggest more consistent spiral ganglion survival along the length of the cochlea in *GJB2*-related HL, which appears to involve a decreasing gradient of spiral ganglion survival from the apex to the base of the cochlea.

Most genotype-phenotype correlation studies have indicated that HL of the subjects with *GJB2* mutations shows a non-progressive pattern [33,34], however, some studies indicated a progressive pattern. [23,35,36]. Considering that early CI is well known to be one of the most important factors for the better postoperative performance for children with congenital HL, even in children with progressive hearing loss due to *GJB2* mutation, we might be able to prepare for early CI for those children if we were aware of it. The early screening of *GJB2* mutation for newborns with severe to profound HL might be advisable.

5. Conclusions

Despite the limits imposed by the small sample size, this study points to the importance of routine genetic assessments. The long-term results of this study also show that CI is also effective in the development of speech performance after CI in Japanese children with *GJB2*-related hearing impairments as HL due to other etiologies. If a child through genetic assessment is diagnosed as having a *GJB2*-related hearing impairment, CI can provide considerable benefits.

Conflict of interest

None.

References

[1] Morell RJ, Kim HJ, Hood LJ, Goforth L, Friderici K, Fisher R, et al. Mutations in the connexin 26 gene (*GJB2*) among Ashkenazi Jews with nonsyndromic recessive deafness. N Engl J Med 1998;339:1500–5.

[2] Van Camp G, Smith RJ. Hereditary hearing loss homepage, http://web-h01.ua.ac.be/hhh/ [accessed 25.01.12].

[3] Xavier E, Paolo G. The Connexin-Deafness homepage, http://davinci.crg.es/deafness/ [accessed 25.01.12].

[4] Denoyelle F, Weil D, Maw MA, Wilcox SA, Lench NJ, Allen-Powell DR, et al. Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene. Hum Mol Genet 1997;6. 2173Y7.

[5] Balkany TJ, Hodges AV, Eshraghi AA, Butts S, Bricker K, Lingvai J, et al. Cochlear implants in children—a review. Acta Otolaryngol 2002;122:356–62.

[6] UK Cochlear Implant Study Group. Criteria of candidacy for unilateral cochlear implantation in postlingually deafened adults. II. Cost-effectiveness analysis. Ear Hear 2004;25:336–60.

[7] Green GE, Scott DA, McDonald JM, Teagle HF, Tomblin BJ, Spencer LJ, et al. *Performance of cochlear implant recipients with GJB2-related deafness.* Am J Med Genet 2012;109:167–70.

[8] Fukushima K, Sugata K, Kasai N, Fukuda S, Nagayasu R, Toida N, et al. Better speech performance in cochlear implant patients with *GJB2*-related deafness. Int J Pediatr Otorhinolaryngol 2002;62:151–7.

[9] Sinnathuray AR, Toner JG, Geddis A, Clarke-Lyttle J, Patterson CC, Hughes AE. Auditory perception and speech discrimination after cochlear implantation in patients with connexin 26 (*GJB2*) gene-related deafness. Otol Neurotol 2004;25:930–4.

[10] Wu CC, Lee YC, Chen PJ, Hsu CJ. Predominance of genetic diagnosis and imaging results as predictors in determining the speech perception performance outcome after cochlear implantation in children. Arch Pediatr Adolesc Med 2008;162:269–76.

[11] Chora JR, Matos TD, Martins JH, Alves MC, Andrade SM, Silva LF, et al. DFNB1-associated deafness in Portuguese cochlear implant users: prevalence and impact on oral outcome. Int J Pediatr Otorhinolaryngol 2010;74:1135–9.

[12] Lustig LR, Lin D, Venick H, Larky J, Yeagle J, Chinnici J, et al. *GJB2* gene mutations in cochlear implant recipients: prevalence and impact on outcome. Arch Otolaryngol Head Neck Surg 2004;130:541–6.

[13] Cullen RD, Buchman CA, Brown CJ, Copeland BJ, Zdanski C, Pillsbury IIIrd HC, et al. Cochlear implantation for children with *GJB2*-related deafness. Laryngoscope 2004;114:1415–9.

[14] Dahl HH, Wake M, Sarant J, Poulakis Z, Siemering K, Blamey P. Language and speech perception outcomes in hearing-impaired children with and without connexin 26 mutations. Audiol Neurootol 2003;8:263–8.

[15] Mesolella M, Tranchino G, Nardone M, Motta S, Galli V. Connexin 26 mutations in nonsyndromic autosomal recessive hearing loss: speech and hearing rehabilitation. Int J Pediatr Otorhinolaryngol 2004;68:995–1005.

[16] Enjoji M, Goya N. Enjoji-shiki Bunsekiteki Kensahou. Tokyo: Keioutusin; 1992.

[17] Abe S, Yamaguchi T, Usami S. *Application of deafness diagnostic screening* panel based on deafness mutation/gene database using invader assay. Genet Test 2007;11:333–40.

[18] Usami S, Nishio SY, Nagano M, Abe S, Yamaguchi T, Deafness Gene Study Consortium. Simultaneous screening of multiple mutations by invader assay *improves molecular diagnosis of hereditary hearing loss:* a multicenter study. PLoS One 2012;7:e31276.

[19] Taitelbaum-Swead R, Brownstein Z, Muchnik C, Kishon-Rabin L, Kronenberg J, Megirov L, et al. Connexin-associated deafness and speech perception outcome of cochlear implantation. Arch Otolaryngol Head Neck Surg 2006;132:495–500.

[20] Van Camp G, Willems PJ, Smith RJ. Nonsyndromic hearing impairment: unparalleled heterogeneity. Am J Hum Genet 1997;60:758–64.

[21] Tsukada K, Nishio S, Usami S, Deafness Gene Study Consortium. A large cohort study of *GJB2* mutations in Japanese hearing loss patients. Clin Genet 2010;78: 464–70.

[22] Hayashi C, Funayama M, Li Y, Kamiya K, Kawano A, Suzuki M, et al. Prevalence of *GJB2* causing recessive profound non-syndromic deafness in Japanese children. Int J Pediatr Otorhinolaryngol 2011;75:211–4.

[23] Yoshikawa S, Kawano A, Hayashi C, Nishiyama N, Kawaguchi S, Furuse H, et al. The clinical features of patients with the homozygous 235delC and the compound-heterozygous Y136X/G45E of the *GJB2* mutations (Connexin 26) in cochlear implant recipients. Auris Nasus Larynx 2011;38: 444–9.

[24] Matsushiro N, Doi K, Fuse Y, Nagai K, Yamamoto K, Iwaki T, et al. Successful cochlear implantation in prelingual profound deafness resulting from the common 233delC mutation of the GJB2 gene in the Japanese. Laryngoscope 2002;112:255–61.

[25] Nance WE. The genetics of deafness. Ment Retard Dev Disabil Res Rev 2003;9:109–19.

[26] Zhao HB, Kikuchi T, Ngezahayo A, White TW. Gap junctions and cochlear homeostasis. J Membr Biol 2006;209:177–86.

[27] Lautermann J, ten Cate WJ, Altenhoff P, Grümmer R, Traub O, Frank H, et al. Expression of the gap-junction connexins 26 and 30 in the rat cochlea. Cell Tissue Res 1998;294:415–20.

[28] Lefebvre PP, Weber T, Rigo JM, Delree P, Leprince P, Moonen G. Potassium-induced release of an endogenous toxic activity for outer hair cells and auditory neurons in the cochlea: a new pathophysiological mechanism in Menière's disease? Hear Res 1990;47:83–93.

[29] Lousteau RJ. Increased spiral ganglion cell survival in electrically stimulated, deafened guinea pig cochleae. Laryngoscope 1987;97:836–42.

[30] Kikuchi T, Kimura RS, Paul DL, Adams JC. Gap junctions in the rat cochlea: immunohistochemical and ultrastructural analysis. Anat Embryol (Berl) 1995;191:101–18.

[31] Jun AI, McGuirt WT, Hinojosa R, Green GE, Fischel-Ghodsian N, Smith RJ. Temporal bone histopathology in connexin 26-related hearing loss. Laryngoscope 2000;110:269–75.

[32] Propst EJ, Papsin BC, Stockley TL, Harrison RV, Gordon KA. Auditory responses in cochlear implant users with and without *GJB2* deafness. Laryngoscope 2006;116:317–27.

[33] Denoyelle F, Marlin S, Weil D, Moatti L, Chauvin P, Garabédian EN, et al. Clinical features of the prevalent form of childhood deafness, DFNB1, due to a connexin-26 gene defect: implications for genetic counselling. Lancet 1999;353: 1298–303.

[34] Snoeckx RL, Huygen PL, Feldmann D, Marlin S, Denoyelle F, Waligora J, et al. *GJB2* mutations and degree of hearing loss: a multicenter study. Am J Hum Genet 2005;77:945–57.

[35] Gopalarao D, Kimberling WJ, Jesteadt W, Kelley PM, Beauchaine KL, Cohn ES. Is hearing loss due to mutations in the Connexin 26 gene progressive? Int J Audiol 2008;47:11–20.

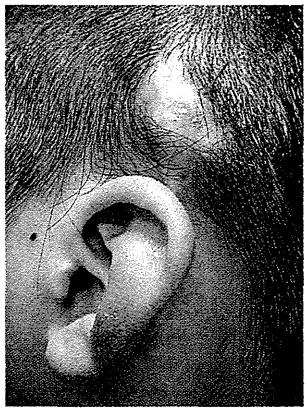
[36] Bartsch O, Vatter A, Zechner U, Kohischmidt N, Wetzig C, Baumgart A, et al. *GJB2 mutations and genotype-phenotype correlation in 335 patients from* Germany with nonsyndromic sensorineural hearing loss: evidence for additional recessive mutations not detected by current methods. Audiol Neurotol 2010;15:375–82.

先天性低ガンマグロブリン血症児の髄膜炎後難聴に対する人工内耳手術

髙橋晴雄，蓑田涼生

髄膜炎で失聴し，人工内耳手術後に感染して再手術を余儀なくされた症例

8歳男児．生下時から難聴の訴えはなく言語発達も問題なかったが，4歳時に髄膜炎で両耳とも失聴した．右耳には真珠腫性中耳炎があり，それに対する鼓室形成術と左耳への人工内耳埋め込み術が行われ，術後問題なく経過していた．6歳時，左埋め込みレシーバー部に反復性に感染，膿瘍形成がみられるようになり，抗菌薬による保存治療や局所の肉芽掻破などの外科的治療にも抵抗した．まもなく先天性低ガンマグロブリン血症と診断され，終生のガンマグロブリン補償療法が開始された．ガンマグロブリン治療開始1年後に再びレシーバー周囲に膿瘍形成がみられ，以前と同様に治療に抵抗して難治化した（❶）．



❶ 感染を起こした人工内耳埋め込みレシーバー部位（→）

言語習得に対する影響や再感染のリスクを考えて，最良の方法を見いだす

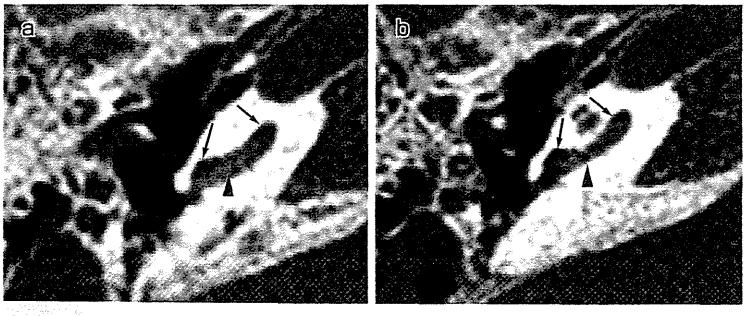
ここで，本症例の治療について次のような選択が考えられた．感染した左人工内耳は抜去する以外には方法はないと思われたが，人工内耳再埋め込みの方法として以下の3つを考えた．

①同時に同側に位置を変えて再埋め込み

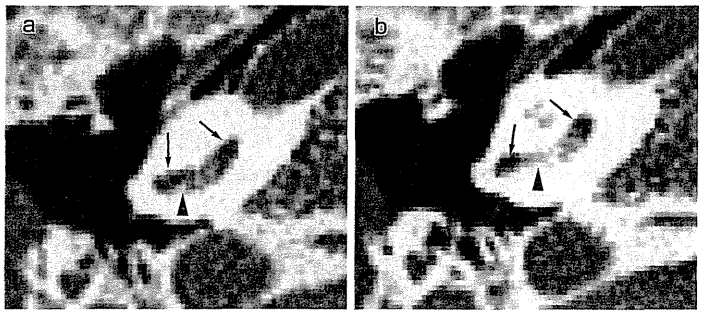
②数か月おいて同側に再埋め込み

③反対側に埋め込み

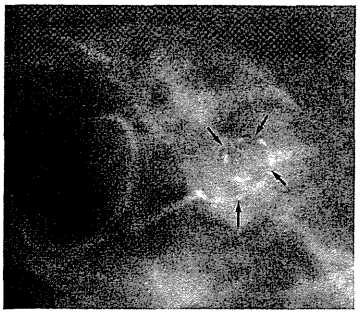
案①には言うまでもなく再感染のリスクがあり，先天性低ガンマグロブリン血症を考えると通常よりそのリスクは高いと思われ，案②では人工内耳装用を中断するため言語習得に障害が生じる可能性があり，数か月おくことにより同側創部の感染は治癒するが広範囲の瘢痕拘縮で再手術が難しいという可能性もある．案③では感染のリスクは低く，言語習得後失聴なので反対側への埋め込



❷ 4歳時の右耳CT所見
蝸牛基底回転の鼓室階にやや濃度が高い陰影がみられ（►），前庭階（→）とは対照的な所見を示す．



❸ 7歳時の右耳CT所見
❷でみられた蝸牛基底回転鼓室階のやや濃度が高い陰影は骨新生に変化していたが（►），前庭階（⟶）は依然として開存している可能性が高いと考えられた．



❹ 術後の耳X線所見
電極は蝸牛内に1回転以上挿入されている（⟶）．

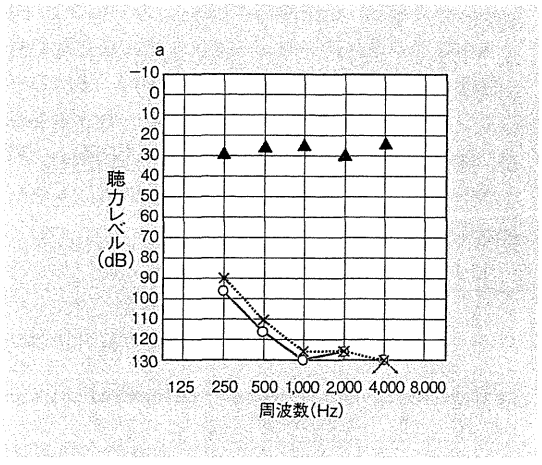
みでも言語獲得は可能と考えられたが，1つ大きな問題があった．それは過去の髄膜炎による蝸牛の変化であった．

蝸牛の立体的解剖の理解をオリエンテーションへ応用する

4歳時の髄膜炎後の側頭骨CTでは蝸牛基底回転に通常よりやや高濃度の陰影があり肉芽，瘢痕形成が疑われ（❷），7歳時には基底回転には明らかな骨新生がみられた（❸）．しかし詳細に観察すると，骨化は鼓室階で生じており，前庭階にはスペースがみられることがわかった．

そこで卵円窓直下に開窓して電極を前庭階に挿入し，卵円窓前下部の蝸牛第2回転にも開窓して電極のより深部への挿入を補助し，全活動電極が挿入できた（❹）．

現在術後2年9か月経過したが，術創感染はみられず，半年時人工内耳装用時純音聴力検査にて，



❺ 術後半年時の裸耳、人工内耳装用時（音場）純音聴力検査結果
十分な環境音聴取能が得られたことが分かる。

良好な聴取能を示し（❺），語音聴取は，術後8か月の単語聴取は聴覚のみで64%，術後1年時において単語聴取は聴覚のみで96%となっている．

ブレークスルーのポイント

- 人工内耳手術を行う際には，通常の手術に必要な範囲以上の詳細かつ広範囲の蝸牛の立体解剖を十分に理解し，非定型的な例でもCT読影や手術でのオリエンテーションを考案できるようにしておくことが重要である．
- 人工内耳という異物を移植する手術は通常でも感染すると難治化するため，免疫不全という不利な点がある場合には，可能な限り術後感染のリスクを排除する戦略を立てることが必須である．

聴覚系検査から鑑別する

急性難聴は迅速な処置ができるかどうかで予後が異なる

- 難聴は耳鼻咽喉科領域でも最も頻繁に遭遇する主訴の一つであり，そのなかでも急性のものは迅速な処置ができるかどうかによって予後がはっきり異なるものが少なくない．
- その意味で急性難聴の的確な診断，ひいてはそれに必要な検査の進め方は日常臨床において知っておくべき必須の部分であるといえる．
- ちなみに難聴の程度として軽度，中等度などの表現がよく使われるが，それぞれの聴力レベルと日常での聞こえの状態は案外知られていないので，❶に一般的なものをまとめる．
- 本項では諸検査の羅列は避け，必要最小限の，しかも多くの耳鼻咽喉科診療所で所有している診察手段，検査機器でどこまで診断でき，それによりどう対処できるかを中心に述べる．ここでは耳垢栓塞や鼓膜穿孔などのように外耳道，鼓膜に明らかな異常がない耳での急性難聴に限って解説する．

ポイントとなる検査

病歴

特徴的病歴は非常に有力な診断の手がかり

- 本項のタイトルは検査の進め方ではあるが，特徴的病歴は検査を行う前の段階で非常に有力な診断の手がかりとなるため，病歴でのポイントを述べる．

上気道炎

- 上気道炎が先行した病歴がある場合には，滲出性中耳炎，また小児で一側性ならムンプス難聴の可能性が考えられる．

pop音などの耳内雑音

- とくにいきみや力みの直後の耳内でのpop音に続いて難聴，さらにめまいが生じた病歴があれば，外リンパ瘻が強く疑われる．

頭部打撲，外傷

- 交通事故，転落事故などの頭部打撲，外傷の病歴があれば耳小骨離断が，さらにめまい，ふらつきが加われば内耳障害による感音難聴が疑われる．

❶難聴のレベル

難聴の程度	聴力(dB)	日常生活での状態
軽度	21~40	ささやき声が耳元でないと聞こえない．
中等度	41~70	会話中に聞き落としがあるが対面しての会話は可能．70 dBとなると大声でなければ通じない．
高度	71~90	聞き落としが多く，会話はほとんど不可能．耳元に口を近づけて話しかける必要がある．
聾	91≦	言語音，一般環境音ともに聴取不能．