Fig. 1 Overlapping audiograms caused by each genotype indicating that certain genotypes are correlated with certain phenotypes, except for G45E/Y136X (see Discussion)

V37I/G45E/Y136X. Hearing of one patient associated with V37I/T123N was within normal range (Fig. 1).

The comparison between patients homozygous for 235delC or V37I, which are the most and the second most prevalent mutations in Japanese (Ohtsuka et al. 2003), showed significant differences in phenotype (Figs. 1, 2). Those homozygous for the 235delC mutation ($n=11$, mean 100.68 dB, SD 21.25 dB) exhibited a significantly severer phenotype than that caused by V37I ($n=5$, mean 37.75 dB, SD 23.09 dB) ($P=0.003$ Fisher's exact test). Those compound heterozygous for the 235delC mutation ($n=19$, mean 78.75 dB, SD 27.76 dB) were significantly different from those compound heterozygous for V37I ($n=7$, mean 47.14 dB, SD 18.35 dB) ($P=0.021$ Fisher's exact test). Concerning the comparison between a combination of inactivating mutations and a combination of noninactivating mutations, the former ($n=30$, mean 88.33 dB, SD 25.67 dB) showed a severer phenotype than that caused by the latter ($n=11$, mean 47.39 dB, SD 31.19 dB) ($P=0.0003$ Fisher's exact test).

Localization of Cx26 and its mutants

The inherent fluorescence of GFP determined the intracellular localization of the recombinant fusion proteins. Transfected GFP-Cx26 wt (wild type) were found to be localized as labeled puncta, which may be representative of gap junctions along the plasma membrane. In contrast, GFP- Cx26 235delC was not recognized at the plasma membrane but was retained within the cytoplasm close to the nucleus. Both GFP-Cx26 V27I and GFP- Cx26 V37I were found to be localized along the plasma membrane as well as being dispersed in the cytoplasm, which is a similar pattern to that shown in the wild type. (Fig. 3.)

Discussion

The present study, using different spectrums of GJB2 mutations (Ohtsuka et al. 2003), confirmed that certain genotypes are correlated with certain phenotypes in GJB2 deafness. The most common mutation, 235delC, exhibited severer hearing impairment whereas V37I, which is the second most common mutation, showed significantly mild hearing impairment. Audiometric data revealed an additional comparatively severe phenotype as well as a relatively mild phenotype.

Among more than 90 different GJB2 mutations, 35delG, accounts for up to 75% of mutated alleles in populations with European ancestry (Estivill et al. 1998; Gasparini et al. 2000; Van Laer et al. 2001). A series of reports has described that patients associated with

Fig. 2 Overlapping audiograms caused by 235delC/non 235delC, V37I/non V37I, inactivating mutation/inactivating mutation, and noninactivating mutation/noninactivating mutation. Note that patients associated with 235delC show relatively severer hearing loss whereas V37I-involved patients show a relatively mild phenotype. It is also evident that patients associated with inactivating mutation/inactivating mutation showed a severer phenotype than patients with noninactivating mutation/noninactivating mutation
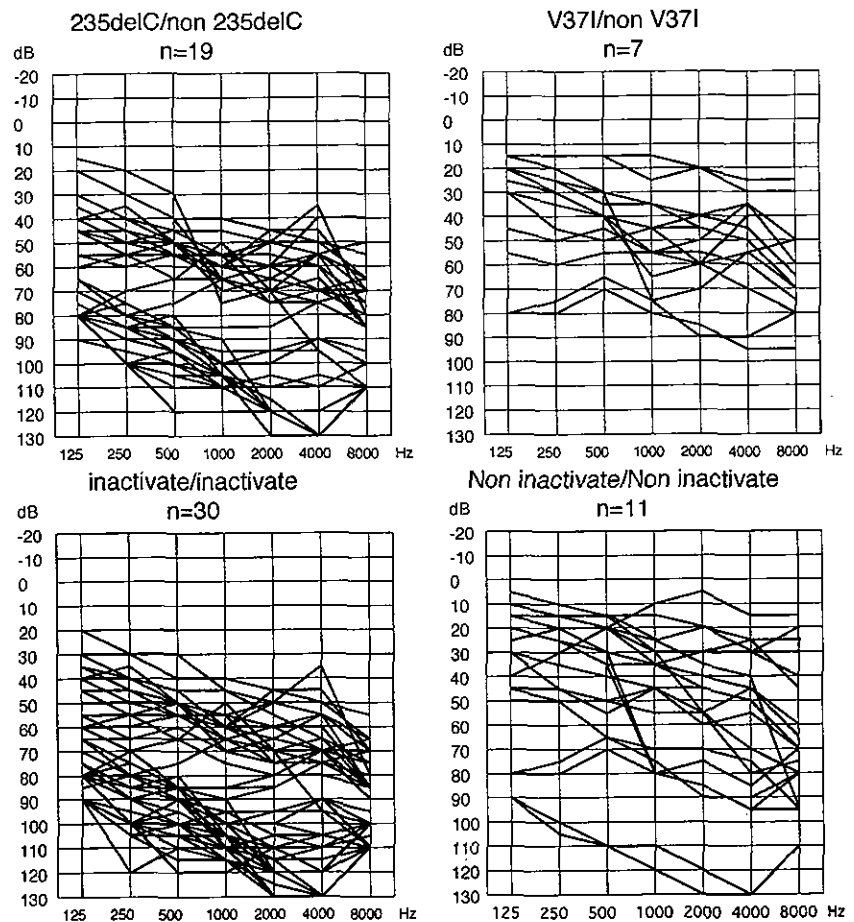
Fig. 3 Protein expression in transfected COS-7 cells. COS-7 cells transfected with GFP-Cx26 wt, GFP-Cx26 V27I, and GFP-Cx26 V37I, which were associated with normal–mild phenotypes, showed a characteristic puncta along the membrane. In contrast, only perinuclear staining was seen in GFP-Cx26 235delC. *Red* actin filament (TRITC- conjugated phalloidin): cell membrane, *Blue* DAPI: nucleus, *Green* Green fluorescent protein: chimeric protein
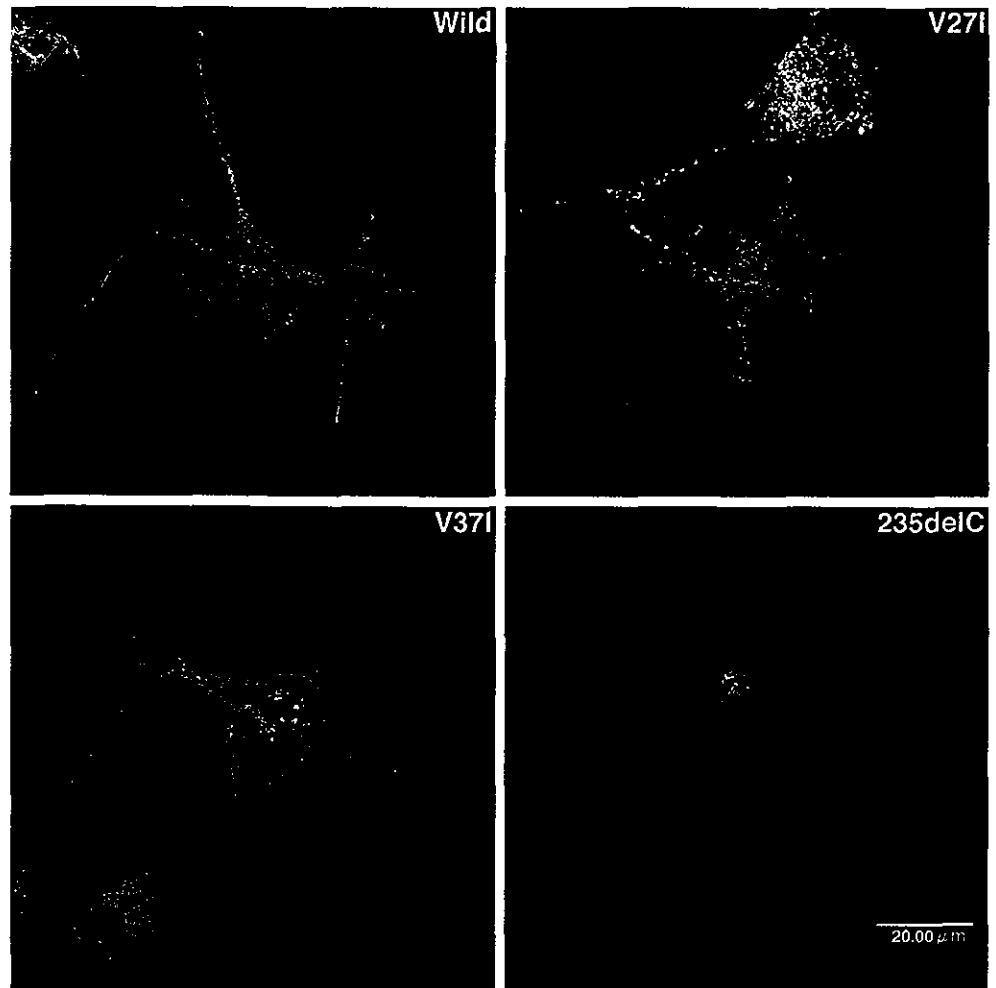
35delG exhibit severe-to-profound hearing impairment (Cohn et al. 1999; Cryns et al. 2004; Denoyelle et al. 1997, 1999; Green et al. 1999; Marlin et al. 2001; Wilcox et al. 2000). The status of the 235delC mutation, which seems to be a unique mutation in populations with Asian ancestry, is comparable to the 35delG mutation in Caucasoid populations. High prevalence of 35delG and 235delC mutations in the respective populations are due to a founder effect (Ohtsuka et al. 2003; Van Laer et al. 2001). Patients homozygous or compound heterozygous for the 235delC mutation exhibit a comparatively severer phenotype (Fig. 2), indicating that this frequent mutation should be the first to be considered when genetic screening for congenitally deaf patients is performed in Asian populations.

Several reports have indicated the existence of less-severe phenotypes correlated with certain specific mutations, especially in association with V37I (Bason et al. 2002; Cryns et al. 2004; Marlin et al. 2001; Rabionet et al. 2000; Wilcox et al. 2000). The exact phenotype has been rather difficult to prove because of the relatively small number of patients with V37I. The V37I mutation was originally reported as a polymorphism (Kelley et al. 1998), but the fact that valine 37 residue is

highly conserved among different connexins, and that a series of reports identified homozygous or compound heterozygous V37I deafness patients (Abe et al. 2000; Bason et al. 2002; Marlin et al. 2001; Rabionet et al. 2000; Wilcox et al. 2000), indicate that it may be a disease-causing mutation. There seem to be ethnic differences in the allele frequency of V37I, as it was not detected in the control subjects from Italy, Spain, Germany, Greece, Israel, Ghana, or Austria (see Discussion in Bason et al. 2002) in spite of a high prevalence in the Japanese population (Abe et al. 2000; Kudo et al. 2000; Ohtsuka et al. 2003). The reported patients in whom the ethnic background was known were all of eastern-Asian origin (Abe et al. 2000; Bason et al. 2002; Kudo et al. 2000; Ohtsuka et al. 2003). In Japanese, V37I is the second most frequent mutated allele, and in this study, it was possible to collect a significant number of patients, and the present data confirmed a less severe phenotype caused by V37I. Due to such a mild phenotype, timing of presentation at clinics and diagnosis may be comparatively delayed. For patients with V37I/V37I, hearing impairment was noticed at the age of 20.6 (range 7–49, SD 17.08) years of age in contrast with 0.33 (range 0–3, SD 1.00) years for patients with 235delC/235delC. It

should therefore be noted that patients with *GJB2* mutations can also be found among less-severe hearing-impaired populations.

A recent multi-center-based genotype–phenotype correlation study clearly showed that severity of hearing impairment is correlated with some particular genotype and proposed a hypothetical general rule that inactivating mutations (stop or frameshift mutations) cause more severe phenotypes than those caused by noninactivating mutations (Cryns et al. 2004). Concerning the comparison between combinations of inactivating mutations and combinations of noninactivating mutations, the present study also showed that the former cause a severer phenotype than that caused by the latter. Therefore, our study supports the above hypothetical general rule.

Overlapped audiograms showed high-frequency-predominant sensorineural hearing loss regardless of genotype. Overall, there seemed to be certain rules regarding genotype and phenotype correlations. Particular genotypes tended to have similar audiograms with minor exceptions (Fig. 1). Therefore, genotype is a fundamental factor to predict phenotype. However, variations among the same phenotypes still exist (Fig. 1). These variations may be explained by the following factors involved in phenotypes: (1) alterations in promoter regions, (2) additional genes such as *GJB6* (del Castillo et al. 2002), (3) modifier genes (Abe et al. 2001), (4) environmental factors. Concerning patients with G45E/Y136X, there was great variability in their phenotypes, ranging from normal to profound. A segregation study indicated that either G45E or Y136X situated on the same allele or different alleles. Our subcloning experiments confirmed the existence of two types of allele: cis allele and trans allele (data not shown). When two mutations are on different alleles (compound heterozygous state), the patients may exhibit severe-to-profound hearing impairment.

The present study further investigated whether the differences in phenotype could be explained by protein-expression study. In contrast to transfected GFP-Cx26 wt, which were found to be localized as labeled puncta along the plasma membrane (Fig. 3), the localization of transfected GFP-Cx26 235delC was not seen on the cellular membrane but mainly cohered at or around the nucleus. Such abnormal subcellular localization of mutated Cx26 protein with 235delC is consistent with a previous study (Choung et al. 2002). From these results, truncated mutations at the transmembrane domain, such as 235delC, were considered to lead to loss of function, resulting in serious hearing impairment. In the case of V37I, which is categorized as a noninactivating mutation, transfected GFP-Cx26 V37I was found along the membrane as in the wild type, indicating that the V37I protein may retain its function and therefore results in a rather mild phenotype. As expected, V27I, a known polymorphism, showed a similar distribution pattern to the wild type and V37I. To summarize, in the present study, the results indicate

that protein expression patterns are well correlated with clinical phenotypes. A series of in vitro studies, including protein expression study, cell-to-cell communication properties, or physiological conductance experiments, sometimes provided discrepant results when compared to the phenotypic results, and limitations have been suggested (see discussion in Cryns et al. 2004). In the case of V37I, a complete loss of junctional properties has been reported (Bruzzone et al. 2003) in spite of a rather mild phenotype shown in a series of studies. The protein expression experiments in the current study, however, were in line with the phenotype associated with this mutation.

In conclusion, the present genotype–phenotype correlation results supported the view that phenotypes caused by the truncating *GJB2* mutations are severer than those caused by missense mutations. Anticipating severity of hearing impairment is sometimes difficult, but if such general rules can be drawn with regard to genotype–phenotype correlation, determination of these correlations will facilitate the prediction of the course of hearing and help in making decisions regarding treatment/intervention.

References

Abe S, Usami S, Shinkawa H, Kelley PM, Kimberling WJ (2000) Prevalent connexin 26 gene (GJB2) mutations in Japanese. J Med Genet 37:41–43

Abe S, Kelley PM, Kimberling WJ, Usami SI (2001) Connexin 26 gene (GJB2) mutation modulates the severity of hearing loss associated with the 1555A->G mitochondrial mutation. Am J Med Genet 103:334–338

Bason L, Dudley T, Lewis K, Shah U, Potsic W, Ferraris A, Fortina P, Rappaport E, Krantz ID (2002) Homozygosity for the V37I Connexin 26 mutation in three unrelated children with sensorineural hearing loss. Clin Genet 61:459–464

Bruzzone R, Veronesi V, Gomes D, Bicego M, Duval N, Marlin S, Petit C, D'Andrea P, White TW (2003) Loss-of-function and residual channel activity of connexin26 mutations associated with non-syndromic deafness. FEBS Lett 533:79–88

Choung YH, Moon SK, Park HJ (2002) Functional study of GJB2 in hereditary hearing loss. Laryngoscope 112:1667–1671

Cohn ES, Kelley PM, Fowler TW, Gorga MP, Lefkowitz DM, Kuehn HJ, Schaefer GB, Gobar LS, Hahn FJ, Harris DJ, Kimberling WJ (1999) Clinical studies of families with hearing loss attributable to mutations in the connexin 26 gene (GJB2/DFNB1). Pediatrics 103:546–550

Cryns K, Orzan E, Murgia A, Huygen PL, Moreno F, del Castillo I, Chamberlin GP, Azaiez H, Prasad S, Cucci RA, Leonardi E, Snoeckx RL, Govaerts PJ, Van de Heyning PH, Van de Heyning CM, Smith RJ, Van Camp G (2004) A genotype-phenotype correlation for GJB2 (connexin 26) deafness. J Med Genet 41:147–154

del Castillo I, Villamar M, Moreno-Pelayo MA, del Castillo FJ, Alvarez A, Telleria D, Menendez I, Moreno F (2002) A deletion involving the connexin 30 gene in nonsyndromic hearing impairment. N Engl J Med 346:243–249

Denoyelle F, Weil D, Maw MA, Wilcox SA, Lench NJ, Allen-Powell DR, Osborn AH, Dahl HH, Middleton A, Houseman MJ, Dode C, Marlin S, Boulila-ElGaied A, Grati M, Ayadi H, BenArab S, Bitoun P, Lina-Granade G, Godet J, Mustapha M, Loiselet J, El-Zir E, Aubois A, Joannard A, Petit C et al. (1997) Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene. Hum Mol Genet 6:2173–2177

Denoyelle F, Marlin S, Weil D, Moatti L, Chauvin P, Garabedian EN, Petit C (1999) Clinical features of the prevalent form of childhood deafness, DFNB1, due to a connexin-26 gene defect: implications for genetic counselling. Lancet 353:1298–1303

Estivill X, Fortina P, Surrey S, Rabionet R, Melchionda S, D'Agruma L, Mansfield E, Rappaport E, Govea N, Mila M, Zelante L, Gasparini P (1998) Connexin-26 mutations in sporadic and inherited sensorineural deafness. Lancet 351:394–398

Fukushima K, Sugata K, Kasai N, Fukuda S, Nagayasu R, Toida N, Kimura N, Takishita T, Gunduz M, Nishizaki K (2002) Better speech performance in cochlear implant patients with GJB2-related deafness. Int J Pediatr Otorhinolaryngol 62:151–157

Gasparini P, Rabionet R, Barbujani G, Melchionda S, Petersen M, Brondum-Nielsen K, Metspalu A, Oitmaa E, Pisano M, Fortina P, Zelante L, Estivill X (2000) High carrier frequency of the 35delG deafness mutation in European populations. Genetic Analysis Consortium of GJB2 35delG. Eur J Hum Genet 8:19–23

Govaerts PJ, Yperman M, De Ceulaer G, Daemers K, Van Driessche K, Somers T, Offeciers FE (2001) A Two-stage bipodal screening model for universal neonatal hearing screening. Otol Neurotol 22:850–854

Green GE, Scott DA, McDonald JM, Woodworth GG, Sheffield VC, Smith RJ (1999) Carrier rates in the midwestern United States for GJB2 mutations causing inherited deafness. JAMA 281:2211–2216

Joint Committee on Infant Hearing (2000) Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. Joint Committee on Infant Hearing, American Academy of Audiology, American Academy of Pediatrics, American Speech-Language-Hearing Association, and Directors of Speech and Hearing Programs in State Health and Welfare Agencies. Pediatrics 106:798–817

Kelley PM, Harris DJ, Comer BC, Askew JW, Fowler T, Smith SD, Kimberling WJ (1998) Novel mutations in the connexin 26 gene (GJB2) that cause autosomal recessive (DFNB1) hearing loss. Am J Hum Genet 62:792–799

Kenneson A, Van Naarden Braun K, Boyle C (2002) GJB2 (connexin 26) variants and nonsyndromic sensorineural hearing loss: a HuGE review. Genet Med 4:258–274

Kudo T, Ikeda K, Kure S, Matsubara Y, Oshima T, Watanabe K, Kawase T, Narisawa K, Takasaka T (2000) Novel mutations in the connexin 26 gene (GJB2) responsible for childhood deafness in the Japanese population. Am J Med Genet 90:141–145

Marlin S, Garabedian EN, Roger G, Moatti L, Matha N, Lewin P, Petit C, Denoyelle F (2001) Connexin 26 gene mutations in congenitally deaf children: pitfalls for genetic counseling. Arch Otolaryngol Head Neck Surg 127:927–933

Matsushiro N, Doi K, Fuse Y, Nagai K, Yamamoto K, Iwaki T, Kawashima T, Sawada A, Hibino H, Kubo T (2002) Successful cochlear implantation in prelingual profound deafness resulting from the common 233delC mutation of the GJB2 gene in the Japanese. Laryngoscope 112:255–261

Mehl AL, Thomson V (2002) The Colorado newborn hearing screening project, 1992–1999: on the threshold of effective population-based universal newborn hearing screening. Pediatrics 109:E7

Murgia A, Orzan E, Polli R, Martella M, Vinanzi C, Leonardi E, Arslan E, Zacchello F (1999) Cx26 deafness: mutation analysis and clinical variability. J Med Genet 36:829–832

National Institutes of Health (1993) Early identification of hearing impairment in infants and young children. NIH Consens Statement 11:1–24

Ohtsuka A, Yuge I, Kimura S, Namba A, Abe S, Van Laer L, Van Camp G, Usami S (2003) GJB2 deafness gene shows a specific spectrum of mutations in Japan, including a frequent founder mutation. Hum Genet 112:329–333

Orzan E, Polli R, Martella M, Vinanzi C, Leonardi M, Murgia A (1999) Molecular genetics applied to clinical practice: the Cx26 hearing impairment. Br J Audiol 33:291–295

Rabionet R, Zelante L, Lopez-Bigas N, D'Agruma L, Melchionda S, Restagno G, Arbones ML, Gasparini P, Estivill X (2000) Molecular basis of childhood deafness resulting from mutations in the GJB2 (connexin 26) gene. Hum Genet 106:40–44

Van Laer L, Coucke P, Mueller RF, Caethoven G, Flothmann K, Prasad SD, Chamberlin GP, Houseman M, Taylor GR, Van de Heyning CM, Fransen E, Rowland J, Cucci RA, Smith RJ, Van Camp G (2001) A common founder for the 35delG GJB2 gene mutation in connexin 26 hearing impairment. J Med Genet 38:515–518

Wilcox SA, Saunders K, Osborn AH, Arnold A, Wunderlich J, Kelly T, Collins V, Wilcox LJ, McKinlay Gardner RJ, Kamarinos M, Cone-Wesson B, Williamson R, Dahl HH (2000) High frequency hearing loss correlated with mutations in the GJB2 gene. Hum Genet 106:399–405

Yoshinaga-Itano C, Sedey AL, Coulter DK, Mehl AL (1998) Language of early- and later-identified children with hearing loss. Pediatrics 102:1161–1171

急性低音障害型感音難聴典型例と非典型例の比較

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急性低音障害型感音難聴典型例と非典型例の比較

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要旨：平成12〜14年の全国疫学調査登録例を対象として，急性低音障害型感音難聴の診断基準を満たす一側性典型例317例（平均37.8歳）と高音域の基準を満たさない非典型例91例（平均56.0歳）の疫学的特徴を比較検討した。両者の疫学的特徴には類似点（①女性に多い，②発症時期は春〜夏に多い，③低音域の聴力悪化レベルに差はない，④初診時聴力レベルは予後と相関する）も多いが，相違点（①非典型例では中高音域の聴力悪化レベルが典型例より大きい，②年齢と予後との相関の有無の相違，③発症から受診までの日数と予後との相関の有無の相違）もあり，両者の病態は異なる可能性が示唆された。

－キーワード－
急性低音障害型感音難聴，診断基準，聴力型

は じ め に

厚生労働省急性高度難聴研究班の試案[1] による急性低音障害型感音難聴の診断基準は高音域3周波数(2000，4000，8000Hz)の合計が60dB 以下と規定しているため，もともと高音域に難聴を有する例は除外されてしまう。しかし，この中には診断基準を満たす例と同様な病態の存在が示唆されている[2〜4]。

今回我々は，高音域3周波数の診断基準を満たさない非典型例と基準を満たす典型例の類似点と相違点を明らかにするため，平成12，13，14年度に厚生労働省急性高度難聴研究班が急性低音障害型感音難聴を対象として行った全国疫学調査（北海道大，岩手医大，東京医歯大，慶応大，北里大，信州大，浜松医大，名古屋大，兵庫医大，愛媛大，岡山大，宮崎医大)の登録例を基に比較検討したので報告する。

対象と方法

低音域3周波数(125，250，500Hz)の合計が70dB以上，かつ高音域の3周波数(2000，4000，8000Hz)の合計が60dB 以下の診断基準をみたすものを急性低音障害型感音難聴典型例，低音域の基準は満たすが高音域の合計が65dB 以上で診断基準を満たさないものを非典型例として検討した。なお，非典型例の調査時の診断名は急性低音障害型感音難聴疑い例または参考例である。

平成12年1月から平成14年12月までの全国疫学調査登録患者のうち，一側性典型例317例と一側性非典型例91例を対象として①年齢分布，性差，月別発症例数，②自覚症状，③聴力悪化レベル（患側と健側の差），④予後，⑤予後を規定する因子について比較検討した。統計学的有意差の検定にはχ^2検定，t 検定を用い，危険率5％未満(p<0.05)を有意差ありと判定した。なお，予後の判定には以下の基準を用いた[1]。

（1）治療：低音3周波数(125，250，500Hz)の聴力レベルいずれも20dB 以内に戻ったもの。あるいは健側聴力と同程度まで回復したとき。
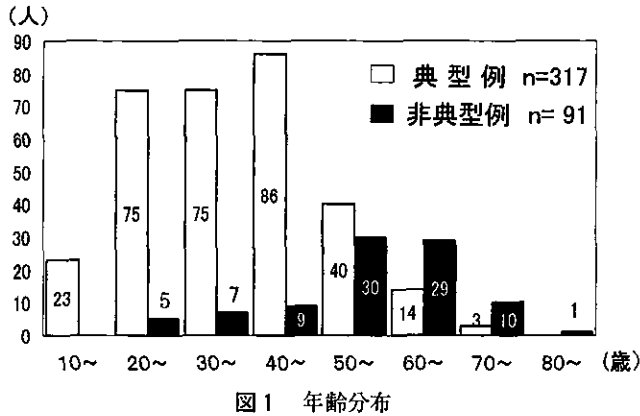
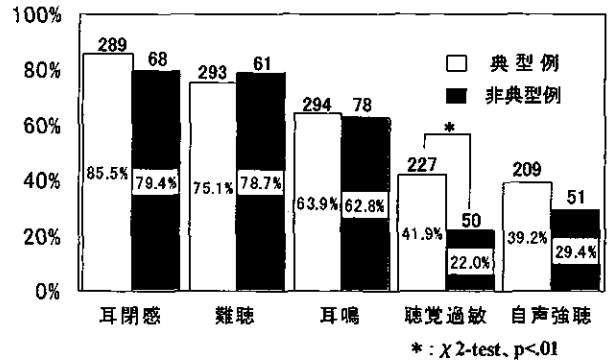（2）改善：低音3周波数の聴力レベルの平均が10dB 以上回復し，かつ治癒に至らないもの。

(人)

図1　年齢分布
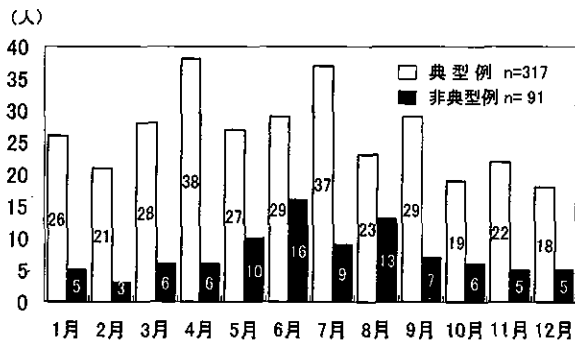

図2　発症月別分布

図3　自覚症状の比較
グラフ内の各バーの上の数字は例数を示す。
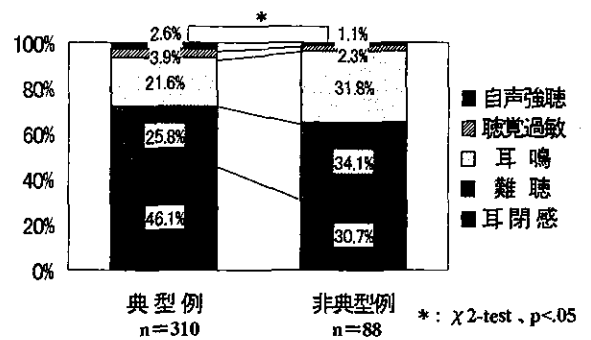
図4　主訴の比較

（3）　不変：低音3周波数の聴力レベルの平均が10
dB 未満の変化。
（4）　悪化：（1）（2）（3）以外のもの。

結　　　果

①年齢分布，性差，月別発症例数

　平均年齢は典型例で37.8歳（11～75歳），非典型例
で56.0歳（23～81歳）と非典型例で18.2歳高く，典
型例は20歳～40歳代，非典型例は50歳～60歳代にピ
ークを認めた（図1）。性別は典型例（男性102例，
女性215例，男女比は1：2.1），非典型例（男性36例，
女性55例，男女比は1：1.5）とも女性に多く認めら
れた。発症月別の頻度をみると典型例は4月（38例），
7月（37例），非典型例は6月（16例），8月（13例）
にピークを有し，両群とも春～夏に多く秋～冬にか
けて少ない傾向が認められた（図2）。
②自覚症状

　5項目の自覚症状（耳閉感，難聴，耳鳴，聴覚過
敏，自声強聴）の有無に関して記載のあった例での
頻度を比較した。それぞれの症状の頻度は典型例で

85.5%（247/289），75.1%（220/293），63.9%（188
/294），41.9%（95/227），39.2%（82/209），非典型
例で79.4%（54/68），78.7%（48/61），62.8%（49
/78），22.0%（11/50），29.4%（15/51）であった。
聴覚過敏については両者の間に有意差を認めたが，
他の4症状（耳閉感，難聴，耳鳴，自声強聴）の頻
度には有意差を認めなかった（図3）。

　上記5項目以外の症状は典型例で2例（めまい感
1例，頭痛1例），非典型例で2例（浮動感2例）あ
り，主訴の記載の無い例は典型例で5例，非典型例
で1例認められ，これらを除く典型例310例と非典型
例88例で主訴の頻度を比較した。主訴となった症状
は，典型例310例のうち耳閉感が143例（46.1%）と
最も多く，次いで難聴80例（25.8%），耳鳴67例（21.6
%），聴覚過敏12例（3.9%），自声強聴8例（2.6%）
であった。一方，非典型例では88例のうち難聴が30
例（34.1%）と最も多く，次いで耳鳴28例（31.8%），
耳閉感27例（30.7%），聴覚過敏2例（2.3%），自声
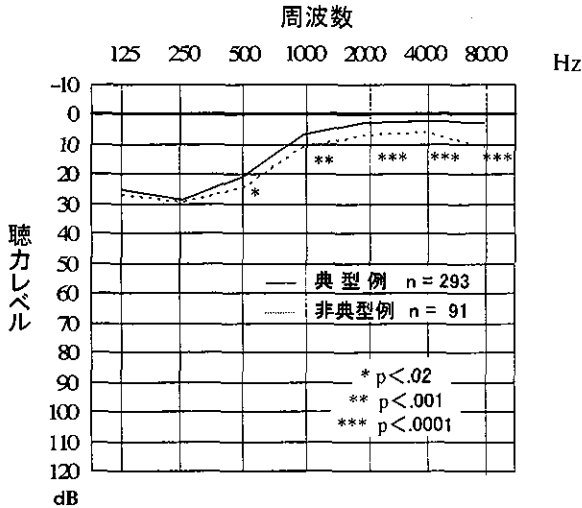強聴1例（1.1%）であり，両群の主訴の頻度には有
意差が認められた（図4）。
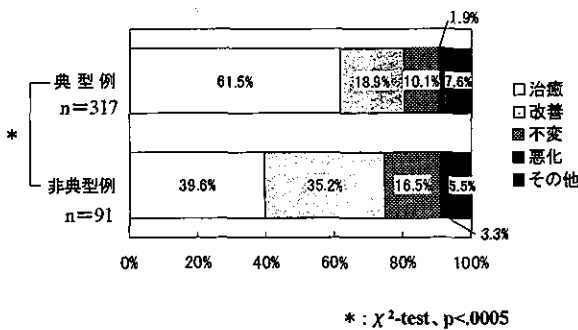
周波数

図5　聴力悪化レベルの比較

図6　予後の比較
　　　その他の内訳は典型例が変動治癒11例，メニエール病
　　　移行例6例，再発7例，非典型例が変動治癒3例，メ
　　　ニエール病移行例2例である。

③聴力悪化レベル

　典型例317例のうち健側聴力の記載がない5例，健
側高音部3周波数の合計が65dB以上の感音難聴を有
する19例を除く293例と非典型例91例について患側・
健側の聴力レベル差を比較した。典型例の7周波数
(125〜8000Hz)における患側・健側気導差はそれぞ
れ25.4±10.9dB, 28.5±11.5dB, 20.6±13.0dB, 6.5
±9.8dB, 2.6±6.4dB, 2.1±6.2dB, 2.8±8.2dB,
非典型例は27.0±11.5dB, 29.4±12.1dB, 24.6±13.5
dB, 10.8±11.8dB, 7.0±8.1dB, 6.3±9.1dB, 10.8
±13.6dBであった。両群間で125Hz, 250Hzの患側
・健側気導差には有意差を認めなかったが，500Hz
以上の5周波数では有意差が認められた（図5）。
④予後

　治癒は典型例で195例（61.5%），非典型例で36例
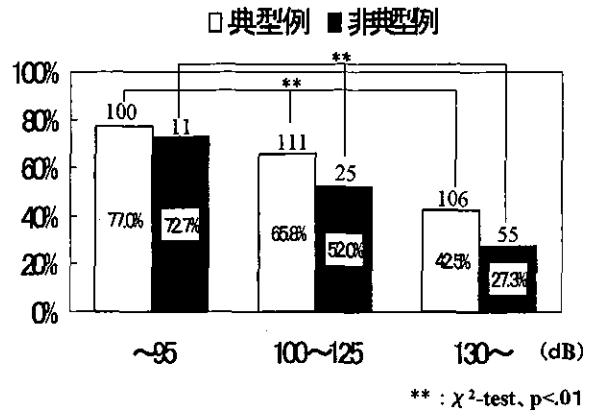（39.6%），改善は典型例60例(18.9)，非典型例32例
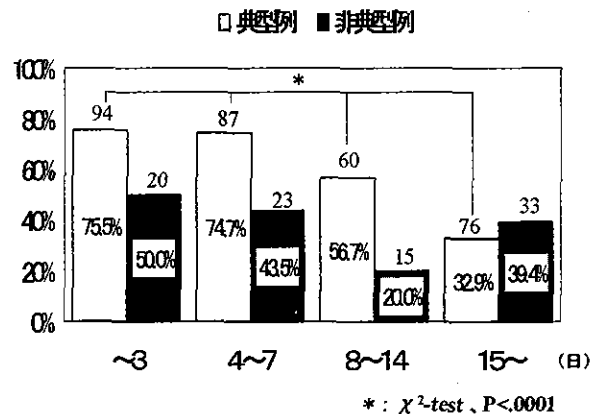

図7　初診時聴力レベルと予後の比較
　　　グラフ内の各バーの上の数字は例数を示す。

図8　治療開始までの期間と予後の比較
　　　グラフ内の各バーの上の数字は例数を示す。

（35.2%），不変は典型例32例(10.1%)，非典型例15
例（16.5%），悪化は典型例6例（1.9%），非典型例
3例（3.3%），その他（変動治癒例，メニエール病
移行例）は典型例24例（7.6%），非典型例5例（5.5
%）であり，典型例の予後は非典型例に比べ有意に
良好であった（図6）。
⑤予後を規定する因子

　①初診時聴力レベル：低音3周波数の合計を100dB
未満，100dB以上130dB未満，130dB以上の3群に
分け，治癒率を比較すると典型例，非典型例ともに
聴力障害が軽度なほど有意に予後良好であった（図
7）。

　②発症から受診までの期間：受診までの期間を3
日以内，4〜7日以内，8〜14日以内，15日以後の
4群に分け，受診までの日数と治癒率の関係を両者
で比較した。典型例では発症から受診までの日数が
短いほど有意に予後は良好であったが，非典型例で

□典型例 ■非典型例

98　71.4%　5　20.0%　75　64.0%　7　42.9%　86　58.1%　9　66.7%　58　46.7%　70　37.0%
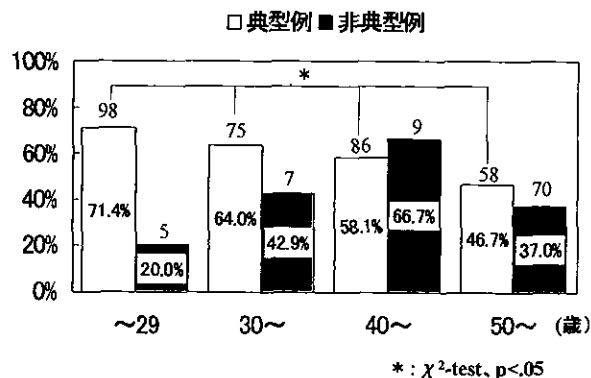
〜29　　30〜　　40〜　　50〜（歳）

*：χ²-test、p<.05

図9　年齢と予後の比較
グラフ内の各バーの上の数字は例数を示す。

は受診までの日数と予後との相関は認められなかった（図8）。

③年齢：30歳未満，30歳代，40歳代，50歳以上の4群に分けて年齢と予後との関係を両者で比較した。典型例では年齢が若いほど予後は良好で年齢と有意の相関が認められたが，非典型例では20歳代，30歳代の予後が40歳代より不良であり年齢との有意の相関はみられなかった（図9）。

考　察

高音域3周波数聴力レベルの合計が65dB以上の診断基準を満たさない非典型例と診断基準を満たす典型例との間には，聴力悪化レベルや予後に差はないとする報告[2〜4]と反復例の頻度[5]や予後[5〜7]に差があるとする報告の両者がみられる。しかし，本報告を含めいずれの報告も非典型例の平均年齢は典型例に比べ高いという点は一致しており[3〜7]，非典型例における高音域の感音難聴は主として加齢による聴力障害を反映したものと考えられる。一般に急性低音障害型感音難聴では，高齢者の聴力予後は不良なことから[1,2,6]，両者の予後の相違はその年齢差が主な要因と推測される。また，典型例，非典型例とも耳閉感，難聴，耳鳴の頻度に差はないが，主訴となった症状の頻度を比較してみると，典型例では耳閉感，非典型例では難聴が最も多いことがわかった。これは非典型例では既存の高音部聴力障害に低音部の聴力障害が加わるため，典型例よりも難聴が自覚されやすいためと思われる。

阿部ら[3]および西田[4]はそれぞれ終診時あるいは治療後の患側オージオグラムの初診時との差を比較し，

両者の聴力悪化レベルに差はないと報告している。これらの報告では典型例と非典型例の聴力予後に差を認めていないが，今回の検討を含め非典型例の聴力予後は不良とする報告が多い[5〜7]。両者の予後が同じであれば，聴力悪化レベルを患側の初診・終診時聴力差で評価してもよいが，予後が異なる場合は正しい聴力悪化レベルを評価し得ない。そのため今回は，初診時の患側・健側聴力差で両者の聴力悪化レベルを比較した。その結果，低音域では阿部ら[3]，西田[4]の報告と同様に差がみられなかったが，中高音域における聴力悪化レベルは典型例より非典型例で大きいことがわかった。非典型例において中高音域の聴力悪化レベルが大きい理由としては，もともと高音域に聴力障害があるため高音域にも障害を生じやすい（易受傷性）という可能性，あるいは非典型例の中に軽度山型の突発性難聴が含まれていた可能性，の両者が考えられる。

典型例と非典型例の疫学的特徴には①女性に多い，②発症時期は春〜夏に多い，③低音域の聴力悪化レベルに差はない，④初診時聴力レベルは予後と相関する，など類似点も多く，これらの点では両者は本質的には同一の疾患とする報告[3〜6]を支持する結果といえる。しかし，①非典型例では中高音域の聴力悪化レベルが典型例より大きい，②非典型例では年齢と予後との相関がみられない，③非典型例では発症から受診までの日数と予後との相関がみられない，などの相違点もあり，両者の病態は異なる可能性が示唆された。

ま　と　め

1．典型例，非典型例のいずれも女性に多く，発症時期は春〜夏に多い傾向を認めた。

2．典型例，非典型例の聴力悪化レベルは125Hz，250Hzでは差がないが，500〜8000Hzには有意差が認められた。

3．主訴は典型例では耳閉感，非典型例では難聴が最も多く，また非典型例の予後は典型例に比べ有意に不良であった。

4．典型例，非典型例ともに初診時聴力レベルと予後との相関が認められた。

5．典型例では発症から受診までの期間，年齢と予後との相関が認められたが，非典型例では認めら

れなかった。

　6．典型例と非典型例では疫学的に共通点も多い
が，相違点もあり病態が異なる可能性が示唆された。

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Acute Low Tone Sensorineural Hearing Loss : Comparison of Epidemiological Characteristics between Typical and Atypical Cases

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Acute low-tone sensorineural hearing loss is defined by the following criteria : the sum of hearing levels at low-tone frequencies (125, 250 and 500Hz) must be 70dB or more and that at high-tone frequencies (2000, 4000 and 8000Hz) must be 60dB or loss. However, several studies have suggested that a similar etiology exists among patients in whom the sum of hearing levels at high-tone frequencies is 65dB or more. We compared the epidemiological characteristics of typical cases meeting these criteria to those of atypical cases, whose hearing levels exceeded 65dB at high frequencies. All the subjects had unilateral hearing loss (317 typical cases and 91 atypical cases) ; all patients were registered in nationwide epidemiological surveys conducted between 2000 and 2002. Many similarities in the epidemiological characteristics of the two groups were seen (more prevalent in females than in males and in spring/summer than in winter ; hearing recovery depended on initial hearing level ; severity of hearing loss at low-tone frequencies), but several differences were also noted (levels of hearing impairment at middle to high-tone frequencies ; correlation of prognosis with age and the number of days from onset to the first examination), suggesting differences in the pathophysiological features of typical and atypical cases.

参 考 文 献

1）佐藤宏昭，村井和夫，岡本牧人・他：急性低音障害型感音難聴の平成12年全国疫学調査結果。Audiology Japan 45：161-166, 2002

2）千田英二，佐藤信清，犬山征夫：急性低音障害型感音難聴の検討。Audiology Japan 33：571-572, 1990

3）阿部　隆，立木　孝：低音域の急性感音難聴と低音障害型突発難聴。Audiology Japan 45：167-175, 2002

4）西田吉直：急性低音障害型感音難聴類似疾患の取り扱い。Audiology Japan 45：182-186, 2002

5）伊藤真郎，李　雅次，新井雅之，斎藤啓光，高瀬二郎，船坂宗太郎：低音型突発難聴の臨床観察。耳鼻臨床 82：1055-1062, 1989

6）井上泰宏，神崎　仁，大内利昭，小川　郁，小川茂雄，土橋信明，山本美奈子，池田俊也：低音障害型感音難聴の検討。Otol Jpn 3：203-210, 1993

7）朝隈真一郎：急性低音障害型感音難聴—10年間，241例の検討—。日耳鼻 102：299-304, 1999

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