別にみると，A群の56%（9/16），B群の36%（4/11）に眼振を認めたが，眼振の有無に関して有意差はなかった（$p = 0.4450$）。
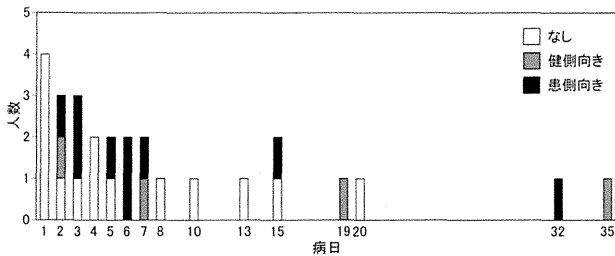

図3 難聴発症からの病日と眼振所見
27例中13例（48%）に眼振を認める。第8病日以降においても，患側向き眼振と健側向き眼振はそれぞれ2例に認められる。

5．聴力予後

突発性難聴・聴力回復の判定基準に基づき聴力予後を判定すると，2つの予後判定に分類される症例が18例（A群：9例，B群：9例）と全症例の49%に認められた（図4A）。具体例を示すと，谷型聴力型を示したA群の1例では，左平均聴力レベルの変化が10dB以上30dB未満（35dBから9dB）であり回復に分類されたが，平均聴力レベルは20dB以内に戻っているため治癒にも分類された（図5A）。本症例の聴力予後は，聴力固定時の聴力レベルが全周波数で20dB以内であるため治癒と判定するのが妥当と考えられた。高音漸傾型を示したA群の他の1例では，左平均聴力レベルは10dB未満の変化（23dBから15dB）であるため不変に分類されるが，平均聴力レベルは20dB以内に戻っているため
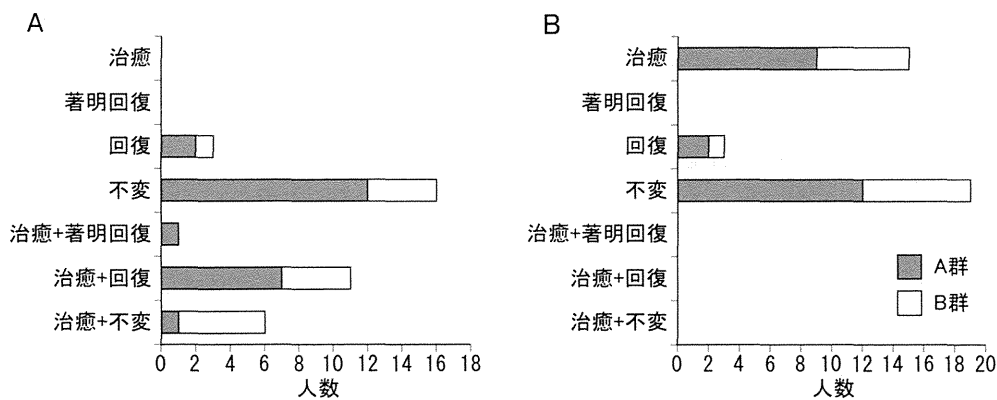

図4 聴力予後
A：突発性難聴・聴力回復の判定基準に準じると，18例（49%）が2つの予後判定に分類される。
B：実際には，治癒15例（41%），回復3例（8%），不変19例（51%）と判定される。

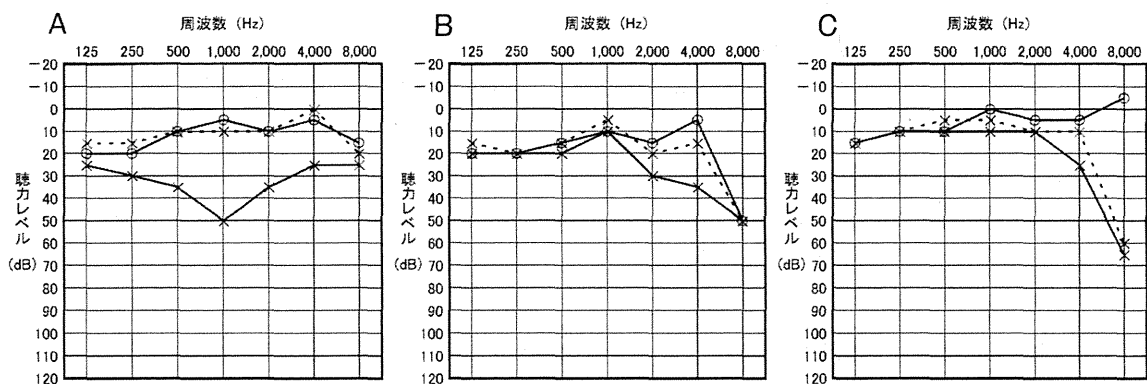**図5** 代表例のオージオグラムの変化
初診時オージオグラム（実線）と患側の固定時オージオグラム（点線）を示す。突発性難聴・聴力回復の判定基準に準じると，Aは治癒・回復，BとCは治癒・不変の2つに分類される。AとBは治癒，Cは不変と判定するのが妥当である。

治癒にも分類された（図5B）。8000Hzの聴力レベルは罹患側と同様に非罹患側でも低下していることを考慮すれば，本症例の聴力予後は治癒と判定すべきであると考えられた。高音急墜型のB群の1例では，左平均聴力レベルの変化は10dB未満（13dBから9dB）であるが固定時平均聴力レベルは20dB以内であるため，不変および治癒に分類された（図5C）。8000Hzの聴力レベルは罹患側で低下しているが，非罹患側の8000Hzの聴力レベルが正常であることを考えれば，不変と判定すべきであると考えられた。このように，A群では，治癒・回復と判定される症例が7例と最も多く，治癒・著明回復や治癒・不変と判定される症例も各1例存在したが，全例治癒と判定されるのが妥当と考えられた。一方，B群では，治癒・回復もしくは治癒・不変と判定される症例が各々4例と5例存在したが，6例は治癒，他の3例は不変と判定されるべきものと考えられた。全症例でみると，聴力予後は治癒15例（41％），回復3例（8％），不変19例（51％）と判定することが妥当であり，軽度の急性感音難聴の予後は必ずしも良好ではなかった（図4B）。

考　察

昭和48年に作成された突発性難聴診断の手引に「難聴の性質は高度の感音難聴である」ことが記載された理由は，軽度の感音難聴の原因となりうるメニエール病や内リンパ水腫を除外するためとされている[6]。しかし，本手引を作成した当初，軽度の急性感音難聴の多くを占めていたと考えられる低音障害型のものは急性低音障害型感音難聴（ALHL: acute low-tone sensorineural hearing loss）という別の疾患として除外されつつある。そして，ALHLの病態の1つとして内リンパ水腫が考えられている[7]ため，ALHLを除外した軽度の急性感音難聴の病態はメニエール病や内リンパ水腫とは異なる可能性がある。また，手引きには「必ずしも高度である必要はない」とする説明が付記されているものの，これまでの突発性難聴に関する報告ではGrade 2～4の症例を対象としていることが多く，ALHLを除外した軽度の急性感音難聴は十分に検討されているとは言えない。

突発性難聴の好発年齢は30～60歳代で，特に50歳代が多く，性差はないとされている[8]。メニエール病では，男性では50歳代，女性では60歳代に多く，女性が60％以上を占める[9]。ALHLの約75％は20～40歳代とされ，男女比は1：1.2～1：3.4と女性に多い傾向がみられる[10]。今回のA群では50歳代にピークをもつ年齢分布を示し，女性の比率は高くなかった。症例数は少ないため断定はできないが，A群の年齢分布や性比は突発性難聴に最も類似していた。一方，B群では60歳以上の症例は認められなかった。非罹患耳の聴力レベルはB群よりもA群で高値を示したことから，聴覚の加齢性変化の程度がB群の偏った年齢分布に影響を及ぼしたものと考えられた。

新基準案では，昭和48年の突発性難聴診断の手引にあった主症状「突然に難聴が発生すること」は「突然発症」のみの記載に変更されている。すなわち，新基準案に準じると自覚的な難聴の有無は突発性難聴の診断に必ずしも必要ない。このため，今回の研究では，難聴のみならず耳鳴が急性あるいは突発性に発症した症例も対象とした。全症例中難聴は73％に認められたのに対して，耳鳴は91％とより多くの症例が自覚していた。一方，難聴を自覚した頻度はA群では70％であり，より難聴の程度が軽いと考えられるB群でも79％であったことから，平均聴力レベル40dB未満の軽度難聴においても難聴を自覚する症例は確実に存在する。

突発性難聴全体でみると，聴力型は水平型（37-51％），高音障害型（15-21％）の割合が高く，山型のものは5-9％と少ない[11][12]。一方，今回の検討では，全症例中高音障害型を示す例が62％と最も多く，水平型は11％と少なかった。最近，八木ら[13]はGrade 1の突発性難聴を検討している。ALHL確実例と準確実例を除いた40例を対象とすると聴力型は高音障害型（40％），水平型（15％），谷型（6％），山型（5％）の順に少なくなり，今回の検討とほぼ同様の結果であった。平均聴力レベルが40dB未満の軽度の急性感音難聴では，聾型，聾やALHLに該当する低音障害型の聴力型が除外されるため，重症度に反映されない125，8000Hzの聴力レベルが低下した山型，高音障害型の割合が相対的に多くなるものと考えられる。しかし，水平型が軽度の急性感音難聴に占める割合が少なくなった正確な理由は

不明である。突発性難聴の原因は不明であるが，ウイルス感染や循環障害が病因として考えられている[1][6]。聴力レベル上全ての周波数をほぼ均等かつ軽度に障害させるような難聴は，病態として急性感音難聴では起こりにくい可能性がある。平均聴力レベルが40dB未満の水平型の感音難聴が突然に生じても，難聴や耳鳴を自覚しにくく今回の対象から除外されている可能性も考えられる。

めまいは突発性難聴全体の22-38%程度に合併する[12][14][15]が，今回の検討では全症例の22%に認められ，群別ではA群（26%）よりもB群（14%）で低率であった。難聴の重症度が軽度化すればめまい合併率も低くなる[14][15]ため，今回の軽度急性感音難聴におけるめまい合併率は妥当な数値と考えられた。突発性難聴の眼振の向きは，発症3-4日目は患側向きの眼振が出現し，その後健側向きに移行するとされてきた[16]。今回の症例では，5日目以降も患側向きの眼振を示す例が存在した。しかし，発症10日前後では健側向き，2週から1カ月で再度患側向きになるとする報告[17]もあるため，軽度の急性感音難聴における眼振の経時的変化の検討は病態を知るうえでも重要である。

今回の症例は聴力改善が悪い紹介例が含まれている可能性があること，統一した治療法がなされていないことから真の聴力予後を反映していない可能性がある。しかし，ALHL例を除いたGrade 1の突発性難聴の予後は約半数が不変とされており[18]，今回の結果からも軽度の急性感音難聴の予後は必ずしも良好ではない。一方，突発性難聴・聴力回復の判定基準に関する矛盾は以前より指摘されている[6][19]が，今回の軽度難聴例では2つの予後判定に分類される症例が約半数に及んだ。特に注意が必要と考えられたのが，治癒・不変と判定されたB群の3例において，現行の治癒の判定基準では聴力レベル20dB以内とする周波数に125，8000Hzが含まれていないため，唯一異常が認められる8000Hzの聴力低下が不変でも治癒と判定されうることである。今回のA群には同様の症例は認められなかったが，実際には新基準案にてGrade 1に分類される突発性難聴例においても同様の判定は起こりえる。聴力回復の判定基準に関しては他にも解決すべき課題が残されており[6]，今後の新判定基準の作成が望まれる。

昭和48年の突発性難聴診断の手引が作成されたことにより，外リンパ瘻，ALHL，ステロイド依存性感音難聴などの新しい疾患概念が確立した。そして，今回の新基準案により，これまで必ずしも突発性難聴と診断されなかった軽度の急性感音難聴が本疾患に含まれることになる。Grade 1の突発性難聴を含めた軽度の急性感音難聴をさらに検討することで，急性感音難聴の新しい病態や疾患概念が明らかになる可能性があると考えられる。

Evaluation of mild and acute sensorineural hearing loss

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In the present study, 37 patients (22-78 years, 20 males and 17 females) with mild and acute sensorineural hearing loss (ASNHL) were evaluated. All patients met the following criteria: 1) rapid unilateral hearing loss and/or tinnitus, 2) pure-tone average (PTA) at 250, 500, 1000, 2000 and 4000Hz< 40dB, and 3) unknown etiology. Patients with acute low-tone sensorineural hearing loss were excluded. The study patients were divided into two groups: 1) patients with an audiometric threshold ≥ 30dB HL in three connected frequencies (group A) and 2) others (group B). Of all the patients, 70% of group A and 79% of group B complained of hearing loss, and 91% of group A and 92% of group B had tinnitus. The most prevalent audiometric configuration was the high-tone type in both groups. In the positional nystagmus test, 26% of group A and 14%

of group B complained of vertigo and/or dizziness, while 56% of group A and 36% of group B showed unidirectional nystagmus. The hearing prognosis was judged as "unchanged" in 51% of all patients, suggesting that the prognosis of mild ASNHL was not good. Further studies are needed to clarify the nature of mild ASNHL.

参考文献

1) O'Malley MR, Haynes DS : Sudden hearing loss. Otolaryngology Clin North Am **41** : 633-649, 2008

2) 三宅　弘 : 突発性難聴の疫学・病因・治療に関する研究。厚生省特定疾患突発性難聴調査研究班昭和48年度研究報告書 : 1-5, 1974

3) 小川　郁 : 急性高度難聴に関する調査研究。厚生労働科学研究費補助金難治性疾患克服研究事業平成23年度総括・分担研究報告書 : 19, 2012

4) 神崎　仁, 福田宏之, 斎藤誠次, 他 : 聴神経腫瘍の外科的治療。耳展　33（補3）: 203-528, 1990

5) 野村恭也 : 総括研究報告。厚生省特定疾患急性高度難聴調査研究班　昭和59年度研究報告書 : 1-3, 1985

6) 神崎　仁, 神崎　晶 : 突発性難聴の諸問題―治療成績の評価を中心に―。耳展　48 : 336-342, 2005

7) Noguchi Y, Nishida H, Tokano H, et al : A comparison of acute low-tone sensorineural hearing loss versus Meniere's disease by electrocochleography. Ann Otol Rhinol Laryngol **113** : 194-199, 2004

8) 岡田昌浩, 暁　清文 : 突発性難聴。小川　郁編, よくわかる聴覚障害　難聴と耳鳴のすべて, 永井書店, 大阪, 2010, pp137-147

9) 森　望 : メニエール病。小川　郁　編, よくわかる聴覚障害　難聴と耳鳴のすべて, 永井書店, 大阪, 2010, pp156-166

10) 野口佳裕 : 急性低音障害型感音難聴。小川　郁編, よくわかる聴覚障害　難聴と耳鳴のすべて, 永井書店, 大阪, 2010, pp167-173

11) 清水猛史, 大川親久, 臼井智子, 他 : 突発性難聴に対する ATP 大量療法。耳鼻臨床　**91** : 443-449, 1998

12) 北村貴裕, 鎌倉武史, 松代直樹, 他 : 突発性難聴677例の聴力型別治療成績。耳鼻臨床　**104** : 619-623, 2011

13) 八木昌人, 尾関英徳, 井上亜希, 他 : 突発性難聴 grade1 症例における問題点について。Audiology Japan **54** : 56-62, 2011

14) 酒井晶子, 瀬尾　徹, 野出美知子, 他 : 突発性難聴の検討―特に入院加療と聴力予後に関して―。耳鼻臨床　**95** : 565-571, 2002

15) 水野正浩, 平岩　文, 金　永順, 他 : 突発性難聴の神経耳科所見と予後。Equilibrium Res **64** : 484-490, 2005

16) 朴沢二郎 : 突発性難聴患者の平衡機能―特に迷路が障害される過程と平衡機能の恢復する過程について―。Audiology Japan **13** : 150-153, 1970

17) 今手祐二, 関谷　透 : 一側前庭障害例（前庭神経炎, 突発性難聴, メニエール病）―頭位眼振, 温度眼振所見と関連問題について―。Equilibrium Res **49** : 204-215, 1990

18) 鎌倉武史, 松代直樹, 北村貴裕, 他 : 突発性難聴677例の重症度別治療成績。耳鼻臨床　**103** : 421-425, 2010

19) 岡本牧人, 設楽哲也 : 突発性難聴予後判定基準に関する矛盾について―質的判定法と量的判定法について―。耳鼻と臨床　**33** : 684-689, 1987

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Subgroups of Enlarged Vestibular Aqueduct in Relation to *SLC26A4* Mutations and Hearing Loss

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Objectives/Hypothesis: To investigate possible association of hearing loss and *SLC26A4* mutations with the subgroups of enlarged vestibular aqueduct (EVA) morphology in Japanese subjects with hearing loss.
Study Design: Retrospective multicenter study.
Methods: Forty-seven subjects who had vestibular aqueduct with midpoint diameter >1 mm by computed tomography of the temporal bone were enrolled at multiple sites across Japan, and DNA samples and clinical data were collected. EVA morphology was classified into four subgroups by the pattern of enlargement: aperture, aperture and midpoint, midpoint, and borderline enlargement. Venous blood DNA samples were subjected to polymerase chain reaction–based direct sequencing of all exons and exon–intron boundaries of the *SLC26A4*.
Results: Four novel *SLC26A4* mutations were identified in the present study. *SLC26A4* mutations were detected in almost all subjects with aperture, aperture and midpoint, and midpoint enlargement. In contrast, 71% of subjects with borderline enlargement had no *SLC26A4* mutation. No significant difference was found in the distribution of truncating and nontruncating *SLC26A4* mutations between the EVA subgroups. In addition, no significant correlation was observed between the EVA subgroups and hearing levels, incidence of hearing fluctuation, or progression of hearing loss.
Conclusions: Subgroups of EVA morphology were significantly correlated with the presence or absence of *SLC26A4* mutation. In a subgroup analysis of subjects with *SLC26A4* mutations, however, differences in the EVA subgroups were not correlated with *SLC26A4* genotypes or characteristics of hearing loss.
Key Words: Enlarged vestibular aqueduct, Pendred syndrome, DFNB4, *SLC26A4*, computed tomography, hearing loss.
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INTRODUCTION

Enlarged vestibular aqueduct (EVA) is one of the most common inner ear deformities, often identified by computed tomography (CT) in subjects with hearing loss.[1–5] The shape and size of the EVA differ between subjects. As such, a variety of radiographic criteria to define EVA have been published. Valvassori and Clemis[6] defined EVA as a vestibular aqueduct ≥1.5 mm at the midpoint diameter. Jackler and De La Cruz[7] developed a criterion of a midpoint diameter >2.0 mm, whereas Levenson and colleagues[8] proposed a cutoff of 2.0 mm at the external aperture diameter. Okumura et al.[9] suggested an external aperture diameter >4.0 mm. Madden et al.[1] considered external aperture diameter >2.0 mm and midpoint diameter >1.5 mm as definitive, and midpoint diameter of 1.0 to 1.5 mm as borderline enlargement. Vijayasekaran et al.[10] advocated the criteria of 0.9 mm midpoint diameter or 1.9 mm external aperture diameter.

Mutations in the *SLC26A4* have been identified as a major cause of vestibular aqueduct anomalies. *SLC26A4* mutations are known to cause Pendred syndrome (Mendelian Inheritance in Man [MIM] #274600) and nonsyndromic sensorineural deafness autosomal recessive type 4 (DFNB4, MIM #600791).[11–14] Some researchers have identified a correlation between *SLC26A4* mutations, EVA, and hearing loss, whereas others report no significant relationship among *SLC26A4* genotype and these phenotypes.[15] Previous
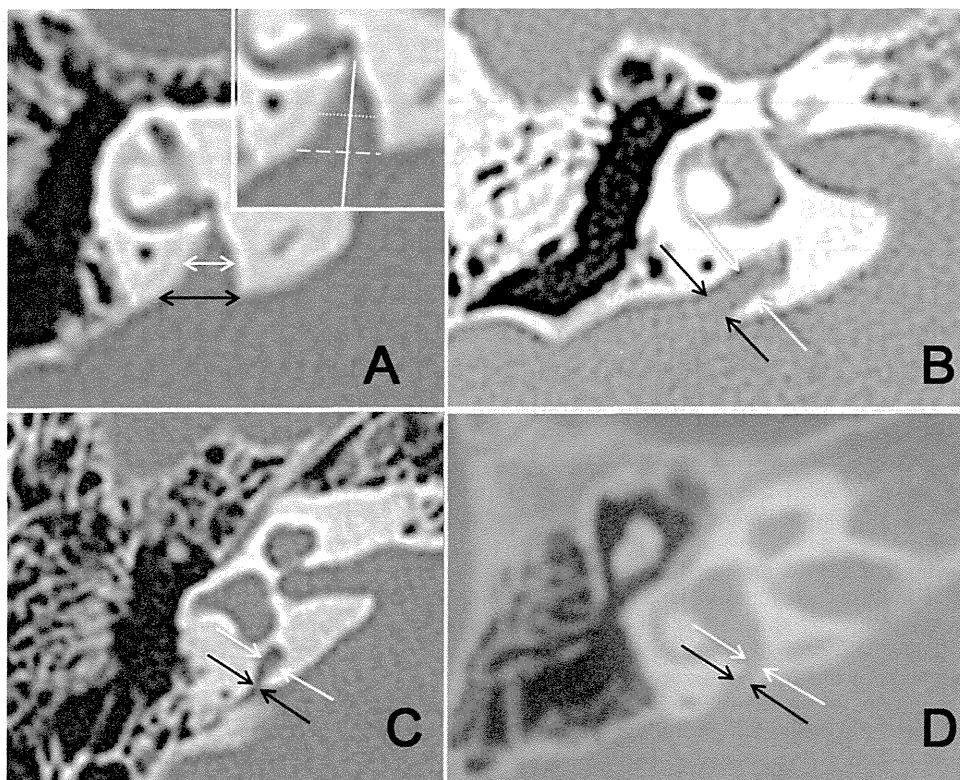
Fig. 1. Typical temporal bone computed tomographic images of the enlarged vestibular aqueduct subgroups. (A) Aperture enlargement. (B) Aperture and midpoint enlargement. (C) Midpoint enlargement. (D) Borderline enlargement. The midpoint and external aperture of the vestibular aqueduct are indicated by white and black arrows, respectively. As shown in the inset of A, the midpoint diameter (dotted line) and aperture diameter (dashed line) were measured perpendicular to the long axis (solid line) of the vestibular aqueduct.

studies have not evaluated the relationship between *SLC26A4* mutations and clinical features of hearing loss taking into consideration morphologic variations of the EVA. We conducted a multicenter study and differentiated subjects into subgroups according to vestibular aqueduct midpoint and external aperture diameters to examine a possible relationship between subgroups of EVA morphology, *SLC26A4* mutations, and hearing loss.

MATERIALS AND METHODS

We enrolled 47 bilateral EVA subjects with unilateral or bilateral sensorineural hearing loss of unknown causes (mean age = 13.5 years, range = 0–56 years; 33 children and 14 adults; 17 males and 30 females), and collected DNA samples and clinical data. Specifically, subjects whose bilateral vestibular aqueduct midpoint diameter was ≥1 mm on temporal bone CT scans were included. The midpoint and external aperture diameters were measured perpendicular to the long axis of the vestibular aqueduct on the transverse plane, as shown in the upper right-hand inset in Figure 1A. Subjects were classified into the following four subgroups based on the morphologic characteristics of the vestibular aqueduct according to the criteria in Table I:

aperture enlargement, aperture and midpoint enlargement, midpoint enlargement, and borderline enlargement.

For mutation analysis, genomic DNA was extracted from venous blood and subjected to polymerase chain reaction–based direct sequencing of the exons and exon–intron boundaries of the *SLC26A4* (GenBank NG_008489). For the purpose of this study, frameshift, splice site, and nonsense mutations were categorized as "truncating," and missense mutations as "nontruncating" mutations. Novel variants were defined as pathogenic if they 1) were nonsynonymous; 2) demonstrated low carrier rates (<1%) in 96 normal control Japanese subjects, absence in database Exome Variant Server[16] and dbSNP,[17] and high amino acid conservation among various mammalian species; and 3) were detected as heterozygous in association with the other allele with another heterozygous mutation already reported as pathogenic. Alteration of splice site was predicted by NNSPLICE.[18] Subjects with *SLC26A4* mutations were analyzed for degree of hearing loss, fluctuations in hearing acuity, and progression of hearing loss to assess the relationship between these hearing parameters and EVA subgroups. Subjects underwent conditioned orientation reflex or conventional pure-tone audiometry, depending on their ages. Auditory steady-state response measurements were utilized for five subjects who did not receive any of these audiometric tests.

TABLE I.
Criteria for the Subgroups of Enlarged Vestibular Aqueduct.

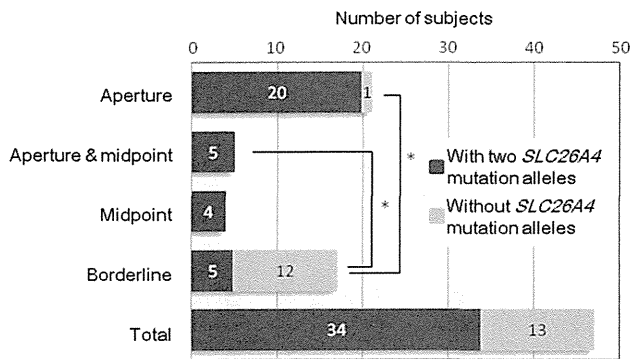| Enlarged Vestibular Aqueduct Subgroup	Midpoint Diameter	External Aperture Diameter
Aperture enlargement	≥1.5 mm	Wider than midpoint
Aperture and midpoint enlargement	≥1.5 mm	Equal to midpoint
Midpoint enlargement	≥1.5 mm	Narrower than midpoint
Borderline enlargement	1.0 mm to <1.5mm	1.0 mm to <1.5 mm

Fig. 2. Number of subjects with or without *SLC26A4* mutation alleles in each enlarged vestibular aqueduct subgroup. *Significant difference (*P* <.0125).

Hearing level was evaluated based on averages at 500, 1,000, 2,000, and 4,000 Hz (slight, 26–40 dB; moderate, 41–60 dB; severe, 61–80 dB; profound, ≥81 dB) according to the World Health Organization Grades of Hearing Impairment.[19] Subjects were considered to have fluctuating hearing loss if they had at least one bout of aggravation of hearing loss and recovery (at least 15 dB in one frequency). Subjects were considered to have progressive hearing loss if they showed aggravation of hearing loss by 10 dB or more at one or more frequencies within a 10-year interval. Statistical significance was assessed using the Fisher exact test.

All procedures were approved by the Ethics Review Committee of National Hospital Organization Tokyo Medical Center, Japan and other participating institutions, and were conducted only after written informed consent had been obtained from each subject or from the parents of the subjects.

RESULTS

Subgrouping of EVA and Its Association With SLC26A4 Mutations

Figure 1 shows typical CT findings in subjects with aperture enlargement (Fig. 1A), aperture and midpoint enlargement (Fig. 1B), midpoint enlargement (Fig. 1C), and borderline enlargement (Fig. 1D). Among 47 subjects, 21 (44%) were classified with aperture enlargement, 17 (36%) with borderline enlargement, five (11%) with aperture and midpoint enlargement, and four (9%) with midpoint enlargement (Fig. 2). All subjects had the same subgroup of enlargement bilaterally.

Genetic analysis of the 47 subjects showed that 34 (72%) had two *SLC26A4* mutation alleles (Table II), and the other 13 (28%) had no *SLC26A4* mutation alleles. None had a single *SLC26A4* mutation allele. The 34 subjects with two *SLC26A4* mutation alleles were diagnosed with Pendred syndrome or DFNB4. The majority of these subjects had aperture enlargement (n = 20, 59%), followed by aperture and midpoint enlargement (n = 5, 14%), borderline enlargement (n = 5, 14%), and midpoint enlargement (n = 4, 12%; Fig. 2). Conversely, most of the subjects without *SLC26A4* mutation alleles had borderline enlargement (n = 12, 91%), whereas the one remaining subject (8%) had aperture enlargement. The frequency of subjects without *SLC26A4* mutation alleles in the borderline enlargement subgroup was signifi-

cantly higher than in the aperture enlargement and aperture and midpoint enlargement subgroups (*P* <.0125). It tended to be higher than in the midpoint enlargement subgroup, but this difference was not statistically significant (*P* =.021), probably due to the small number of subjects in the midpoint enlargement subgroup (n = 4).

SLC26A4 Mutations and Genotypes in Association With EVA Morphology in Subjects With Pendred Syndrome or DFNB4

The types and locations of all the *SLC26A4* mutations in 34 subjects with Pendred syndrome or DFNB4 are shown in Table II and Figure 3. Five splice site mutations (c.601-1G>A [intron 5], c.919-2A>G [intron 7], c.1614+1G>A [intron 14], c.1708-32_1708-16del [intron 15], c.1707+5G>A [intron 15]), one nonsense mutation (p.L743X), two insertion/deletion mutations (p.S551Ffs13, p.Q705Wfs18), and 14 missense mutations (p.S28G, p.P76S, p.A372V, p.N392Y, p.R409H, p.T410M, p.T527P, p.I529S, p.Y556C, p.V659L, p.D669E, p.F692L, p.T721M, p.H723R) were detected. These included four novel mutations, p.S28G (c.82A>G), p.D669E (c.2007C>A), p.F692L (c.2074T>C), and c.1708-32_1708-16del (marked with ** in Table II), based on the criteria for novel mutations in the present study (described in Materials and Methods). Electropherograms of the novel mutations and conservation of the amino acid residues among various species are shown in Figure 3B and C. NNSPLICE predicted c.1708-32_1708-16del to decrease the probability of an acceptor site at exon 16 from 0.49 (for a normal allele) to 0.19 (for a mutation allele), which is likely to cause aberrant splicing (Fig. 3C).

The list of subjects with two *SLC26A4* mutation alleles is shown in Table II. Analysis of genotypes of *SLC26A4* mutation alleles in these subjects showed that 20 (59%) had nontruncating/nontruncating genotypes, 13 (38%) had nontruncating/truncating genotypes, and 1 (3%) had truncating/truncating genotypes (Fig. 4A). Comparison of the incidence of each genotype found no significant statistical difference between the subgroups of EVA morphology (*P* = 1.000).

Characteristics of Hearing Loss in Association With EVA Morphology in Subjects With Pendred Syndrome or DFNB4

The hearing levels, incidence of hearing fluctuation, and progression of hearing loss in subjects with two *SLC26A4* mutation alleles are shown in Table II. The relation between the hearing level and EVA morphology was examined in the ears of 34 subjects (68 ears; Fig. 4B). Thirty-four ears (50%) had profound hearing loss in total. No significant differences in the hearing levels were detected between the subgroups of EVA morphology (*P* =.462). To exclude the effect of aging in this analysis, we also stratified the subjects into two groups (age 0–9 and ≥10 years) and conducted the same analysis. These analyses also demonstrated the same results, indicating that the difference in ages among subgroups did

TABLE II.
Types of *SLC26A4* Mutations and Characteristics of Hearing Loss in 34 Subjects With Pendred Syndrome or DFNB4 by EVA Subgroups.

EVA Morphology	Age at Deafness Diagnosis, yr	Age, yr	Allele 1			Allele 2			T/N	Hearing Level, R/L, dBHL*	Fluctuation of Hearing	Progression of Hearing Loss
			Exon/Intron	DNA Change	Amino Acid Change or Splicing Mutation	Exon/Intron	DNA Change	Amino Acid Change or Splicing Mutation				
Aperture enlargement	0	1	Intron 15	c.1707+5G>A	Splice site mutation	19	c.2106–2110dup5	p.Q705Wfs18	T/T	90/70†	−	+
	0	33	15	c.1652insT	p.S551Ffs13	19	c.2168A>G	p.H723R	T/N	95/95	−	+
	2	6	Intron 7	c.919-2A>G	Splice site mutation	19	c.2168A>G	p.H723R	T/N	53.75/63.75	−	+
	0	27	Intron 7	c.919-2A>G	Splice site mutation	19	c.2168A>G	p.H723R	T/N	98.75/100	+	+
	0	1	Intron 15	c.1707+5G>A	Splice site mutation	19	c.2168A>G	p.H723R	T/N	85‡	Unknown	+
	0	31	Intron 5	c.601-1G>A	Splice site mutation	19	c.2168A>G	p.H723R	T/N	73.75/60	+	+
	3	11	Intron 5	c.601-1G>A	Splice site mutation	19	c.2168A>G	p.H723R	T/N	70/87.5	+	+
	0	4	Intron 15	c.1707+5G>A	Splice site mutation	2	c.82A>G**	p.S28G**	T/N	61.25/61.25	−	Unknown
	0	35	Intron 5	c.601-1G>A	Splice site mutation	10	c.1229C>T	p.T410M	T/N	80/73.75	+	+
	3	12	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	82.5/106.25	+	+
	3	3	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	62.5/73.75	−	−
	0	4	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	55/70	+	−
	0	2	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	37.5‡	Unknown	Unknown
	0	1	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	102.5/115§	−	−
	0	0.5	10	c.1229C>T	p.T410M	19	c.2228T>A	p.L743X	N/N	73.75‡	Unknown	Unknown
	0	1	9	c.1115C>T	p.A372V	10	c.1226G>A	p.R409H	N/N	92.5‡	−	−
	0	20	19	c.2168A>G	p.H723R	14	c.1579A>C	p.T527P	N/N	97.5/101.25	−	−
	0	4	15	c.1667A>G	p.Y556C	14	c.1579A>C	p.T527P	N/N	77.5/75	−	+
	0	6	3	c.266C>T	p.P76S	14	c.1579A>C	p.T527P	N/N	17.5/93.75	−	+
	0	9	10	c.1174A>T	p.N392Y	19	c.2162C>T	p.T721M	N/N	103.75/110	+	+
Aperture and midpoint enlargement	0	15	Intron 15	c.1708-32_1708-16del**	Splice site mutation**	19	c.2168A>G	p.H723R	T/N	76.25/91.25	+	+
	0	9	Intron 7	c.919-2A>G	Splice site mutation	17	c.2007C>A**	p.D669E**	T/N	100/100	+	−
	0	1	19	c.2168A>G	p.H723R	14	c.1579A>C	p.T527P	N/N	115‡	−	−
	5	6	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	47.5/62.5	−	−
	1	2	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	105/93.75§	Unknown	Unknown
Midpoint enlargement	0	3	Intron 7	c.919-2A>G	Splice site mutation	17	c.2007C>A**	p.D669E**	T/N	82.5/93.75#	+	+
	0	8	19	c.2168A>G	p.H723R	18	c.2074T>C**	p.F692L**	N/N	75/115	+	+
	7	10	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	60/15	+	+
	0	35	10	c.1229C>T	p.T410M	17	c.1975G>C	p.V659L	N/N	97.5/87.5	+	+

TABLE II.
(Continued)

EVA Morphology	Age at Deafness Diagnosis, yr	Age, yr	Allele 1			Allele 2				Hearing Level, R/L, dBHL*	Fluctuation of Hearing	Progression of Hearing Loss
			Exon/Intron	DNA Change	Amino Acid Change or Splicing Mutation	Exon/Intron	DNA Change	Amino Acid Change or Splicing Mutation	T/N			
Borderline enlargement	0	5	Intron 7	c.919-2A>G	Splice site mutation	19	c.2168A>G	p.H723R	T/N	73.75/77.5	+	+
	2	2	Intron 14	c.1614+1G>A	Splice site mutation	10	c.1229C>T	p.T410M	T/N	55‡	Unknown	Unknown
	4	4	19	c.2168A>G	p.H723R	19	c.2168A>G	p.H723R	N/N	106.25/88.75#	Unknown	+
	0	6	14	c.1586T>G	p.I529S	19	c.2168A>G	p.H723R	N/N	80/66.25	–	–
	4	14	10	c.1229C>T	p.T410M	19	c.2168A>G	p.H723R	N/N	118.75/58.75	+	+

*Value without slash indicates binaural stimulus.
†Auditory brainstem response.
‡Conditioned Orienting Response.
**Candidate novel mutation.
§Auditory steady state response.
#Conditioned Play Audiometry.
EVA = enlarged vestibular aqueduct; L = left; N = nontruncating; R = right; T = truncating.

not affect distribution of subjects among different hearing levels (data not shown). Next, the relation between hearing fluctuation and EVA morphology was investigated in 28 subjects for whom relevant audiometric data were available (Fig. 4C). Hearing fluctuations were detected in 15 subjects (54%) in total, and no significant differences were noted in the incidence of hearing fluctuations between the subgroups of EVA morphology ($P = .209$). Lastly, the relation between progression of hearing loss and EVA morphology was analyzed in 29 subjects for whom relevant clinical data were available (Fig. 4D). Twenty subjects (69%) had progressive hearing loss in total, and the results showed no significant differences in the incidence of progressive hearing loss between the subgroups of EVA morphology ($P = .207$).

DISCUSSION

Although a variety of EVA criteria using the midpoint and aperture diameters of the vestibular aqueduct have been proposed to date,[1,6–10] our study is the first attempt to divide EVA into subgroups based on the shape and size of the vestibular aqueduct, and the first to investigate the possible relationship of these subgroups with genotypes and audiometric findings. SLC26A4 mutations were detected in 72% of the Japanese subjects with bilateral EVA. Among these SLC26A4 mutations, four mutations were novel. The discovery of these novel mutations would expand the SLC26A4 mutation spectrum, thereby contributing to a more accurate gene-based diagnosis of hearing loss with EVA.

Nearly all subjects with aperture, aperture and midpoint, and midpoint enlargement presented SLC26A4 mutations, suggesting that subjects with these EVA subgroups are most likely to be diagnosed with Pendred syndrome or DFNB4. Conversely, only approximately 30% of subjects with borderline enlargement had SLC26A4 mutation, which suggests that the majority of subjects in this EVA subgroup have a pathological mechanism other than Pendred syndrome or DFNB4.

None of the 47 EVA subjects enrolled in the present study had only a single SLC26A4 mutation allele. This finding is in striking contrast with previous research reporting single SLC26A4 mutation alleles in approximately one third of Caucasian subjects with EVA.[3,4,20–22] This discrepancy might be associated with Japanese subjects, who were reported to have a spectrum of SLC26A4 mutations distinct from that of Caucasian subjects.[22] One possible explanation is that the development of EVA in the Caucasian population may more frequently involve mutations in the introns or promoter regions of the SLC26A4 than that in the Japanese population. Another possibility is that the Caucasian population may have higher mutation frequencies in genes than the Japanese population, causing digenic hearing loss in association with heterozygous SLC26A4 mutations (e.g., KCNJ10 and FOXI1).[23–25] The other possible explanation for the discrepancy is that the present study registered only subjects with bilateral EVA, whereas previous studies included those with unilateral hearing loss or unilateral EVA. This implicates the hypothesis that
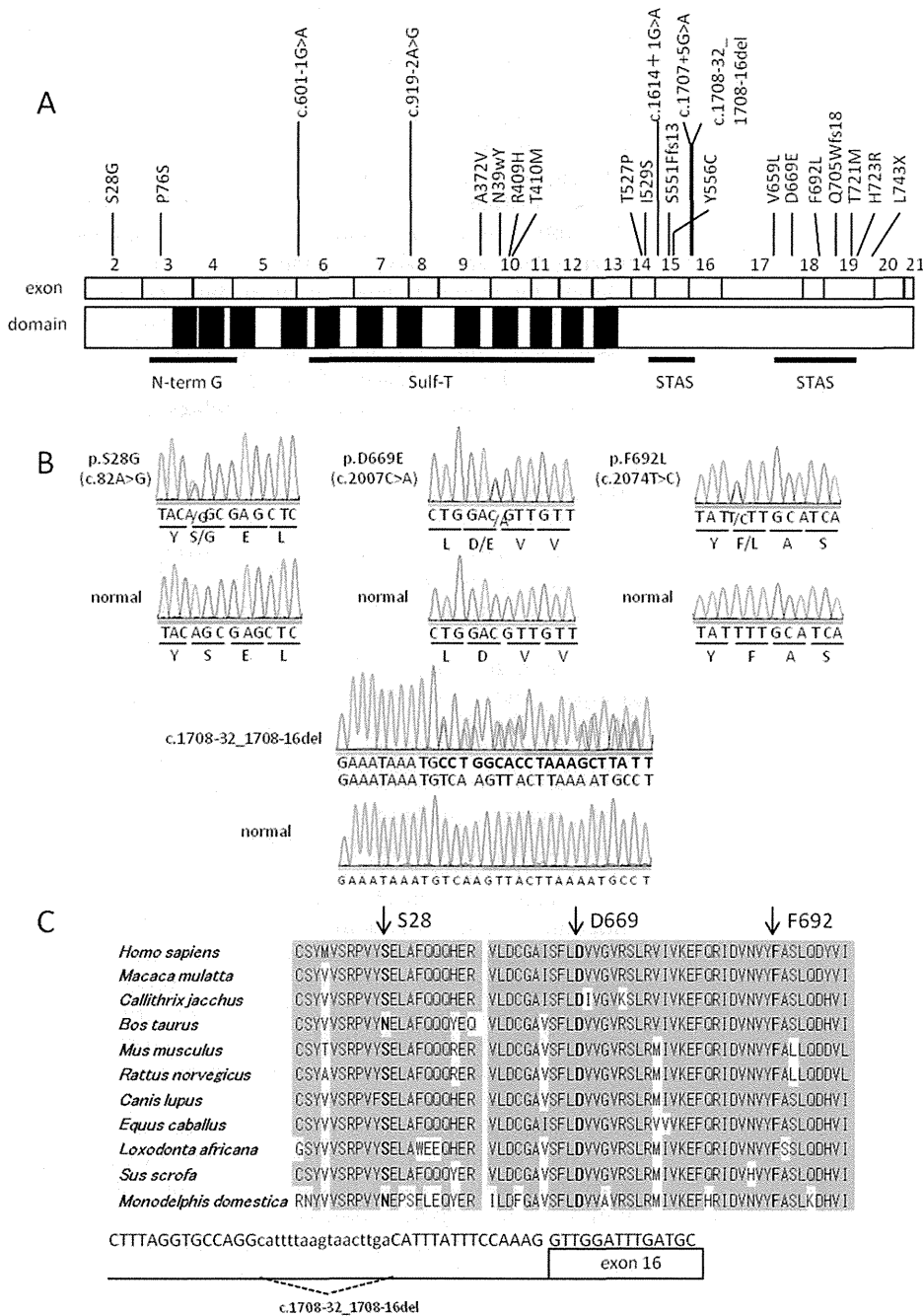
Fig. 3. The location of each mutation in *SLC26A4*, the evolutionary conservation of the amino acids, and nucleotides affected by the novel missense and splice site mutations. (A) Location of the *SLC26A4* mutations found in this study. Putative transmembrane regions are shown in black. N-term G = sulfate transporter N-terminal domain with Gly motif; STAS = sulfate transporter and anti–sigma factor antagonist domain; Sulf-T = sulfate transporter family domain. (B) electropherograms of the novel mutations and the corresponding sequence from normal alleles. Note that the nucleotide sequence of c.1708-32_1708-16del is shown reverse complementary. (C) Upper: multiple alignments of SLC26A4 protein orthologues at two noncontiguous regions. Arrows indicate affected amino acids. Conserved amino acids are shaded in gray. Lower: boundaries between intron 15 and exon 16 and deleted nucleotides are indicated at the bottom.

biallelic mutations of *SLC26A4* are more strongly associated with bilateral EVA.

Our analysis of subjects with *SLC26A4* mutations revealed no significant difference in the proportion of truncating and nontruncating *SLC26A4* mutations between subgroups of EVA morphology. This suggests that, in addition to malfunction of the *SLC26A4* protein, environmental factors or genes other than *SLC26A4* may contribute to variations in vestibular aqueduct morphology.

Some researchers argue that there is no significant relationship between the degree of the EVA and the severity and progression of hearing loss and hearing fluctuations, whereas others propose that there is a significant relationship.[26] In the present study, no significant differences were detected in the level, fluctuation, and progression of hearing loss between the subgroups of EVA morphology, indicating that characteristics of hearing loss cannot be predicted based on the EVA morphology in subjects with Pendred syndrome or DFNB4.

CONCLUSION

Almost all the subjects with aperture, aperture and midpoint, and midpoint enlargement of EVA had two *SLC26A4* mutation alleles, whereas more than two thirds
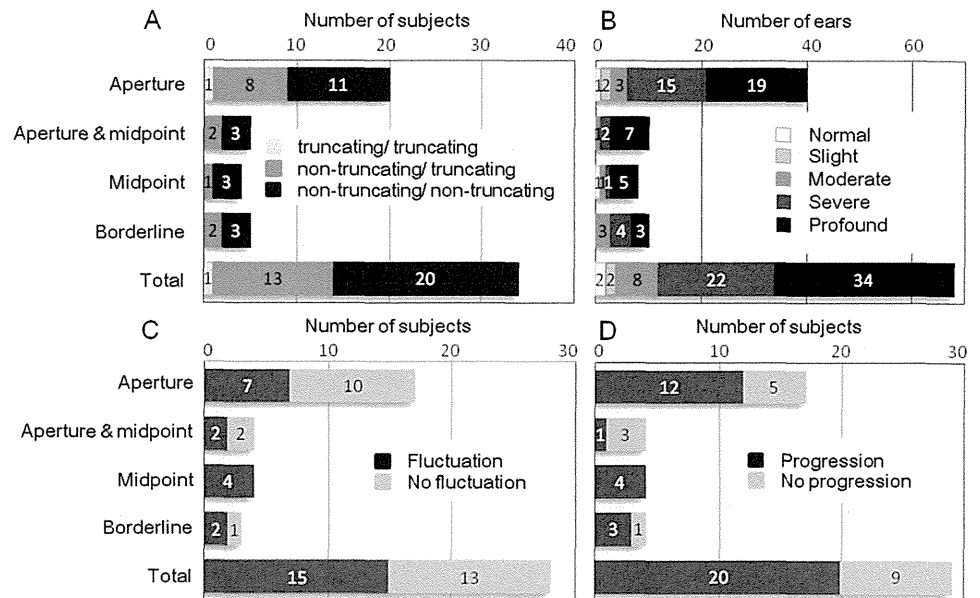
Fig. 4. Association of enlarged vestibular aqueduct (EVA) subgroups with SLC26A4 genotypes or characteristics of hearing loss in subjects with biallelic SLC26A4 mutations. (A) Proportion of SLC26A4 genotypes in subjects of each EVA subgroup. (B) Proportion of different hearing levels in ears of each EVA subgroup. (C) Prevalence of fluctuating hearing loss in subjects of each EVA subgroup. (D) Prevalence of progressive hearing loss in subjects of each EVA subgroup.

of subjects with borderline enlargement of EVA had no SLC26A4 mutation alleles. Analysis of subjects with two SLC26A4 mutation alleles revealed no significant correlation between the morphologic subgroups of EVA and SLC26A4 genotypes or characteristics of hearing loss, suggesting that the subgroups of EVA morphology may be associated with factors other than genotypes of SLC26A4 mutations and that the subgroups of EVA morphology are not a predictive factor for characteristics of hearing loss.

BIBLIOGRAPHY

1. Madden C, Halsted M, Benton C, Greinwald J, Choo D. Enlarged vestibular aqueduct syndrome in the pediatric population. Otol Neurotol 2003; 24:625–632.
2. Madden C, Halsted M, Meinzen-Derr J, et al. The influence of mutations in the SLC26A4 gene on the temporal bone in a population with enlarged vestibular aqueduct. Arch Otolaryngol Head Neck Surg 2007; 133:162–168.
3. Pryor SP, Madeo AC, Reynolds JC, et al. SLC26A4/PDS genotype-phenotype correlation in hearing loss with enlarged vestibular aqueduct (EVA): evidence that Pendred syndrome and non-syndromic EVA are distinct clinical and genetic entities. J Med Genet 2005;42:159–165.
4. Azaiez H, Yang T, Prasad S, et al. Genotype-phenotype correlations for SLC26A4-related deafness. Hum Genet 2007;122:451–457.
5. Choi BY, Stewart AK, Madeo AC, et al. Hypo-functional SLC26A4 variants associated with nonsyndromic hearing loss and enlarged vestibular aqueduct: genotype-phenotype correlation or coincidental polymorphisms? Hum Mutat 2009;30:599–608.
6. Valvassori GE, Clemis JD. The large vestibular aqueduct syndrome. Laryngoscope 1978;88:723–728.
7. Jackler RK, De La Cruz A. The large vestibular aqueduct syndrome. Laryngoscope 1989;99:1238–1242.
8. Levenson MJ, Parisier SC, Jacobs M, Edelstein DR. The large vestibular aqueduct syndrome in children. A review of 12 cases and the description of a new clinical entity. Arch Otolaryngol Head Neck Surg 1989; 115:54–58.
9. Okumura T, Takahashi H, Honjo I, Takagi A, Mitamura K. Sensorineural hearing loss in patients with large vestibular aqueduct. Laryngoscope 1995;105:289–293.
10. Vijayasekaran S, Halsted MJ, Boston M, et al. When is the vestibular aqueduct enlarged? A statistical analysis of the normative distribution of vestibular aqueduct size. Am J Neuroradiol 2007;28:1133–1138.
11. Smith SD, Harker LA. Single gene influences on radiologically-detectable malformations of the inner ear. J Commun Disord 1998;31:391–408; quiz 409–410.
12. Everett LA, Glaser B, Beck JC, et al. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet 1997;17:411–422.
13. Phelps PD, Coffey RA, Trembath RC, et al. Radiological malformations of the ear in Pendred syndrome. Clin Radiol 1998;53:268–273.
14. Usami S, Abe S, Weston MD, Shinkawa H, Van Camp G, Kimberling WJ. Non-syndromic hearing loss associated with enlarged vestibular aqueduct is caused by PDS mutations. Hum Genet 1999;104:188–192.
15. Reyes S, Wang G, Ouyang X, et al. Mutation analysis of SLC26A4 in mainland Chinese patients with enlarged vestibular aqueduct. Am Acad Otolaryngol Head Neck Surg 2009;141:502–508.
16. National Heart, Lung, and Blood Institute Exome Sequencing Project. Exome variant server. Available at: http://evs.gs.washington.edu/EVS/. [Visited May 13, 2013].
17. National Center for Biotechnology Information. dbSNP. Available at: http://www.ncbi.nlm.nih.gov/snp/. [Visited May 13, 2013].
18. Reese MG, Eeckman, FH, Kulp, D, Haussler, D. Improved splice site detection in Genie. J Comp Biol 1997;4:311–323.
19. World Health Organization. Grades of hearing impairment. Available at: http://www.who.int/pbd/deafness/hearing_impairment_grades/en/index.html. [Visited May 13, 2013].
20. Albert S, Blons H, Jonard L, et al. SLC26A4 gene is frequently involved in nonsyndromic hearing impairment with enlarged vestibular aqueduct in Caucasian populations. Eur J Hum Genet 2006;14:773–779.
21. Campbell C, Cucci RA, Prasad S, et al. Pendred syndrome, DFNB4, and PDS/SLC26A4 identification of eight novel mutations and possible genotype-phenotype correlations. Hum Mutat 2001;17:403–411.
22. Tsukamoto K, Suzuki H, Harada D, Namba A, Abe S, Usami S. Distribution and frequencies of PDS (SLC26A4) mutations in Pendred syndrome and nonsyndromic hearing loss associated with enlarged vestibular aqueduct: a unique spectrum of mutations in Japanese. Eur J Hum Genet 2003;11:916–922.
23. Madeo AC, Manichaikul A, Reynolds JC, et al. Evaluation of the thyroid in patients with hearing loss and enlarged vestibular aqueducts. Arch Otolaryngol Head Neck Surg 2009;135:670–676.
24. Yang T, Vidarsson H, Rodrigo-Blomqvist S, Rosengren SS, Enerback S, Smith RJ. Transcriptional control of SLC26A4 is involved in Pendred syndrome and nonsyndromic enlargement of vestibular aqueduct (DFNB4). Am J Hum Genet 2007;80:1055–1063.
25. Yang T, Gurrola JG Jr, Wu H, et al. Mutations of KCNJ10 together with mutations of SLC26A4 cause digenic nonsyndromic hearing loss associated with enlarged vestibular aqueduct syndrome. Am J Hum Genet 2009;84:651–657.
26. Gopen Q, Zhou G, Whittemore K, Kenna M. Enlarged vestibular aqueduct: review of controversial aspects. Laryngoscope 2011;121:1971–1978.

原　　著

一側性メニエール病における MRI による両側内リンパ腔サイズの評価

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MRI evaluation of the bilateral endolymphatic space in patients with unilateral Meniere's disease

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Development of 3-tesla enhanced magnetic resonance imaging (MRI) provides a tool for the visualization of endolymphatic hydrops (EH). This technique was first developed in animal experiments and adapted in patients with inner ear diseases including Meniere's disease (MD). Up to the present, we have demonstrated EH in many MD patients. Recently, we have succeeded in obtaining a 3 D-real IR-like image even after intravenous standard-dose gadolinium administration. This type of image was named the HYDROPS (HYbriD of Reversed image Of Positive endolymph Signal and native image of positive perilymph signal). The relationship between unilateral MD and EH has not yet been explored. We studied 76 patients with unilateral MD who were evaluated using MRI. The mean age of the subjects was 53.4 years (range 17 to 80 years). Forty-two were women and 34 were men. Symptomatic and non-symptomatic ears were categorized into 4 groups (healthy, 76; possible, 48; Probable, 13; and definite, 15) based on AAO-HNS definitions. MRI was performed 4 hours after intravenous gadolinium administration. Overall, 152 ears were evaluated. EH in the cochlea was present in 57 of 76 symptomatic ears (73.7%) and 34 of 76 (44.7%) non symptomatic ears. Ears with definite MD had EH more frequently in the cochlea than ears in the healthy ears groups. Furthermore, EH in the vestibule with definite MD was larger than ears in any of the other groups. Our reports showed for the first time that there was Ba relationship between the degrees of EH and the stage of MD. Moreover, in fewer than half of unilateral MD patients EH was seen in the cochlea with non-symptomatic ears. EH in healthy ears may be an indicator of bilateral MD. Using MRI to identify this covert EH in asymptomatic patients may offer the possibility of early detection or prevention of MD.

緒　言

　メニエール病は難聴，耳鳴，めまいを三主徴とし発作を反復する疾患であるが難聴は通常初期には一側性である。しかし，経過中に両側性へと移行する症例もあり，経過年数の長期化とともに症例数が増加する傾向にある。メニエール病の本態は特発性内リンパ水腫であるため一側性メニエール病であった症例が経過中，反対側の健側耳にも内リンパ水腫が形成されると考えられる。当科ではメニエール病症例や周辺疾患の内耳ガドリニウム造影によるMRIによる内リンパ水腫の評価を行なってきた[1,2]。現在ではほとんどのメニエール病症例でMR画像上内リンパ水腫を認めることが分かっている。最近のMR画像のシークエンスの進歩により，通常量のガドリニウム造影剤を用いて内リンパ水腫を評価することが可能となり[3,4]，一度の撮影で両耳の評価が可能となった。また，非定型メニエール病の症例や耳鳴のみの症例にも内リンパ水腫も少なからず存在することも明らかになった[5~7]。今回，一側性メニエール病の内リンパ水腫の内耳障害への影響およびその健側耳の評価について考察する。

方　法

　2007年7月から2012年6月までに当科受診したメニエール病症例で臨床症状は一側性であった症例76例152耳。症例は男性34名，女性42名で平均年齢は53.6歳（17歳〜80歳）であった。聴力の評価は三分法（500, 1 K, 2 KHzの平均）にて行った。症例は1995年に作成されたAmerican Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)の診断基準（表1）に基づいて，definite, probable, possible Meniere's diseaseとその健側耳の4群に分類を行った。MRIは全例でメニエール病間歇期に3テスラ（Trio；Siemens, Erlangen, Germany）を用いガドリニウム（Omniscan®）0.1 mmol/kg静注4時間後に撮

影を行った。パルスシークエンスは以前より基本的にheavily T 2-weighted three-dimensional fluid-attenuated inversion recovery（3 D-FLAIR）やthree-dimensional inversion-recovery sequence with real reconstruction （3 D-real IR）を用いてきた。3 D-FLAIRはT 1強調画像では感度が低く描出が困難であった外リンパ造影剤の陽性信号を捉えられる。3 D-FLAIRでは外リンパは白く，内リンパは黒く見えるが周囲の骨も黒く描出されるため内リンパと骨の境界の判別が難しい。この問題点を解決するため鼓室内ガドリニウム注入法においてreal IRが新たに用いられるようになった。real IRでは内リンパが黒く，外リンパおよび骨は白く描出されるため内リンパの程度評価がしやすい。さらにHYbriD of Reversed image Of Positive endolymph Signal and native image of positive perilymph signal（HYDROPS）では静注法で造影剤の濃度が薄い条件においてもreal IRのような画像の描出を可能とした[3]。内リンパ水腫の有無の評価は3 D-FLAIRを用いることで造影剤の濃度が薄くても基本的に可能である。現在ではほとんどの症例においてHYDROPSでの内リンパ水腫の程度評価が可能となっているが，やや外リンパでの造影剤の濃度が薄い場合には3 D-FLAIRを用いて評価を行なっている。臨床経過を伏せた状態でMR画像を放射線科医が読影，評価を行い内リンパ水腫のグレード分類を行った。グレード分類は過去に報告したのと同様に，水腫なし，軽度，著明の三段階評価とした[8]。MRIによる内リンパ水腫の程度として表2のような分類を報告した。前庭では面積の3分の1，2分の1を正常，軽度水腫，著明水腫の境とした。前庭に関しては，面積比が蝸牛に比して求めやすく比を示すことは前庭の水腫程度のよい指標となる。蝸牛水腫について我々は，表2のように分類し，基底回転と上方回転で程度が違う場合は，高度な方を採用することとした。現在の画像レベルでは，蝸牛の全回転にわたって内外リンパ腔の線引きをすることが難しい場合が多く比を示
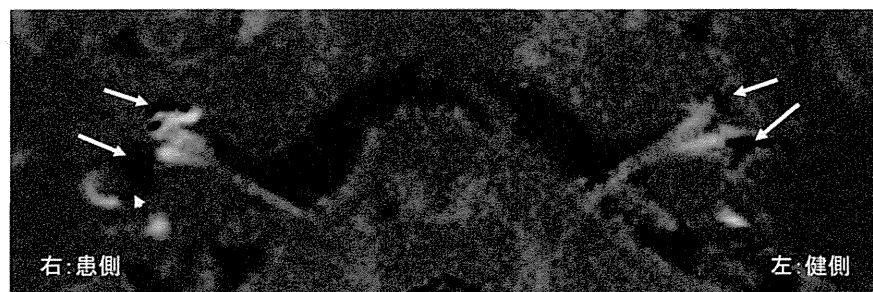
名古屋大学大学院医学系研究科頭頸部・感覚器外科学講座耳鼻咽喉科

図1　26歳女性。9年前に発症の右 probable MD。右難聴，耳閉感，耳鳴，めまい（1回の回転性めまい発作）あり。4分法で右 77.5 dB，左 13.8 dB であった。右蝸牛前庭に著明な内リンパ水腫（矢印）を認め，右前庭には内リンパ水腫（矢印）の外側半規管へのヘルニア（短矢印）を認める。左は蝸牛に著明な内リンパ水腫（矢印），前庭には軽度の内リンパ水腫（矢印）を認める。

表1　AAO-HNS のメニエール病診断基準

Certain Meniere's disease（確認例）
確実例の死後，病理解剖により内リンパ水腫を確認
Definitive Meniere's disease（確実例）
20分以上の自発性回転性めまい発作が2回以上
1回以上の聴力検査により難聴の確認
難聴側の耳鳴または耳閉感
他の原因疾患が否定
Probable Meniere's disease（疑い例）
1回の明らかな回転性めまい
1回以上の聴力検査により難聴の確認
難聴側の耳鳴または耳閉感
他の原因疾患が否定
Possible Meniere's disease（見込み例）
回転性めまい発作を繰り返すが難聴のない場合，
あるいは
明らかなめまい発作ではない非回転性めまいと（変動あるいは
固定した）難聴を認める場合
他の原因疾患が否定

すことはできなかった。さらに一部の症例について前庭機能検査（前庭誘発筋電位（VEMP），温度刺激検査）を行ったが，VEMP の有無，CP の有無は過去の報告に従って判定した[9)10)]。年齢，罹病期間，水腫の有無と程度について4群で比較，検討を行った。解析には SPSS ver. 20（SPSS, IBM, Armonk, New York, USA）を用いてカイ二乗検定および一元配置分散分析（多

重比較にはボンフェローニ法を適用）を行った。本研究は，名古屋大学医学部倫理委員会の承認を得て行った。

結　果

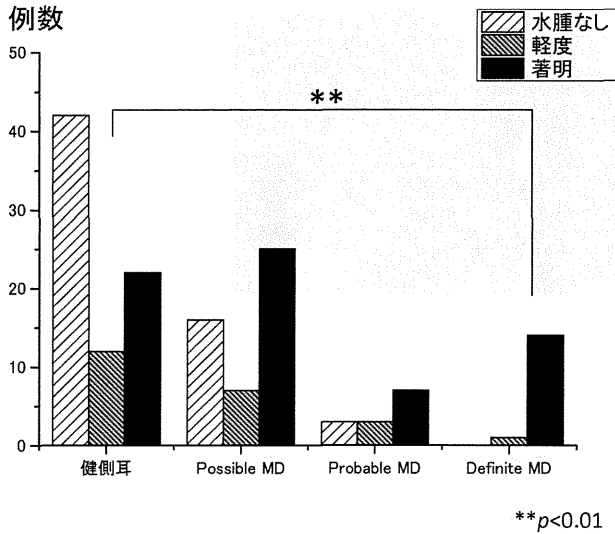蝸牛の内リンパ水腫は患側内耳で76耳中57耳（うち著明水腫46耳），健側内耳で76耳中34耳（うち著明水腫22耳）であった。また，前庭の内リンパ水腫はメニエール病患側内耳で76耳中66耳（う

（249）

例数

**p<0.01

図2　AAO-HNS のクライテリアでみた蝸牛内リンパ水腫の程度。健側耳と比較して Definite MD 群で内リンパ水腫の割合が有意に多い。

***p<0.001, *p<0.05

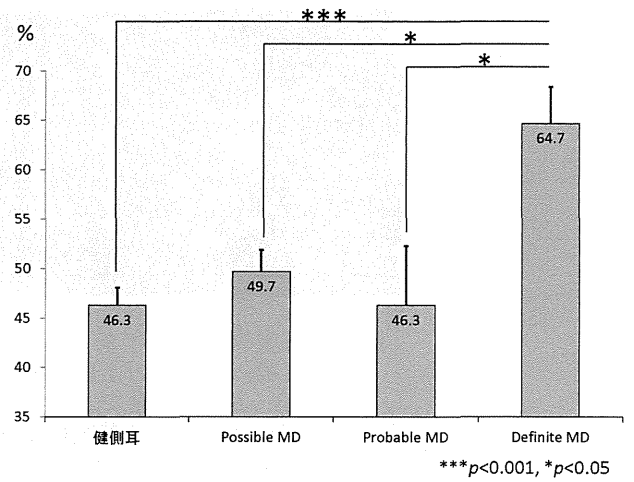図3　AAO-HNS のクライテリアでみた前庭内リンパ水腫の程度。前庭内リンパ腔の内外リンパ腔に対する面積比で評価を行った。Definite MD で他の群と比較して有意に前庭内リンパ水腫が大きかった。

表2　MRI における内リンパ水腫の程度分類

	前庭 内リンパ腔の内外リンパ腔に対する面積比	蝸牛
水腫無	3分の1まで	ライスネル膜伸展なし
水腫軽度	2分の1まで	蝸牛管面積≦前庭階面積
水腫高度	2分の1超	蝸牛管面積＞前庭階面積

蝸牛水腫の評価で回転により水腫程度が異なる時は，より高い方を選択

ち著明水腫48耳)，健側内耳で76耳中57耳（うち著明水腫32耳）であった。表3に示す通り，蝸牛内リンパ水腫は最も割合の少ない健側耳（44.7％）から AAO-HNS のグレードに応じて徐々に増加し definite MD では100％で認めた。前庭の内リンパ水腫に関しても同様の結果で最も少ない健側耳（75.0％）から徐々に増加し definite MD では100％で内リンパ水腫を認めた。（表3）図1に probable MD（右）で健側（左）にも水腫を認めた症例の MRI を示す。この症例では右蝸牛前庭に著明な内リンパ水腫，左蝸牛に著明な内リンパ水腫，左前庭に軽度の内リンパ水腫を認めた。蝸牛内リンパ水腫のサイズを4群間で比較すると健側耳に比較し definite 症例では有意に内

リンパ水腫が大きかった（$p<0.01$；カイ二乗検定）。（図2）また，前庭内リンパ腔の内外リンパ腔に対する面積比と比較した場合，definite MD で他の症例に比較して有意に大きい前庭内リンパ水腫を認めた（健側：$p<0.001$, possible, probable MD：$p<0.05$；一元配置分散分析）。（図3）また，平均罹病期間については possible から definite に進展するにつれて長い傾向にあった。（表3）また，健側耳の内リンパ水腫について対側耳の AAO-HNS クライテリア別に程度の評価を行った結果では，蝸牛について probable MD 群で definite MD 群と比較して有意に著明な内リンパ水腫が多かった（$p<0.05$；カイ二乗検定）が，前庭ではクライテリアごとでは有意差を認めなか
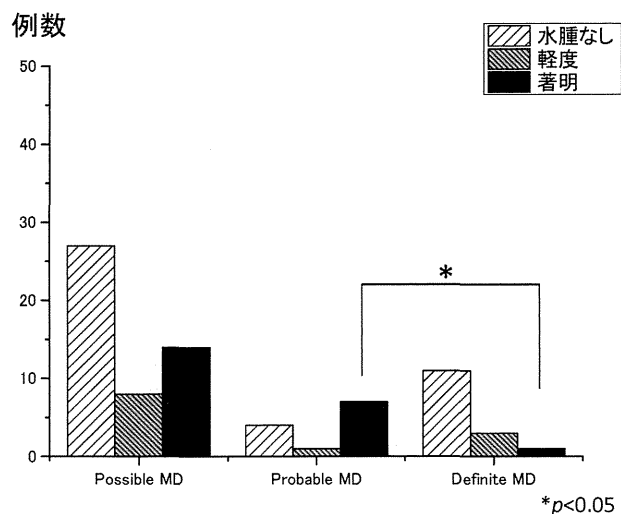
（250）

図4 AAO-HNS のクライテリア別にみた健側耳の
蝸牛内リンパ水腫の程度。

Probable MD の健側耳にて Definite MD の
健側耳よりも有意に著明な内リンパ水腫を多
く認めたが，それ以外は有意差を認めなかっ
た。
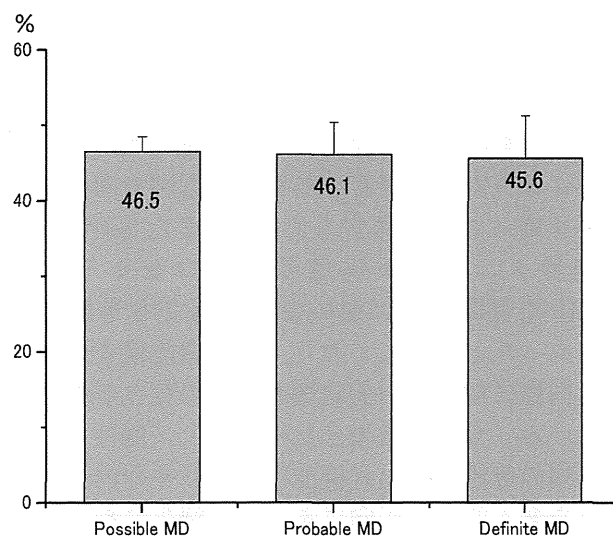
図5 AAO-HNS のクライテリア別にみた健側耳の
前庭内リンパ水腫の程度。

すべての項目について有意差を認めなかっ
た。

表3 メニエール病分類と MRI 検査結果

	健側耳	Possible MD	Probable MD	Definite MD
症例数	76	48	13	15
平均年齢	53.6	53.3	54.7	53.6
蝸牛水腫の有無	34/76 (44.7%)	32/48 (66.7%)	10/13 (76.9%)	15/15 (100%)*
前庭水腫の有無	57/76 (75.0%)	41/48 (85.4%)	10/13 (76.9%)	15/15 (100%)
平均聴力 (dB)	17.9	34.4	46.6	44.5
平均罹病期間(月)		48.7	50.5	75.6

蝸牛前庭ともに軽度水腫以上を内リンパ水腫有りとした。

平均聴力：三分法平均聴力 (500, 1 K, 2 K)

った。（一元配置分散分析）（図4，5）probable
MD 群で蝸牛著明水腫の症例（72.3カ月）では水
腫軽度，なしの症例（25.2カ月）に比して罹病期
間が長い傾向にあった。さらに VEMP を7例，
温度刺激検査を4例に施行した。VEMP で反応
なかった2耳では著明な前庭内リンパ水腫を認め
た。また温度刺激検査は definite MD の1例のみ
で CP であったが，この症例では右前庭内リンパ
水腫の外側半規管へのヘルニアを認めた。
　考　察
　メニエール病の症状についてはこれまでに有病
率や長期経過について多数の報告がある。メニエ
ール病の患側耳についてはメニエール病186症例
中，11%が初診時から両側性であり，一側性のメ
ニエール病の14%が経過中に両側性に移行したと
の報告がある[11]。今回の検討では一側性メニエー
ル病健側内耳は蝸牛前庭ともに画像上内リンパ水
腫のサイズが小さい傾向にあったが，健側でも水
腫が存在する割合が高いことがわかった。しか
し，対側患耳の臨床的重症度とは相関がなかっ
た。メニエール病健側耳の内リンパ水腫に関して
過去の検討では内耳機能検査を用いたものが多

い。メニエール病の健側内耳144耳と無症状耳114耳の蝸電図を比較した報告ではメニエール病健側耳で10％以上に内リンパ水腫を強く疑う所見を認めたが，無症状耳では２％以下であった[12]。さらにメニエール病健側耳で35％に蝸電図で内リンパ水腫を疑ったとの報告もある[13]。またSeo[14]らは一側性メニエール病患者のフロセミド負荷VEMP患側陽性例において健側耳でも半数で陽性であったと報告しており，前庭機能検査においても同様に健側耳の前庭機能障害の存在が指摘されている。今回の結果と比較すると一側性メニエール病の健側耳は内耳機能検査よりやや内リンパ水腫を多く認める傾向にあるが，蝸牛にやや少なく前庭には多いという点では一致している。我々の施設でも過去に蝸電図SP/AP比の大きさは，前庭水腫より蝸牛水腫と関連がある[15]ことや，VEMPの消失は蝸牛水腫より前庭水腫と関連があった[14]ことを報告している。また，温度刺激検査のCPと蝸牛，前庭，外側半規管の内リンパ水腫はいずれも関連がなかった[15]。今回の検討では１例にCPを認めたがこの症例では前庭内リンパ水腫の外側半規管へのヘルニアを認めた。Gurkov[16][17]らは，水腫ヘルニアと温度刺激検査CPとの関係について報告した。我々も，今後，症例を増やして水腫ヘルニアと症状，検査所見との関係について検討していく予定である。Definite MDでは内リンパ水腫の出現率も非常に高く，またサイズも大きい。メニエール病の進展例では罹病期間も長い症例が多いため，年月を経て内リンパ水腫が徐々に大きくなった可能性も考えられる[18]。Fiorino[19]らは罹病期間５年以上のメニエール病患者では80％以上で蝸牛基底回転に内リンパ水腫を認め，100％で前庭内リンパ水腫を認めたと報告している。メニエール病患側耳および健側耳において内リンパ水腫のサイズは経過とともに増大傾向にあると考えられる。一側性メニエール病の健側耳にも画像的に約半数で内リンパ水腫を認めることが示され，今後のメニエール病の病態解明や新たな視点からの治療に貢献すると考えられる。

謝　　辞

文　　献

１）Nakashima T, Naganawa S, Teranishi M, et al.: Endolymphatic hydrops revealed by intravenous gadolinium injection in patients with Meniere's disease. Acta Otolaryngol 130: 338–343, 2010

２）Naganawa S, Komada T, Fukatsu H, et al.: Observation of contrast enhancement in the cochlear fluid space of healthy subjects using a 3 D-FLAIR sequence at 3 Tesla. Eur Radiol 16: 733–737, 2006

３）Naganawa S, Yamazaki M, Kawai H, et al.: Imaging of Ménière's disease after intravenous administration of single dose gadodiamide: Utility of subtraction image. Magn Reson Med Sci 11: 213–219, 2012

４）Iida T, Teranishi M, Yoshida T, et al.: Magnetic resonance imaging of the inner ear after both intratympanic and intravenous gadolinium injections. Acta Otolaryngol 2013 in press

５）Kato M, Sugiura M, Shimono M, et al.: Endolymphatic hydrops revealed by magnetic resonance imaging in patients with atypical Meniere's disease. Acta Otolaryngol 133: 123–129, 2013

６）Yoshida T, Teranishi M, Kato M, et al.: Endolymphatic hydrops in patients with tinnitus as the major symptom. Eur Arch Otorhinolaryngol 2013, in press

７）Pyykkö I, Nakashima T, Yoshida T, et al.: Meniere's disease: a reappraisal supported by a variable latency of symptoms and the MRI visualisation of endolymphatic hydrops. BMJ Open 3: e 001555, 2013

８）中島　務，寺西正明，片山直美，他：めまいの新しい疾患概念　MRIによる内リンパ水腫の画像診断．Equilibrium Res 70: 197–203, 2011

９）Katayama N, Yamamoto M, Teranishi M, et al.: Relationship between endolymphatic hydrops and vestibular-evoked myogenic potential. Acta Otolaryngol 130: 917–923, 2010

10) Kato M, Teranishi M, Katayama N, et al.: Association between endolymphatic hydrops as revealed by magnetic resonance imaging and caloric response. Otol Neurotol 32: 1480–1485, 2011

11) House JW, Doherty JK, Fisher LM, et al.: Meniere's disease: Prevalence of contralateral ear involvement. Otology & Neurotology 27: 355–361, 2006

12) Conlon BJ, Gibson WPR: Meniere's disease: The incidence of hydrops in the contralateral asymptomatic ear. Laryngoscope 109: 1800–1802, 1999

13) Moffat DA, Baguley DM, Harries MLL, et al.: Bilateral electrocochleographic findings in unilateral Menieres-disease. Otolaryngol Head Neck Surg 107: 370–373, 1992

14) Seo T, Saka N, Sakagami M: Furosemide-loading vestibular evoked myogenic potential testing can suggest developing bilateral involvement of unilateral Meniere's disease. Acta Otolaryngol 132: 632–636, 2012

15) Yamamoto M, Teranishi M, Naganawa S, et al.: Relationship between the degree of endolymphatic hydrops and electrocochleography. Audiol Neurotol 15: 254–260, 2010

16) Gürkov R, Flatz W, Louza Jet al.: Herniation of the membranous labyrinth into the horizontal semicircular canal is correlated with impaired caloric response in Ménière's disease. Otol Neurotol 33: 1375–1379,2012

17) Gürkov R, Flatz W, Ertl-Wagner Bet al.: Endolymphatic hydrops in the horizontal semicircular canal: a morphologic correlate for canal paresis in Ménière's disease. Laryngoscope 123: 503–506, 2013

18) Gürkov R, Flatz W, Louza J, et al.: In vivo visualized endolymphatic hydrops and inner ear functions in patients with electrocochleographically confirmed Ménière's disease. Otol Neurotol 33: 1040–1045, 2012

19) Fiorino F, Pizzini FB, Beltramello A, et al.: Progression of endolymphatic hydrops in Ménière's disease as evaluated by magnetic resonance imaging. Otol Neurotol 32: 1152–1157, 2011

Characteristics and Prognosis of Hearing Loss Associated with Vogt-Koyanagi-Harada Disease

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Abstract

Objective: To clarify the characteristics and prognosis of hearing loss associated with Vogt-Koyanagi-Harada (VKH) disease. *Methods:* We retrospectively examined 85 patients diagnosed with VKH disease between January 1996 and December 2012. The control group included age- and gender-matched individuals without definitive ear disease. The patients with VKH disease were treated with high-dose systemic corticosteroids, which were tapered off gradually over a period of 6 months or more by the treating ophthalmologists according to the severity of the ocular inflammation. The features of hearing loss were analyzed based on pure tone audiometric data obtained at the initial presentation according to diagnostic criteria based on the ISO 7029 standard. The efficacy of corticosteroid therapy was evaluated by audiometry at the initial presentation and during therapy for 3–6 months. *Results:* In patients with VKH disease, the rate of hearing loss detected by audiometry was significantly higher than that of either subjective hearing loss (p < 0.001) or tinnitus (p < 0.001). Bilateral symmetrical hearing loss was the most common type of auditory disturbance associated with VKH disease. The degree of hearing loss was generally low, with no patients showing profound hearing loss. Hearing thresholds were significantly elevated at high frequencies compared with those at low-to-mid frequencies (p < 0.001). Hearing thresholds at all frequencies after high-dose corticosteroid therapy were significantly better than those at initial presentation (p < 0.001), and the rate of patients who returned to within normal-range pure tone thresholds at all frequencies was 74.8%. *Conclusions:* As auditory manifestations cannot be detected through history taking alone, audiometry should be performed to evaluate hearing loss associated with VKH disease. Early administration of high-dose systemic corticosteroids is effective for treating the auditory manifestations, which generally show a relatively good short-term prognosis. © 2013 S. Karger AG, Basel

Introduction

Vogt-Koyanagi-Harada (VKH) disease is an idiopathic, multisystem autoimmune disorder characterized by bilateral granulomatous uveitis with neurologic, auditory or dermatologic manifestations. The pathophysiology of

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this disorder involves T-cell-mediated autoimmunity against melanocyte-associated antigens in the choroid, meninges, cochlea and skin [Sugita et al., 2006]. Patients with VKH disease typically present with symptoms of aseptic meningitis initially followed by bilateral uveitis. Dermatologic changes occur several weeks or months after the onset of the ocular symptoms [Mondkar et al., 2000]. Otologic complaints may include sensorineural hearing loss, tinnitus and/or vertigo that typically coincide with the onset of ocular pathology [Kitamura et al., 2005; Ondrey et al., 2006].

The diagnosis of VKH disease is based on ocular and systemic symptoms and signs, established according to the revised diagnostic criteria for VKH disease by an international committee on nomenclature [Read et al., 2001]. Among these diagnostic criteria, extraocular symptoms and signs include neurologic, auditory and dermatologic findings. Although there have been reports of VKH patients with auditory manifestations other than tinnitus [Kitamura et al., 2005; Ondrey et al., 2006], the current diagnostic criteria only include tinnitus, not hearing loss, as an auditory finding. Meanwhile, the nature and extent of hearing loss associated with VKH disease has not been described well in the literature.

In this retrospective study, we analyzed auditory system abnormalities in patients diagnosed with VKH disease, with the aim of clarifying the characteristics and prognosis of hearing loss associated with VKH disease.

Materials and Methods

Patients and Controls

We retrospectively examined consecutive patients diagnosed with VKH disease in the Department of Otolaryngology – Head and Neck Surgery, Hokkaido University Hospital, between January 1996 and December 2012. We used the revised diagnostic criteria for VKH disease of the international committee on nomenclature [Read et al., 2001], as follows:

1 No history of penetrating injury or surgery
2 No clinical or laboratory evidence suggestive of other ocular disease
3 Bilateral ocular involvement consisting of anterior uveitis and diffuse or multifocal choroiditis with or without evidence of a retinal detachment; late manifestations or ocular findings consist of areas of retinochoroid depigmentations, nummular chorioretinal depigmented scar, retinal pigment epithelial clumping and peripapillary chorioretinal atrophy with or without chronic anterior uveitis
4 Neurologic and auditory findings include meningismus, malaise, fever, headache, stiffness of the back or neck, tinnitus or cerebrospinal fluid pleocytosis

5 Dermatologic findings of alopecia, poliosis and vitiligo

A diagnosis of 'complete VKH disease' was based on all 5 criteria being met, and of 'incomplete VKH disease' on criteria 1–3 and either criterion 4 or 5. A diagnosis of 'probable VKH disease' was based on criteria 1–3 only being met. Both patients with complete and those with incomplete VKH disease were included in this analysis. We excluded patients with definitive ear disease such as chronic otitis media, Ménière's disease, familial hearing loss, chronic noise exposure, ototoxic drug intake, head trauma, acoustic neuroma and inner ear malformation, and also those with a history of metabolic, neurological vascular, systemic and autoimmune disease, such as diabetes mellitus, hypercholesterolemia, cerebral infarction, encephalorrhagia, hypertension, ischemic heart disease, hypothyroidism, sarcoidosis and connective tissue disease. Presbycusis is the most common hearing problem in older people. In general, people aged over 50 years are likely to lose some hearing each year [Gates and Mills, 2005]. Therefore, we divided the subjects into those aged 50 years or under and those over 50 years.

The control group included age- and gender-matched ear-disease-free individuals who visited our department for physical examination during the same period. They had no history of the diseases described above for the patient groups. This research adhered to the tenets of the Declaration of Helsinki and was approved by our institutional review board.

Examination

We performed a number of routine tests, including history taking, physical examination, pure tone audiometry, impedance audiometry, distortion product otoacoustic emissions (DPOAE), and magnetic resonance imaging and/or computed tomography imaging. Apart from routine blood tests including a full blood count and blood biochemistry, serological and immunological tests were used to screen for other ocular and otologic diseases. These tests included those for rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, angiotensin-converting enzymes, Krebs von den Lungen-6, soluble interleukin-2 receptor and human T-cell lymphotropic virus type 1 antibodies as well as a *Treponema pallidum* hemagglutination test.

Audiometric Data

Audiometry was performed using a pure tone audiometer (AA-76; Rion Co., Japan) in a silent cabin by experienced audiologists. The pure tone thresholds for each ear were determined at frequencies of 125, 250, 500, 1,000, 2,000, 4,000 and 8,000 Hz for air conduction, and at 250, 500, 1,000, 2,000 and 4,000 Hz for bone conduction, with masking as appropriate. There are no specific diagnostic and outcome criteria for hearing loss associated with VKH disease. Thus, based on the ISO 7029 standard [International Organization for Standardization, 2000], hearing loss in this analysis was considered to exist if the pure tone thresholds were greater than or equal to the age-specific 95th percentile of the normal population for at least 1 frequency. We evaluated the hearing thresholds during high-dose corticosteroid therapy for 3–6 months from initial presentation. Recovery from hearing loss was concluded if the pure tone thresholds at all frequencies returned to within normal ranges at the final audiogram.

The severity of hearing loss was categorized into 5 grades based on the initial pure tone audiogram, using the World Health Organization (WHO) classification [World Health Organization, 2000]:

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