first visit, suggesting left MD at that time. CT demonstrated bony erosion around the retrolabyrinthine air cells in the left ear (Figure 1B) and MRI revealed a T1 moderate, T2 moderate, and gadolinium slightly enhanced lesion at the area concerned with CT findings (Figure 1C). This case was clinically diagnosed as left ELST and taken for tumor removal surgery.

According to the surgical processes of endolymphatic sac decompression [9], a simple mastoidectomy was performed and the endolymphatic sac was clearly exposed in the area between the sigmoid sinus and the inferior margin of the posterior semicircular canal. An oozing inflammatory tumor-like lesion was located adjacent to the endolymphatic sac (Figure 2A). The lesion was totally resected with adequate retrolabyrinthine air cells. This case was histopathologically diagnosed as inflammatory granulation adjacent to the endolymphatic sac, i.e. pseudo-ELST (Figure 2B) [1].

Five years later, vertigo was completely controlled and the hearing level in the left ear was kept at the preoperative level. This case was followed up with MRI at 2 year intervals.

Case 2

A 49-year-old male patient visited our hospital in 2009 with complaints of bilateral hearing loss and tinnitus with episodic vertigo. He had suffered from fluctuating sensorineural hearing loss with no vertigo in the right ear since 2004 and then progressive sensorineural hearing loss with episodic vertigo in the left ear since 2006. He showed moderate sensorineural hearing loss bilaterally with positive signs in the G-test (Figure 3A) and ECoG only in the left side, and moderate semicircular canal paresis in the left side at the first visit, suggesting bilateral MD at that time. CT demonstrated bony erosion around the retrolabyrinthine air cells, vestibular aqueduct, and posterior semicircular canal only in the left side (Figure 3B) and MRI revealed a T1 moderate, T2 moderate, and gadolinium slightly enhanced lesion at the area concerned with CT findings (Figure 3C). This case was also clinically diagnosed as left ELST with idiopathic fluctuating hearing loss on the right side and taken for tumor removal surgery.

Through the same surgical processes as in case 1, the endolymphatic sac was clearly exposed in the area between the sigmoid sinus and the inferior margin of the posterior semicircular canal. A tumor was observed to generate from the intraosseous endolymphatic sac (Figure 4A). The tumor was totally resected with adequate retrolabyrinthine air cells and part of intact tissues of the vestibular aqueduct and posterior semicircular canal. Fascia was inserted between the posterior semicircular canal and posterior fossa dura. This case was histopathologically diagnosed as benign papillary adenoma of the endolymphatic sac, i.e. ELST (Figure 4B). Brain CT detected an angioma-like lesion adjacent to the fourth ventricle, indicating von Hippel Lindau disease (VHL) syndrome (data not shown) [10]. However, a couple of genetic examinations for VHL syndrome were negative [11], resulting in the case being followed as suspected VHL syndrome.

Two years later, vertigo was completely controlled but the hearing level in the left ear was totally deaf. This case was followed up with hearing aids in the right better hearing ear and examined with MRI once a year.

Molecular examination for vasopressin receptor

Patients and controls. Before surgery, we obtained permission for collection of the endolymphatic sac

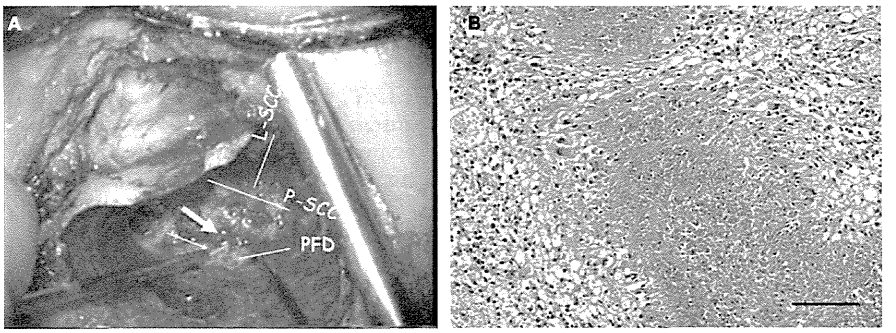


Figure 2. Surgical (A) and histopathological (B) findings in case 1. (A) An oozing inflammatory tumor-like lesion (T, thick arrow) was observed adjacent to the intact endolymphatic sac (ELS, thin arrow). (B) Histopathological observation diagnosed as inflammatory granulation, i.e. pseudo-endolymphatic sac tumor. L-SCC, lateral semicircular canal; P-SCC, posterior semicircular canal; PFD, posterior fossa dura.

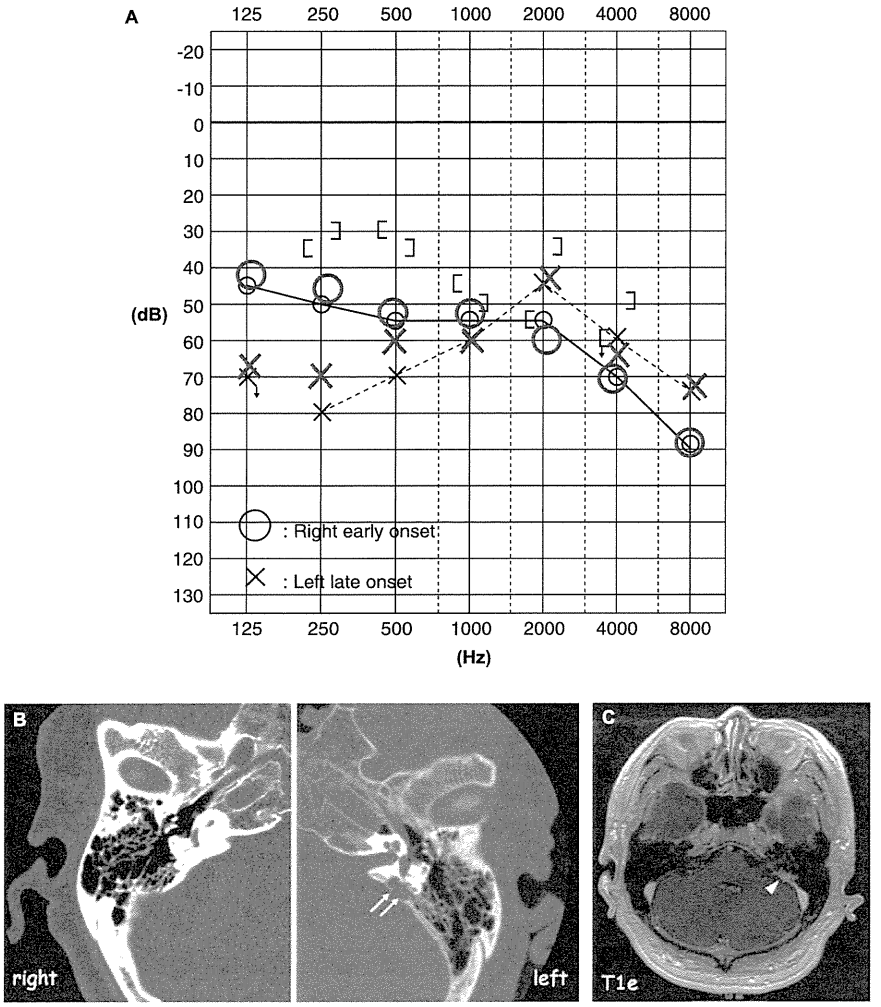


Figure 3. Audiogram (A), CT (B), and MRI (C) findings in case 2. (A) Case 2 showed moderate sensorineural hearing loss bilaterally with positive glycerol test only in the left side at the first visit, suggesting bilateral Meniere's disease at that time. The gray-colored O and X stand for hearing level 2 h after 2.6 ml/kg of 50% glycerol intake in the right side and left side, respectively. (B) CT demonstrated bony erosion around the retrolabyrinthine air cells, vestibular aqueduct, and posterior semicircular canal (arrows) only in the left side. (C) MRI revealed a T1-weighted gadolinium-enhanced lesion (T1e) at the area concerned with CT findings above (arrowhead), diagnosed as left endolymphatic sac tumor.

tissue during surgery from both the patients with ELST described above. Four tissue samples were obtained from different portions of the endolymphatic sac in each case with ELST to determine the average ± standard deviation (SD) of amounts of V2R expression. We also prepared 12 MD cases as examples of endolymphatic hydrops disease and 6 vestibular schwannoma (VS) cases as a non-endolymphatic hydrops disease control [4]. VS patients with direct endolymphatic sac damage and/or with positive signs in the G-test/ECoG were excluded from the present study. Tissue samples from a part of the endolymphatic sac, in ELST, MD, and VS groups, were collected during surgery (endolymphatic sac drainage for MD, and schwannoma removal surgery for VS). There were no significant differences in patients' background (sex, age) between MD (M:F = 4:5, 47.9 ± 4.9) and VS (M:F = 3:3, 53.0 ± 6.5).

Tissue preparation. For real-time PCR (ELST, 1–2; MD, 1–12; VS, 1–6), tissues were obtained from the endolymphatic sac during each type of surgery, replaced immediately in chilled phosphate-buffered saline (pH 7.3) and frozen with dry ice powder.

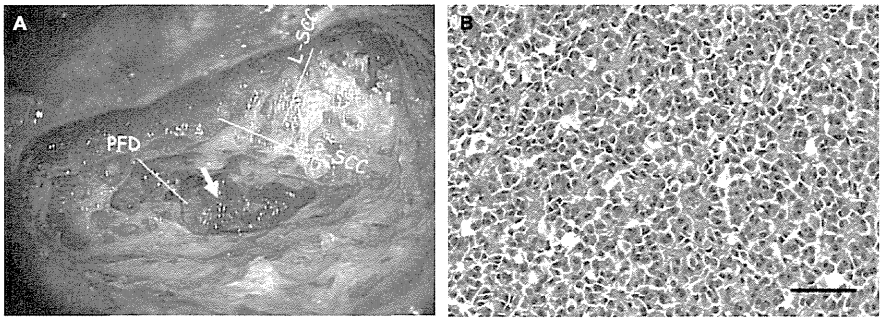


Figure 4. Surgical (A) and histopathological (B) findings in case 2. (A) An endolymphatic sac tumor (ELST, thick arrow) was generated from the part of intraosseous endolymphatic sac. (B) Histopathological observation diagnosed as papillary adenoma of ELST. L-SCC, lateral semicircular canal; P-SCC, posterior semicircular canal; PFD, posterior fossa dura.

Real-time PCR. Total RNA was extracted from dissected frozen tissues using TRIzol reagents (Gibco BRL, USA). Briefly, samples were homogenized in 0.8 ml of TRIzol reagent. Chloroform was then added and the mixture was centrifuged to separate the RNA phase from the DNA phase. The RNA phase was used for RNA precipitation using isopropyl alcohol. The RNA samples were rinsed with ethanol and dissolved with RNase-free water. Finally, the RNA samples were treated with RNase-free Dnase I (Roche, USA) to remove contaminated genomic DNAs before reverse transcription.

The reverse transcription mixture included 10 µl of 10× PCR Taq Gold buffer II (Applied Biosystems, USA), 30 µl of 25 mM $MgCl_2$, 4 µl of 25 mM of each dNTP, 5 µl of 100 µM of random primers (Gibco BRL), 2 µl of RNasin (Applied Biosystems, USA), 1.25 µl of Super-Script II (Applied Biosystems, USA), and 5 µl (250 ng) of DNA-free total RNA in a final volume of 100 µl. The mixture was incubated at 25°C for 10 min, 48°C for 30 min, and 95°C for 5 min in a 9600 Thermocycler (Applied Biosystems, USA).

Samples with reverse transcriptase were forwarded for PCR (95°C for 12 min and 35 cycles at 95°C for 15 s and 60°C for 1 min) and electrophoresed on 1.5% agarose gel to check the results of reverse-transcriptase PCR. Samples without reverse transcription were also forwarded for PCR as negative controls to insure there was no genomic DNA contamination.

PCR products were electrophoresed on 3% Seakem GTG agarose gel (FMC Bioproducts, USA) and purified using QIA quick Gel Extraction Kit (QIAGEN, USA). Sequencing was accomplished by means of an ABI Prism dRhodamine Terminator Cycle Sequencing Ready Reaction Kit with ABI 310 DNA sequencer (Applied Biosystems, USA).

PCR reactions were performed in the presence of the oligonucleotide primers for V2R (Takara, Japan) and β-2 microglobulin (B2M) (Takara, Japan) shown in Table I and quantified by SYBR Green PCR reagents (Applied Biosystems, USA). B2M, an endogenous housekeeping gene, was used as an internal control for this method. Each sample determination was performed in triplicate.

The PCR mixture included 5 µl of 10× SYBR PCR buffer, 6 µl of 25 mM $MgCl_2$, 4 µl of each dNTP (blended with 2.5 mM dATP, dGTP, and dCTP, and 5 mM dUTP), 2.5 µl of each gene-specific primer (5 µM), 0.5 µl of AmpErase UNG (0.5 units), 0.25 µl of AmpliTaq Gold (1.25 units), and 5 µl of cDNA (250 ng) in a final volume of 50 µl. The conditions for the real-time PCR were as follows: 50°C for 2 min, 95°C for 12 min, and 35 cycles at 95°C for 15 s and 60°C for 1 min in an ABI PRISM 7700 Sequence Detection System (Applied Biosystems, USA). 7700 Sequence Detection software was used for instrument control, automated data collection, and data analysis.

Data analysis. The number of PCR cycles was recorded until the fluorescence intensity exceeded the predetermined threshold. The quantification of the initial amounts of template molecules relied on this number

Table I. Gene-specific primers for real-time PCR of human V2 receptor and β-2 microglobulin.

Gene	Primer
V2 receptor (NM: 000054)	fw: actgtgaggatgacgctagtgattg
	rv: ggacacgctgctgctgaaag
β-2 Microglobulin (NM: 004048)	fw: cgggcattcctgaagctga
	rv: ggatggatgaaacccagacacatag

fw, forward primer; rv, reverse primer.

of PCR cycles, which is termed the cycle threshold (CT). The dCT represents the CT of the target gene normalized to the human endogenous B2M ($dCT = CT_{target} - CT_{B2M}$). Relative quantification of the mRNA expression levels of target genes (= fold range) was calculated using the 2^{-ddCT} method, where $ddCT = (CT_{target} - CT_{B2M})_A - (CT_{target} - CT_{B2M})_B$ [12]. V2R gene expression in the endolymphatic sac of ELST compared with that of VS was quantified as the fold range: 2^{-ddCT} ($ddCT = (CT_{V2R} - CT_{B2M})_{ELST} - (CT_{V2R} - CT_{B2M})_{VS}$), when amounts of V2R mRNA expression of a case of VS were defined as 1.

Statistical analysis

Statistical differences in patients' backgrounds (sex, age) between MD and VS were examined by Mann-Whitney U test. Statistical differences in the data between MD and VS in Figure 5 were determined by unpaired t test. All the values of $p < 0.05$ were considered to indicate statistical significance. All the statistical analyses in the present study were carried out using SPSS version 14.0 (SPSS Inc., USA).

Results

Histopathologically, the first case was diagnosed as inflammatory granulation adjacent to the apparently intact endolymphatic sac, i.e. pseudo-ELST as described previously (Figure 2B) [1]. The second case was diagnosed as papillary adenoma of ELST generated from part of the intraosseous endolymphatic sac (Figure 4B) [10].

Using real-time PCR methods, V2R mRNA expression both in the intact portion of the endolymphatic sac of case 1 (12.85 ± 4.32 fold) and in ELST of case 2 (17.58 ± 5.23 fold) were up-regulated as seen in MD (n = 12: 24.89 ± 6.65 fold) compared with controls of VS (n = 6: 0.62 ± 0.10 fold) (unpaired t test: $p = 0.022 < 0.05$) (Figure 5).

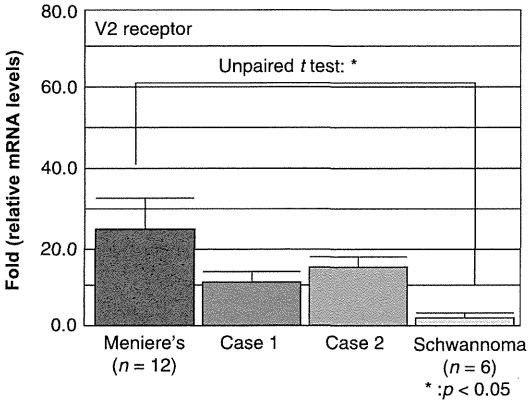


Figure 5. V2 receptor (V2R) mRNA expression levels in the endolymphatic sac (ELS) in endolymphatic sac tumor (ELST) patients. V2R mRNA expression in the ELS in case 1 (12.85 ± 4.32 fold) and that in the ELST in case 2 (17.58 ± 5.23 fold) were up-regulated as seen in Meniere's disease (n = 12: 24.89 ± 6.65 fold) compared with vestibular schwannoma (VS) (n = 6: 0.62 ± 0.10 fold) (unpaired t test: $p = 0.022 < 0.05$). Amounts of V2R mRNA expression of a case of VS patients are defined as 1.

Discussion

We experienced two cases of ELST demonstrating MD-like symptoms [3]. The histopathological examination revealed that one was inflammatory granulation (case 1) and the other was papillary adenoma (case 2). Diaz et al. reported that ELSTs were extremely rare tumors of the petrous temporal bone [1]. Strictly speaking, in case 1, the inflammatory granulation was not a real tumor but a so-called pseudo-ELST, for which the mechanisms of inflammation have not yet been clarified. Lonser et al. reported that papillary adenoma was seen in approximately 10% of ELST patients with VHL syndrome [10]. The syndrome was autosomal dominant, resulting from a germline mutation in the VHL gene on chromosome [11]. The VHL gene was strongly involved in tumor genesis in patients with VHL syndrome, including renal cysts and renal carcinoma, pheochromocytoma, pancreatic cysts, neuroendocrine tumors, cystadenomas of the reproductive adnexal organs, and hemangioblastomas of the cerebellum, spinal cord, brainstem, and retina. Although case 2 had a papillary adenoma in the endolymphatic sac and an angioma-like lesion adjacent to the fourth ventricle, a couple of genetic examinations for VHL syndrome were negative. Although lesions in both cases were surgically removed, the imaging examination should be planned periodically for 5–10 years.

For the first time we report that inner ear hydrops were detected in both cases of ELST by means of neuro-otological examinations [4]. These findings suggest that MD-like symptoms could be due to inner ear hydrops [13,14] induced by ELSTs. Furthermore, the molecular biological examination also revealed that V2R mRNA expression in the endolymphatic sac of both cases of ELST was up-regulated, as seen in MD, compared with controls of VS [5,7]. Based on our recent molecular biological studies in the endolymphatic sac of MD [5,6] and delayed endolymphatic hydrops [7], there was a strong relationship between the pathogenesis of inner ear hydrops and the intracellular signal cascade of V2R in the endolymphatic sac. All these findings suggest that the inflammation in the endolymphatic sac in case 1 and the tumor pressure in the endolymphatic

sac of case 2 might have an effect on the endolymphatic environment, probably through the overexpression of V2R mRNA in the endolymphatic sac.

Regarding vasopressin receptors, V2R molecules were detected in rat [15,16] and human [15,17] inner ear end organs. V2R was clearly distributed together with a V2R-linked water channel molecule, aquaporin-2 (AQP2), in the luminal epithelium of the human endolymphatic sac [17]. Interestingly, the physiological interactions between vasopressin and V2R in the endolymphatic sac attenuated the membranous turnover via cyclic AMP-dependent signaling in a contrasting manner with the kidney in rats [15], and then these interactions also translocated AQP2 from the luminal side to the basolateral side in a contrasting manner with the kidney in human [6]. These findings indicate that V2R and subsequent cyclic AMP-linked signaling could suppress the endolymphatic fluid absorption in the endolymphatic sac, resulting in the inner ear hydrops. In the present study, we detected higher V2R mRNA expression in the endolymphatic sac of ELST patients. All these findings suggest that V2R overexpression in the endolymphatic sac could attenuate the membrane turnover and cause the endolymphatic fluid overflow into the endolymphatic space after even a small increase in plasma vasopressin.

Conclusion

Considering the results of the present ELST study and the discussion above, it is suggested that disorder of V2R signaling in the endolymphatic sac for any reason could be involved in the pathogenesis of inner ear hydrops. Although it is due to tumor genesis in ELST, it is idiopathic in nature in MD. Because of limitations with the number of cases and samples in the present ELST study, further additional investigations should be continued and the results will be reported in later communications.

Acknowledgments

The authors wish to thank Dr Yasusuke Yamagiwa, a registered statistician (certificate number: 0540072), for helpful advice on statistical analysis. This study was supported in part by a Health Science Research Grant for Specific Disease from the Ministry of Health, Labour and Welfare, Japan (2009–2011).

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] Diaz RC, Amjad EH, Sargent EW, Larouere MJ, Shaia WT. Tumors and pseudotumors of the endolymphatic sac. Skull Base 2007;17:379–93.

[2] Hassard AD, Boudreau SF, Cron CC. Adenoma of the endolymphatic sac. J Otolaryngol 1984;13:213–16.

[3] Butman JA, Kim HJ, Baggenstos M, Ammerman JM, Dambrosia J, Patsalides A, et al. Mechanisms of morbid hearing loss associated with tumors of the endolymphatic sac in von Hippel-Lindau disease. JAMA 2007;298:41–8.

[4] Mori N, Asai H, Suizu Y, Matsunaga T. Comparison between electrocochleography and glycerol test in the diagnosis of Meniere's disease. Scand Audiol 1985;14:209–13.

[5] Kitahara T, Doi K, Maekawa C, Kizawa K, Horii A, Kubo T, et al. Meniere's attacks occur in the inner ear with excessive vasopressin type-2 receptors. J Neuroendocrinol 2008;20:1295–300.

[6] Maekawa C, Kitahara T, Kizawa K, Okazaki S, Kamakura T, Horii A, et al. Expression and translocation of aquaporin-2 in the endolymphatic sac in patients with Meniere's disease. J Neuroendocrinol 2010;22:1157–64.

[7] Kitahara T, Maekawa C, Kizawa K, Horii A, Doi K. Plasma vasopressin and V2 receptor in the endolymphatic sac in patients with delayed endolymphatic hydrops. Otol Neurotol 2009;30:812–19.

[8] Committee on hearing and equilibrium. Committee on Hearing and Equilibrium guidelines for diagnosis and evaluation of therapy in Meniere's disease. Otolaryngol Head Neck Surg 1995;113:181–5.

[9] Kitahara T, Kubo T, Okumura S, Kitahara M. Effects of endolymphatic sac drainage with steroids for intractable Meniere's disease. Laryngoscope 2008;118:854–61.

[10] Lonser RR, Kim JH, Butman JA, Vortmeyer, AO, Choo DI, Oldfield EH. Tumors of the endolymphatic sac in von Hippel–Lindau disease. N Engl J Med 2004;350:2481–6.

[11] Shuin T, Yamazaki I, Tamura K, Kamada M, Ashida S. Recent advances in ideas on the molecular pathology and clinical aspects of Von Hippel-Lindau disease. Int J Clin Oncol 2004;9:283–7.

[12] Schmittgen TD, Zakrajsek BA, Mills AG, Gorn V, Singer MJ, Reed MW. Quantitative reverse transcription polymerase chain reaction to study mRNA decay: comparison of endpoint and real-time methods. Anal Biochem 2000; 285:194–204.

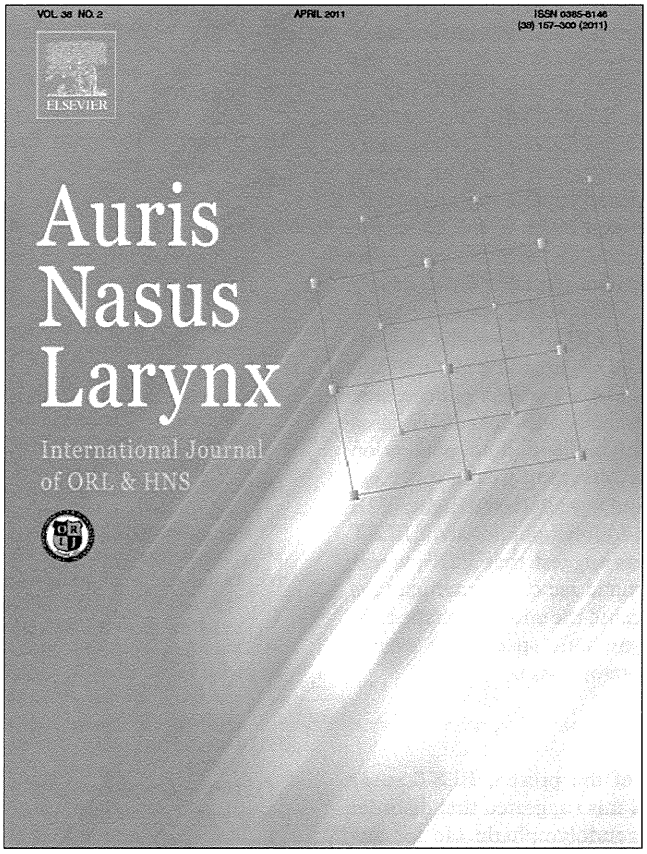
[13] Yamakawa K. Uber die pathologische Veranderung bei einem Meniere-Kranken. J Otolaryngol Jpn 1938;44: 2310–12.

[14] Hallpike CS, Cairns H. Observations on the pathology of Meniere's syndrome. J Laryngol Otol 1938;53:625–55.

[15] Kumagami H, Loewenheim H, Beitz E, Wild K, Schwartz H, Yamashita K, et al. The effect of anti-diuretic hormone on the endolymphatic sac of the inner ear. Pflugers Arch 1998;436:970–5.

[16] Kitano H, Suzuki M, Kitanishi T, Yazawa Y, Kitajima K, Isono T, et al. Regulation of inner ear fluid in the rat by vasopressin. Neuroreport 1999;10:1205–7.

[17] Taguchi D, Takeda T, Kakigi A, Takumida M, Nishioka R, Kitano H. Expressions of aquaporin-2, vasopressin type 2 receptor, transient receptor potential channel vanilloid (TRPV)1, and TRPV4 in the human endolymphatic sac. Laryngoscope 2007;117:695–8.



ELSEVIER

Auris Nasus Larynx 38 (2011) 178–184

AURIS NASUS LARYNX
INTERNATIONAL JOURNAL OF ORL & HNS

www.elsevier.com/locate/anl

Low-tone air-bone gaps after endolymphatic sac surgery

Tadashi Kitahara [a,*], Arata Horii [a], Yasuo Mishiro [b], Takayuki Kawashima [a], Takao Imai [a], Suetaka Nishiike [a], Hidenori Inohara [a]

[a] *Department of Otolaryngology-Head and Neck Surgery, Osaka University, School of Medicine, Osaka, Japan*
[b] *Hyogo Medical Collage, Hyogo, Japan*

Received 13 December 2009; accepted 11 August 2010
Available online 20 October 2010

Abstract

Objectives: We detected chronic low-tone air-bone gaps (LTABGs) in some patients with Meniere's disease after endolymphatic sac surgery. The aim of the present study was to elucidate the mechanism of LTABGs after endolymphatic sac surgery.
Methods: We investigated 50 patients with Meniere's disease, who underwent surgery more than two years prior. LTABGs were defined as the three-tone-average = 20 dB formulated by $(a + b + c)/3$, where a, b, and c are ABGs at 0.25, 0.5, and 1 kHz, respectively (ABG ±). The intra-operative finding was focused on identifying operculum (OPC ±).
Results: The ratio of post-operative ABG(+) was 50.0% (25/50). The ratio of intra-operative OPC(+) was 72.0% (36/50). The surgery results were as follows: the ratio of complete vertigo suppression (VS(+)) was 84.0% (42/50), air-conduction hearing gain (aHG(+)) was 40% (20/50), bone-conduction hearing gain (bHG(+)) was 64% (32/50), and speech discrimination gain (SDG(+)) was 28% (14/50). The post-operative ABG(+) was commonly observed in patients with intra-operative OPC(+) (chi-square test, $p = 0.013$). aHG(+) and SDG(+) results were related to the post-operative ABG(+) (chi-square test, $p = 0.021$ and $p = 0.0018$, respectively).
Conclusions: These data suggest that intra-operative OPC(+) may be causative for post-operative ABG(+), resulting in post-operative aHG(+) and SDG(+). Thus, as enlarged vestibular aqueduct syndrome and superior semicircular canal deficiency syndrome exhibit LTABGs due to the third mobile inner ear window, endolymphatic sac surgery with adequate endolymphatic sac decompression and exposure to high doses of steroids, might induce LTABGs and the beneficial results of endolymphatic sac surgery.

Keywords: Meniere's disease; Endolymphatic sac surgery; Air-bone gaps; Mastoidectomy; The third mobile window

1. Introduction

We previously detected the common occurrence of chronic low-tone air-bone gaps (LTABGs) after endolymphatic sac surgery in patients with Meniere's disease at our hospital. CT scan showed no remarkable findings in the tympanomastoid cavity. Despite LTABGs, speech discrimination (SD) test and tympanometry indicated that the post-operative hearing loss was actually sensorineural. There are a few reports suggesting the presence of LTABGs in some Meniere's disease patients before surgery, however the incidence was low and the size of gaps was limited [1,2]. The aim of the present retrospective study was to elucidate the mechanism of chronic LTABGs in patients with Meniere's disease after endolymphatic sac surgery by means of several neurotologic examinations together with the intra-operative findings.

2. Materials and methods

2.1. Diagnosis

Patients were eligible for enrollment if they had received a clinical diagnosis of Meniere's disease according to the 1995 AAO-HNS criteria [3]. In brief, these criteria were as

Abbreviations: aHG, air-conduction hearing gain; bHG, bone-conduction hearing gain; EVA, enlarged vestibular aqueduct syndrome; LTABG, low-tone air-bone gap; OPC, operculum; PFD, posterior fossa dura; SDG, speech discrimination gain; SCCD, superior semicircular canal deficiency syndrome; VS, vertigo suppression.

* Corresponding author at: Department of Otolaryngology-Head and neck surgery, Osaka University School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan. Tel.: +81 6 6879 3951; fax: +81 6 6879 3959.
E-mail address: tkitahara@ent.med.osaka-u.ac.jp (T. Kitahara).

0385-8146/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.anl.2010.08.002

follows: (1) Repeated attacks of vertigo: a definitive spell was spontaneous vertigo lasting at least 20 min, and a mixed type of spontaneous nystagmus observed during attacks. (2) Fluctuating cochlear symptoms: the hearing test usually reveals marked fluctuation of the threshold in the low and middle tone range. (3) Exclusion of other causes: to exclude other disorders, a thorough history, and neurological, neurotological, and MRI examinations were performed. Intractable Meniere's disease was designated in cases where various forms of medical and psychological management failed for at least six months. Medical management included diuretics, betahistine, diphenidol, dimenhydrinate, and

Table 1
Raw data for the 50 Meniere's disease cases.

Case no.	Sex	Age (years)	Op-ex (months)	ABGpre	ABGpost	OPC	PFD	VS	aHG	bHG	SDG
1	F	55	25	−	+	+	+	+	+	+	+
2	F	63	60	−	+	+	+	+	+	+	+
3	M	48	25	−	+	+	−	−	−	−	−
4	F	39	110	−	+	+	+	+	+	+	+
5	M	55	69	−	+	+	−	+	−	−	−
6	F	68	80	−	+	+	+	+	+	+	−
7	F	30	70	−	+	+	+	+	−	−	−
8	F	40	36	−	+	−	−	+	−	+	−
9	M	58	48	−	+	+	+	+	+	+	+
10	F	45	26	−	+	−	−	+	−	+	−
11	M	60	48	−	+	+	+	+	−	−	−
12	F	65	36	−	+	+	+	+	+	+	+
13	M	61	30	−	+	+	+	+	+	+	+
14	M	56	26	−	+	+	+	−	−	+	−
15	M	50	84	−	+	−	−	+	−	−	−
16	F	43	36	−	+	+	+	+	+	+	+
17	F	35	27	−	+	+	−	+	−	+	−
18	M	57	42	−	+	+	+	+	+	+	+
19	F	42	60	−	+	+	+	+	+	+	+
20	M	66	42	−	+	+	+	−	−	−	−
21	F	71	70	−	+	+	−	+	−	−	−
22	F	68	36	−	+	+	+	+	+	+	+
23	M	56	63	−	+	+	+	+	+	+	−
24	F	44	36	−	+	+	+	+	+	+	+
25	F	65	44	−	+	+	+	+	+	+	+
26	F	33	42	−	−	+	+	+	−	−	−
27	M	42	108	−	−	−	−	−	−	−	−
28	M	52	40	−	−	+	+	+	−	+	−
29	F	57	41	−	−	−	−	−	−	−	−
30	M	66	30	−	−	+	+	+	+	+	+
31	M	60	41	−	−	−	−	+	−	+	−
32	F	50	44	−	−	+	+	+	−	−	−
33	M	72	66	−	−	−	−	+	−	+	−
34	F	66	42	−	−	−	+	+	−	+	−
35	M	52	52	−	−	+	+	+	+	+	+
36	M	44	60	−	−	−	−	−	+	+	−
37	F	55	81	−	−	+	+	+	−	−	−
38	M	38	42	−	−	+	−	+	−	−	−
39	F	42	60	−	−	−	−	+	−	+	−
40	F	68	33	−	−	+	+	+	−	+	−
41	F	67	28	−	−	+	−	+	−	−	−
42	M	49	61	−	−	+	+	−	−	−	−
43	M	64	56	−	−	+	+	+	−	+	−
44	F	66	42	−	−	−	−	+	+	+	−
45	M	45	29	−	−	+	+	+	−	−	−
46	M	41	65	−	−	+	−	+	−	+	−
47	M	39	50	−	−	−	−	−	−	−	−
48	F	40	74	−	−	−	−	+	−	−	−
49	M	52	51	−	−	+	−	+	+	+	−
50	F	57	66	−	−	−	+	+	+	+	−

The raw data included sex (M/F), age of the latest examination (age: years), interval between operation and examination (op-ex: months), air-bone gaps before surgery (ABGpre: ±), air-bone gaps after surgery (ABGpost: ±), identifying operculum during surgery (OPC: ±), exposing posterior fossa dura by CT scan (PFD: ±), results of vertigo suppression (VS: ±), air-conduction hearing gain (aHG: ±), bone-conduction hearing gain (bHG: ±), and speech discrimination gain (SDG: ±).

diazepam, which are considered effective for treatment of persistent symptoms in Meniere's disease [4].

2.2. Surgery

One hundred and forty-five cases designated as having intractable Meniere's disease had endolymphatic sac surgery from 1997 to 2006 [5–7]. The endolymphatic sac surgery procedure involved a simple mastoidectomy that clearly exposed the endolymphatic sac in the area between the sigmoid sinus and the inferior margin of the posterior semicircular canal. If possible, the sac including the rugose portion was exposed until the operculum was identified indirectly under the sac. The sac was opened with an L- (right ear) or backward L- (left ear) shaped incision made along the posterior and distal margins of the lateral wall, and the sac was then filled with a mass of 20 mg of prednisolone. While dissolving the mass in the sac, we prepared a bundle of absorbable gelatin films (approximately 4 mm × 20 mm × 0.7 mm with five sheets) with fan- and stick-shaped ends. These films were tied to each other with biochemical adhesive (human thrombin combined with human fibrinogen) at the stick-shaped end. The fan-shaped end was then inserted into the sac, and small pieces of absorbable gelatin sponge soaked in a high concentration of dexamethasone (32 mg/4 ml) were placed inside and outside the sac lumen expanded with the bundle. The sponges containing dexamethasone placed outside the sac were coated with the adhesive so that dexamethasone was slowly delivered into the sac over a long period of time as a natural sustained-release vehicle. The stick-shaped end extending out of the sac was fixed to the front edge of the mastoid cavity with the same adhesive so that the incision into the sac was also expanded as long as possible. The mastoid cavity was filled with relatively large pieces of absorbable gelatin sponge dipped in steroid antibiotic solution, after which the wound was closed with skin sutures.

2.3. Patients

Between April 2008 and March 2009, we examined 50 out of 145 consecutive patients with Meniere's disease who had undergone surgery more than two years prior and permitted to be enrolled into the present study, using several neurotologic examinations and temporal bone CT scan findings together with the intra-operative findings (Table 1). The enrollment was ended as soon as the number of patients was 50. The cases included 24 females and 26 males with a mean age of 53.1 years (30–72 years). The average duration from the day of surgery to the day of medical examination was 50.7 months (25–110 months). LTABGs were defined as the three-tone-average $\geq$ 20 dB formulated by $(a + b + c)/3$, where a, b, and c are ABGs at 0.25, 0.5, and 1 kHz, respectively (ABG ±). The intra-operative findings were focused on identifying operculum (OPC) in operation records (OPC ±), while the CT scan findings involved exposing the posterior fossa dura (PFD) around the vestibular aqueduct in the latest 1.0 mm horizontal CT slices (PFD ±). At least two of three 1.0 mm horizontal CT slices were judged as PFD clearly exposed to the mastoid cavity, and were defined as PFD(+). Both the OPC(+) and PFD(+) are supposed to be not the best but good markers for enough exposure of endolymphatic sac to the mastoid cavity, although it is not always possible to identify OPC intraoperatively due to the anatomical reason and detect exposure of PFD due to the CT analysis limitation. The SD test, tympanometry and stapedial reflex test were used to determine whether the post-operative hearing loss was conductive or sensorineural.

2.4. Evaluations

A definitive spell lasting more than 20 min was regarded as a Meniere's vertigo attack according to the 1995 AAO-HNS criteria [3]. The frequency of vertigo was calculated based on the number of vertigo attacks during the six months prior to treatment. The frequency of vertigo after treatment at the third follow-up year for example, was calculated based on the number of vertigo attacks during the six months between 30–36 months after treatment. 'Complete' control of vertigo at the third follow-up year was classified as no vertigo attacks during that period, 'better' was classified as $0 <$ after/before ≤ 0.8, 'worse' was classified as $1.2 \leq$ after/before, and the others as 'no change'.

Hearing functions were measured by pure-tone audiometry and the SD test according to the 1995 AAO-HNS criteria [3]. Pure-tone audiometry was evaluated based on the four-tone-average formulated by $(a + b + c + d)/4$, where a, b, c, and d are hearing levels at 0.25, 0.5, 1, and 2 kHz, respectively. The SD test was evaluated based on the percentage of correct answers out of ten words. The worst hearing level during the six months prior to treatment was adopted as the hearing level before treatment, and the worst hearing level during the six months between 42 and 48 months after treatment for example, was adopted as the hearing level at the fourth follow-up year. More than 10 dB or 10% differences in hearing levels before and after treatment were regarded as 'better', less than −10 dB or −10% differences as 'worse', and the others as 'no change'.

2.5. Statistical analysis

Statistical differences in patient sex, age, and interval between operation and examination between ABG(+) and ABG(−) groups were examined by Mann–Whitney U-test. Statistical differences of the data (±) among these groups were determined by chi-square test. $p < 0.05$ was considered statistically significant. All the statistical analyses were performed with SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

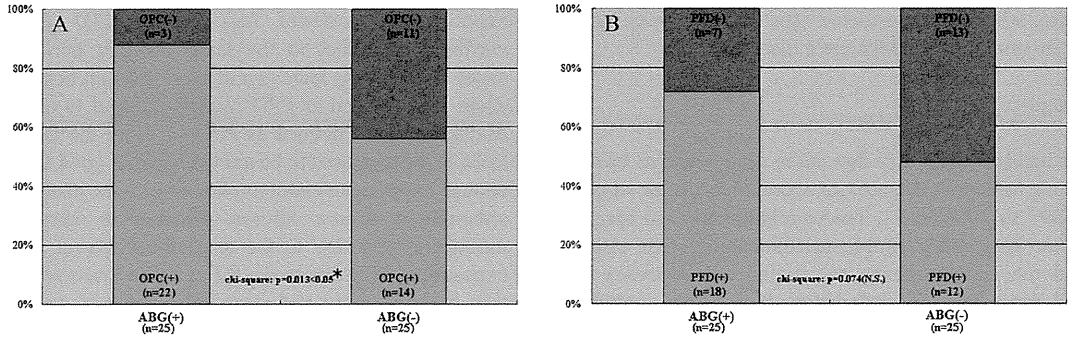


Fig. 1. Post-operative air-bone gaps and structures around the endolymphatic sac. (A) Post-operative air-bone gaps (ABG) were commonly observed in intra-operative operculum-identified patients (OPC) (chi-square test, $*p = 0.013$). (B) There were no significant relationships between the post-operative ABGs and the post-operative posterior fossa dura-exposed CT images (PFD) (chi-square test, $p = 0.074$).

3. Results

The ratio of post-operative ABG(+) was 50.0% (25/50) with no remarkable findings of tympanometry and stapedial reflex test, although no ABG(+) was seen in any cases prior to surgery according to our definition (Table 1). There were no significant differences in the patients' backgrounds between ABG(+) and ABG(−) groups. The ratio of intra-operative OPC(+) was 72.0% (36/50) and the ratio of post-operative PFD(+) was 60.0% (30/50). For surgery results, the ratio of complete vertigo suppression (VS(+)) was 84.0% (42/50), air-conduction hearing gain (aHG(+)) was 40% (20/50), bone-conduction hearing gain (bHG(+)) was 64% (32/50), and SD gain (SDG(+)) was 28% (14/50). Post-operative ABG(+) was commonly observed in patients with intra-operative OPC(+) (chi-square test, $p = 0.013$; Fig. 1A). There were no significant relationships between the post-operative ABG(+) and PFD(+) (chi-square test, $p = 0.074$; Fig. 1B). aHG(+) and SDG(+) were significantly related to post-operative ABG(+) (chi-square test, $p = 0.021$ and

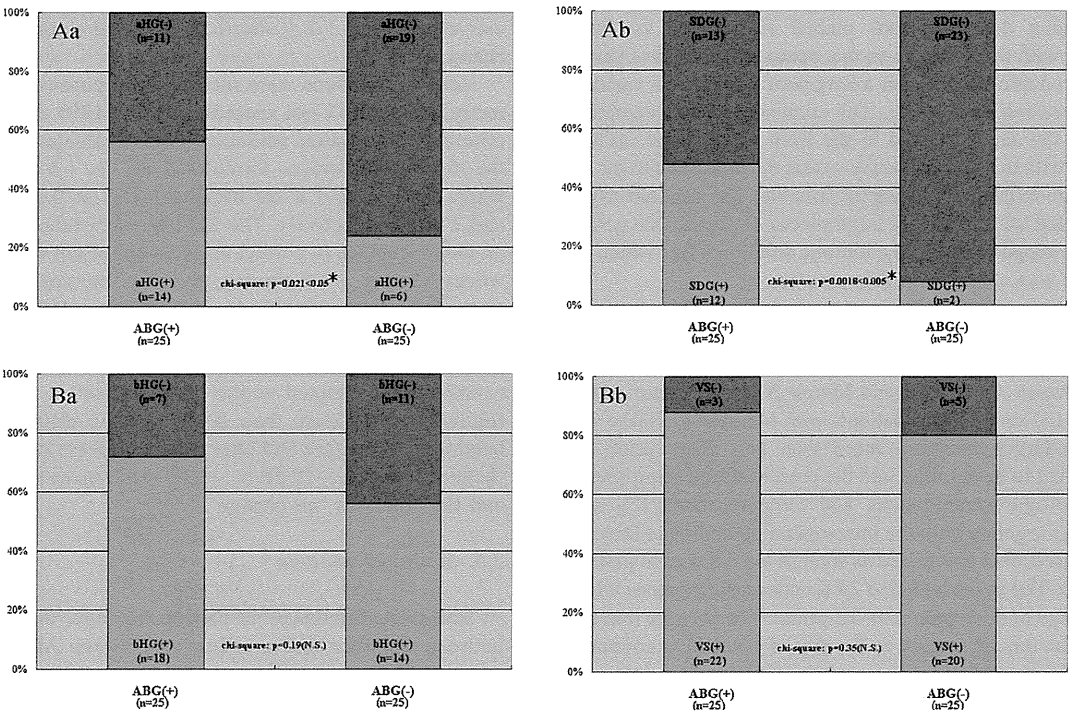


Fig. 2. Post-operative air-bone gaps and affect of endolymphatic sac surgery. (A) Results of air conduction hearing gain (aHG) (Aa) and speech discrimination gain (SDG) (Ab) were significantly related to the post-operative ABGs (chi-square test, $*p = 0.021$ and $*p = 0.0018$, respectively). (B) Results of bone conduction hearing gain (bHG) (Ba) or vertigo suppression (VS) (Bb) were not significantly related to the post-operative ABGs (chi-square test, $p = 0.19$ and $p = 0.35$, respectively).

$p = 0.0018$, respectively; Fig. 2A), while bHG(+) and VS(+) were not (chi-square test, $p = 0.19$ and $p = 0.35$, respectively; Fig. 2B).

A typical case with Meniere's disease (case 4, Table 1) is depicted in Fig. 3. This patient had LTABGs in the right ear for nine years after endolymphatic sac surgery. CT scan showed no remarkable findings in the tympanomastoid cavity and PFD exposed clearly around the posterior semicircular canal-vestibular aqueduct. Despite LTABGs, the SD test and tympanometry indicated that the post-operative hearing loss was sensorineural or mixed.

All 145 cases that received endolymphatic sac surgery demonstrated similar results to those 50 representative cases. The ratio of post-operative ABG(+) was 48.3% (70/145) and the ratio of intra-operative OPC(+) was 72.4% (105/145). Post-operative ABG(+) was commonly observed in patients with intra-operative OPC(+) (chi-square test, $p = 0.0017$; data not shown).

4. Discussion

In our study of 50 representative cases with Meniere's disease, the ratio of post-operative ABG(+) was 50.0%, the ratio of intra-operative OPC(+) was 72.0%, and post-operative ABG(+) was significantly associated with patients

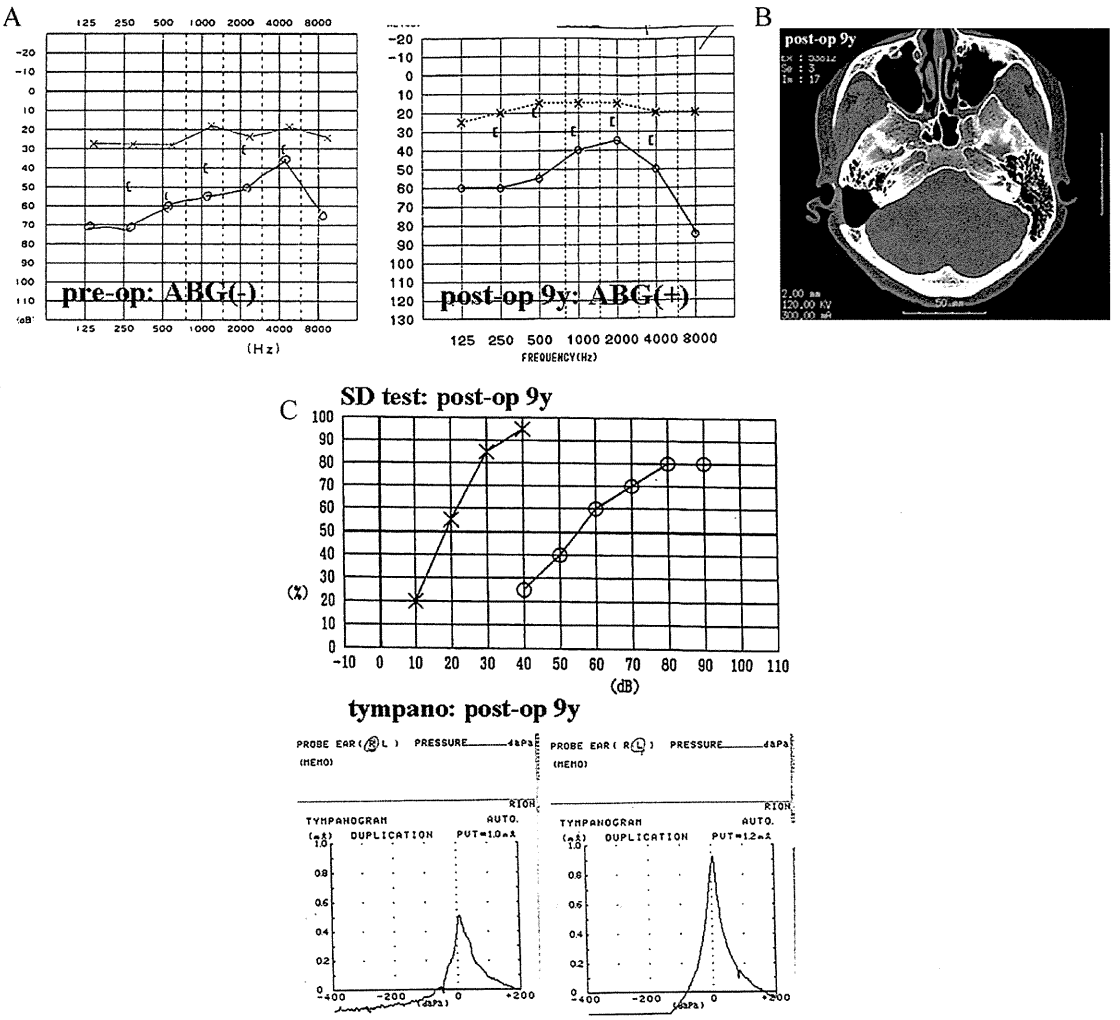


Fig. 3. A typical case with Meniere's disease (case 4, Table 1) showing long-lasting low-tone air-bone gaps after endolymphatic sac surgery. (A) This case with Meniere's disease had low-tone air-bone gaps (ABGs) in the right ear for nine years after endolymphatic sac surgery (post-op 9 year: ABG(+)). There were no ABGs before surgery (pre-op: ABG(−)). (B) CT scan showed no remarkable findings in the tympano-mastoid cavity or posterior fossa dura exposed clearly around the posterior semicircular canal-vestibular aqueduct (arrows) at the ninth post-operative year (post-op 9 year). (C) Despite the good bone conduction at the ninth post-operative year, the speech discrimination test did not reach 100% (SD test: post-op 9 year) and tympanometry was bilaterally type-A (tympano: post-op 9 year), indicating that the post-operative hearing loss was sensorineural.

with intra-operative OPC(+). All 145 cases receiving endolymphatic sac surgery demonstrated similar results. As we usually perform endolymphatic sac surgery to help identify the operculum for adequate exposure of the rugose portion in the area between the sigmoid sinus and the inferior margin of the posterior semicircular canal [8], intra-operative OPC(+) may indicate the subsequent successful removal of osseous pressure around endolymphatic sac and vestibular aqueduct during surgical procedures. According to previous studies, enlarged vestibular aqueduct syndrome (EVA) [9,10] and superior semicircular canal deficiency syndrome (SSCD) [11,12] demonstrate LTABGs due to the third mobile inner ear window other than oval and round windows. Taken together, endolymphatic sac surgery with OPC(+) in Meniere's disease patients might result in a similar condition around the endolymphatic sac to that of EVA, resulting in ABG(+). However, the inner ear structures in Meniere's disease with endolymphatic sac surgery and EVA are totally different. We may try to find another explanation for these postoperative ABGs such as anatomical changes in mastoid-posterior fossa dura-endolymphatic sac. Not only clinical but basic anatomical studies are needed further.

The third mobile window theory of LTABGs in patients with EVA and SSCD was recently reported [13]. EVA and SSCD reduce the sound pressure coming through the oval window, and apparently cause impairment of air conduction similar to a stiffness curve. By comparison, EVA and SSCD reduce the sound pressure at the scala vestibuli and widen the differences of sound compliance between the scala vestibuli and scala tymani, resulting in apparent bone conduction improvement. Thus, impaired air conduction and improved bone conduction may cause the LTABGs in patients with EVA and SSCD. In the present study, the aHG(+) and SDG(+) after endolymphatic sac surgery were 40% and 28%, respectively, and there was a positive relationship between the post-operative ABG(+) and the post-operative aHG(+) and SDG(+). Taken together, these data suggest that endolymphatic sac surgery with adequate opening of the endolymphatic sac, and exposure to high doses of steroids, may actually improve the inner ear function by the therapeutic effects of surgery rather than impairment of the air conduction as per the third mobile window theory. The aHG(±) after endolymphatic sac surgery was calculated by the actual air conduction improvement due to the therapeutic effects of surgery minus the apparent air conduction impairment by the third mobile window theory (aHG after surgery = actual inner ear improvement effect − apparent 3rd mobile window effect).

In the present study, the bHG(+) after endolymphatic sac surgery was markedly greater than the aHG(+) and SDG(+), which, at least partially, may result from the third mobile window-induced effects. However, there were no significant relationships between post-operative ABG(+) and post-operative bHG(+); i.e., most of cases with post-operative ABG(−) also got post-operative bHG(+). Taken together, these data suggest that endolymphatic sac surgery with inadequate opening of the endolymphatic sac, but exposure to high doses of steroids, may also improve the inner ear function by the therapeutic effects of surgery, in addition to improvement of the bone conduction as per the third mobile window theory. The bHG(±) after endolymphatic sac surgery was calculated by the actual bone conduction improvement due to the therapeutic effects of surgery plus the apparent bone conduction improvement by the third mobile window theory (bHG after surgery = actual inner ear improvement effect + apparent 3rd mobile window effect).

In conclusion, endolymphatic sac surgery with identification of operculum and adequate exposure of the rugose portion may induce LTABGs, but improve actual auditory function. There were no relationships between surgical procedures and vertigo results. It was difficult to judge the appropriate surgical procedures by CT scan because of the limitations of imaging analysis. With respect to the third mobile window theory, both pure-tone audiometry and the SD test should be performed to evaluate the actual auditory function after endolymphatic sac surgery.

Acknowledgments

The authors thank Dr. Yasusuke Yamagiwa, a registered statistician (certificate number: 0540072), for helpful advice of statistical analysis.

This study was supported in part by a Health Science Research Grant for Specific Disease from the Ministry of Health, Labour and Welfare, Japan (2007–2009).

References

[1] Muchnik C, Hildesheimer M, Rubinstein M, Arenberg IK. Low frequency air-bone gap in Meniere's disease without middle ear pathology. A preliminary report. Am J Otol 1989;10:1–4.
[2] Yetier S, Kertmen M. Cochlear conductive hearing loss in patients with Meniere's disease. Kulak Burun Bogaz Ihtis Derg 2007;17:18–21.
[3] Committee on hearing and equilibrium. Committee on hearing and equilibrium guidelines for diagnosis and evaluation of therapy in Meniere's disease. Otolaryngol Head Neck Surg 1995;113:181–5.
[4] Claes J, Van de Heyning PH. A review of medical treatment for Meniere's disease. Acta Otolaryngol Suppl 2000;544:34–9.
[5] Kitahara T, Takeda N, Mishiro Y, Saika T, Fukushima M, Okumura S, et al. Effects of exposing the opened endolymphatic sac to large doses of steroids to treat intractable Meniere's disease. Ann Otol Rhinol Laryngol 2001;110:109–12.
[6] Kitahara T, Kondoh K, Morihana T, Okumura S, Mishiro Y, Kubo T. Surgical management for special cases of intractable Meniere's disease: unilateral cases with intact canals and bilateral cases. Ann Otol Rhinol Laryngol 2004;113:399–403.
[7] Kitahara T, Kubo T, Okumura S, Kitahara M. Effects of endolymphatic sac drainage with steroids for intractable Meniere's disease: a long-term follow-up and randomized controlled study. Laryngoscope 2008;118:854–61.

[8] Gianoli GJ, Larouere MJ, Kartush JM. Sac-vein decompression for intractable Meniere's disease: two-year treatment results. Otolaryngol Head Neck Surg 1998;118:22–9.
[9] Nakashima T, Ueda H, Furuhashi A, Sato E, Asahi K, Naganawa S, et al. Air-bone gap and resonant frequency in large vestibular aqueduct syndrome. Am J Otol 2000;21:671–4.
[10] Merchant SN, Nakajima HH, Halpin C, Nadol Jr JB, Lee DJ, Innis WP, et al. Clinical investigation and mechanism of air-bone gaps in large vestibular aqueduct syndrome. Ann Otol Rhinol Laryngol 2007;116:532–41.
[11] Minor LB, Carey JP, Cremer PD, Lustig LR, Streubel SO, Ruckenstein MJ. Dehiscence of bone overlying the superior canal as a cause of apparent conductive hearing loss. Otol Neurotol 2003;24:270–8.
[12] Merchant SN, Rosowski JJ, McKenna MJ. Superior semicircular canal dehiscence mimicking otosclerotic hearing loss. Adv Otorhinolaryngol 2007;65:137–45.
[13] Merchant SN, Rosowski JJ. Conductive hearing loss caused by third-window lesions of the inner ear. Otol Neurotol 2008;29:282–9.

Int. Adv. Otol. 2011; 7:(3) 425-429

CASE REPORT

Secondary Endolymphatic Hydrops Following Sudden Deafness Detected by MRI after Intratympanic Administration of Gadolinium

Arata Horii, Junji Miyabe, Yasuhiro Osaki, Tadashi Kitahara, Takao Imai, Atsuhiko Uno, Suetaka Nishiike, Norihiko Fujita, Hidenori Inohara

Department of Otolaryngology, Suita Municipal Hospital (AH)
Department of Otorhinolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine (AH, TI, AU, SN, HI)
Department of Otolaryngology, Higashiosaka City General Hospital (JM)
Department of Otolaryngology, Faculty of Medicine, Kagawa University (YO)
Department of Otolaryngology, Osaka Rosai Hospital (TK)
Department of Radiology, Osaka University Graduate School of Medicine (NF)

Objective of this report is to alert the existence of secondary endolymphatic hydrops at the beginning of the era for diagnosing the hydrops by image analyses. A 64 years-old female who showed partial recovery of hearing disturbance two months after the onset of sudden deafness underwent inner ear MRI in combination with intratympanic injection of gadolinium. Two-dimensional fluid-attenuated inversion recovery (2D-FLAIR) sequences taken by 3 tesla MR unit showed endolymphatic hydrops in the cochlea. Electrocochleogram could not be performed due to high tone hearing loss. At present, inner ear MRI in combination with intratympanic injection of gadolinium has been mainly used for Meniere's patients to detect endolymphatic hydrops. However, this tool cannot distinguish the secondary hydrops as seen in our case from Meniere's disease and thus should be used with careful attention if used as a routine test for inner ear diseases.

Keywords: secondary endolymphatic hydrops, sudden deafness, MRI, gadolinium

Submitted : 25 February 2011 *Accepted : 15 June 2011*

Introduction

Endolymphatic hydrops is believed to be a pathophysiology of Meniere's disease [1-3]. However, recent cadaver studies revealed the existence of endolymphatic hydrops in temporal bones from non-Meniere's patients without any audio-vestibular symptoms (asymptomatic hydrops) as well as patients with a history of inner ear insults such as middle ear surgery or head trauma but with no Meniere's symptoms (secondary hydrops) [4]. Asymptomatic hydrops might not be a problem in clinical settings, however, this paper suggested that the endolymphatic hydrops does not directly imply the Meniere's disease but we should be aware of the secondary hydrops following inner ear insults [4].

Electrocochleogram (ECoG) has been used for the detection of endolymphatic hydrops, while its usefulness for the detection of hydrops is still controversial. ECoG cannot be performed for patients with profound hearing loss. Recent advances in magnetic resonance imaging (MRI) coupled with intratympanic administration of gadolinium enabled us to visualize the endolymphatic hydrops in a living patient [5-9]. It would be expected that the number of chances we diagnose endolymphatic hydrops by images will be increased in future. However, as

Corresponding address:
Arata Horii
Department of Otolaryngology Suita Municipal Hospital
2-13-20 Katayama-Cho, Suita, OSAKA 564-0082 Japan
Phone: 81-6-6387-3311 • Fax: 81-6-6380-5825
E-mail: ahorii@ent.med.osaka-u.ac.jp

mentioned above, we should distinguish the secondary hydrops from Meniere's disease in the diagnosis and treatment of inner ear diseases, because secondary endolymphatic hydrops is just a result of previous inner ear insults but does not have a causal relation to the latest symptoms of the patient [4]. In the current report, we present a patient with secondary endolymphatic hydrops revealed by 3 tesla (T) MRI in combination with intratympanic gadolinium injection after partial recovery of sudden deafness in whom ECoG could not be performed due to high tone hearing loss.

Case Report

A 64 years-old female patient visited our hospital with complaint of sudden hearing disturbance and tinnitus of the left ear with slight dizziness from two days ago. Pure tone audiogram showed a sensorineural hearing loss involved with all frequencies (Figure 1A). Ear drums were normal and tympanogram showed bilateral type A. She was diagnosed as having left sudden deafness. Combination of intravenous injection of steroid and batroxobin induced partial recovery of patient's hearing disturbance mainly in low frequency (Figure 1B).

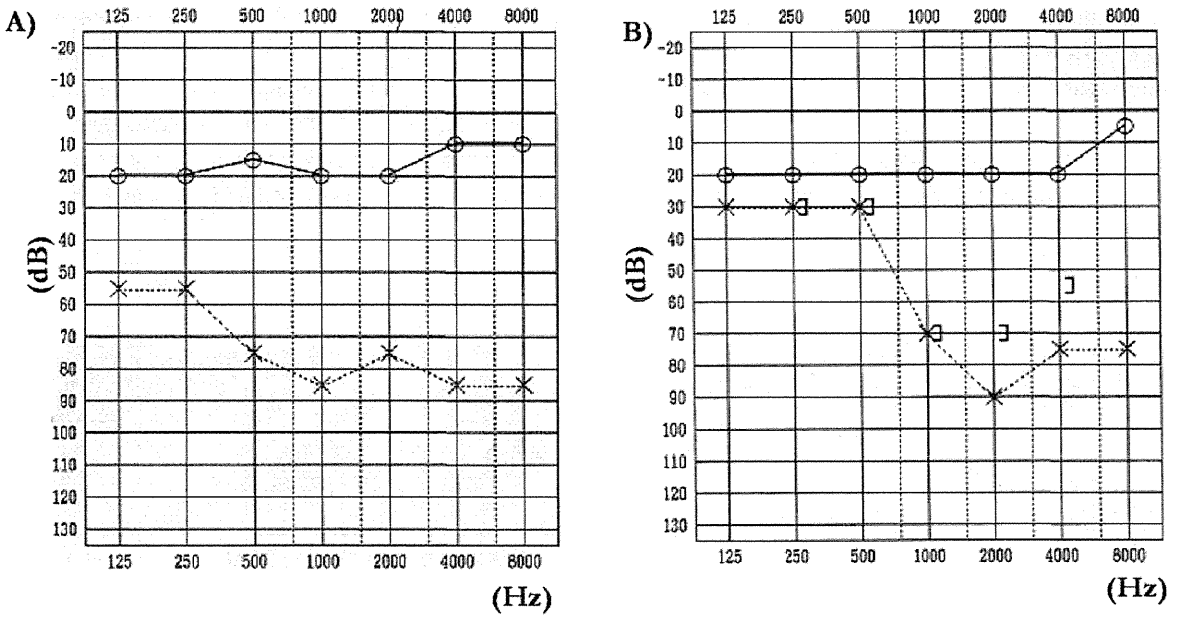


Figure 1. Pure tone audiogram at the time of first visit (A) and just before inner ear MRI two months after the onset of sudden deafness (B) The patient showed profound hearing loss at the first visit (A) and partial recovery of hearing loss was obtained mainly at the low frequency just before the inner ear MRI (B).

Two months after the onset of sudden deafness, she still had a wish for more recovery of hearing and tinnitus suppression. For this purpose, she received an intratympanic injection of steroid. One day before this intervention, endolymphatic image analysis was performed using inner ear MRI with intratympanic injection of gadolinium. The protocol for inner ear MRI in combination with intratympanic injection of gadolinium was approved by Osaka University Hospital (IRB# 08223). Gadodiamide hydrate (Omniscan®) diluted eightfold with saline was injected intratympanically using a 23 gauge needle and syringe. Twenty four hours after the injection, axial images were taken by 3T General Electric (GE) MR unit with fast imaging employing steady state acquisition (FIESTA) and two-dimensional fluid-

attenuated inversion recovery (2D-FLAIR) sequences. As images taken with FIESTA sequence were quite similar to those taken with constructive interference in the steady state (CISS) sequence used by previous studies [4-7], FIESTA images are referred to as CISS images in this study. CISS images are suitable for the detection of the outline of the whole inner ear, because CISS is a heavily T2 weighted images and thus can be sensitive to both the endolymph and the perilymph. Intratympanically injected gadolinium can enter only into the perilymphatic space, leaving the endolymph with no or faint gadolinium enhancement, which explains the good contrast between the perilymph and endolymph in FLAIR sequences [5]. As shown in Fig. 2B, FLAIR images demonstrated that enlarged scala media was shown as low signal intensity area surrounded by perilymphatic space with gadolinium enhancement (arrow). Figure 2A shows a hydrops-negative cochlea in control patient, in which no enlargement of low signal intensity area was shown.

Electrocochleogram showed normal -summating potential/action potential (-SP/AP) for the right ear (-SP/AP=0.37), however, it was impossible to perform for the left ear due to high tone hearing loss. Bithermal caloric test showed left caloric weakness (CP%=60%). Unfortunately, intratympanic injection of steroid had no remarkable effects on her hearing (data not shown). Until the last follow up, she had no fluctuating hearing loss or recurrent vertigo for 22 months.

Discussion

FLAIR images after intratympanic injection of gadolinium showed endolymphatic hydrops in the cochlea, which was shown as low signal intensity area surrounded by perilymphatic space with gadolinium enhancement (Figure 2B, arrow). According to the grading system of endolymphatic hydrops proposed by Nakashima et al. [9], cochlea had a mild hydrops.

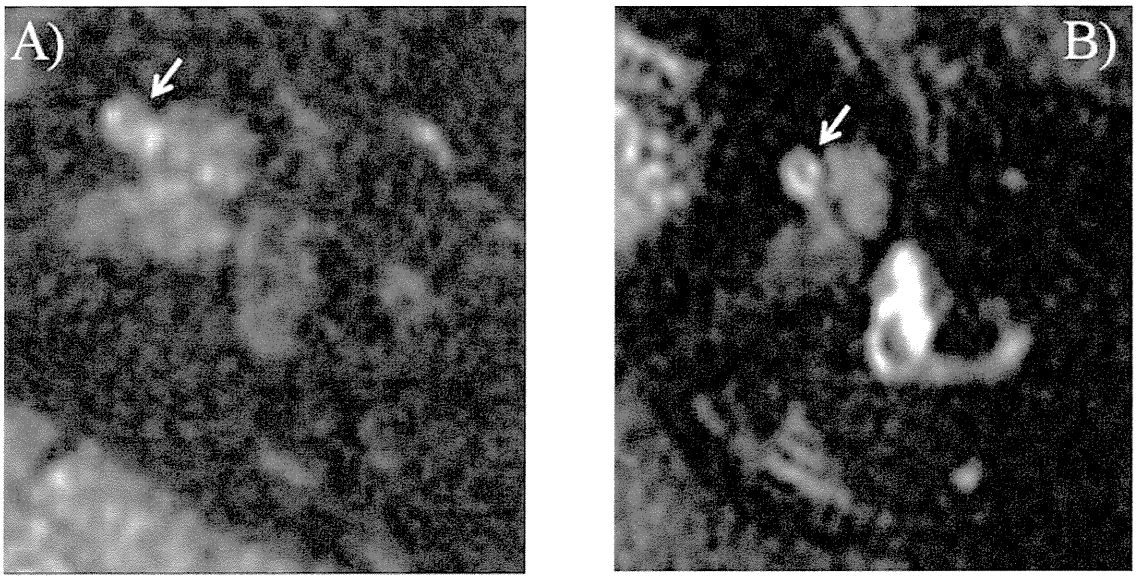


Figure 2. Fig. 2A shows a hydrops-negative cochlea from control patient, in which no enlargement of low signal intensity area was shown. 2D-FLAIR images of the inner ear (Fig. 2B), endolymphatic hydrops were seen at the cochlea as low siginal intensity area surrounded by perilymphatic space with gadolinium enhancement.

MRI was taken after partial recovery of hearing loss two months after the onset of sudden deafness (See Fig. 1B, audiogram at the time of MRI). It was not clear whether these hydrops existed from the early onset of sudden deafness or it developed after the partial recovery from sudden deafness, because inner ear MRIs were not taken at the onset of sudden deafness. However, in any case, these hydrops were not causally related to the pathogenesis of sudden deafness of these patients. If endolymphatic hydrops had been the primary cause of sudden deafness of these patients, the hydrops would have disappeared after partial recovery from hearing loss, which was not evident in these patients. Therefore, it was suggested that these were the secondary hydrops cases. There still remains possibility that the patient showed spontaneous recovery rather than the medication-induced hearing recovery, however, in any case, this was suggested to be the secondary hydrops.

In this case, ECoG could not be performed due to high tone hearing loss. It is indicated that as one of merits of image analysis, this method can demonstrate endolymphatic hydrops even in patients with high tone hearing loss in whom ECoG cannot be performed. If endolymphatic images had not been performed, this patient would have never been diagnosed as having endolymphatic hydrops. Although images revealed endolymphatic hydrops, treatment for endolymphatic hydrops such as endolymphatic sac surgery for this patient at this stage was nonsense and should be avoided.

Recently, inner ear MRI with intratympanic gadolinium injection becomes popular radiological test for detecting endolymphatic hydrops [5-9]. To date, it has been performed mainly for Meniere's patients to confirm the existence of endolymphatic hydrops [5-9]. However, if endolymphatic images will be used as one of routine tests in future, we should pay much attention to the secondary endolymphatic hydrops. As Merchant et al. reported, cadaver studies revealed that endolymphatic hydrops were demonstrated in temporal bones not only from Meniere's patients but also from patients with many kind of inner ear insults who had no Meniere's symptoms [4]. It would be expected that substantial portion of inner ear diseases could cause secondary hydrops following initial manifestation of inner ear dysfunction. Including the current case, we reported that two of eight patients with sudden deafness developed secondary hydrops after partial recovery of hearing disturbance several months after the onset of sudden deafness [10]. However, treatment for endolymphatic hydrops at that time point may be nonsense for recovering from the resultant symptoms by the primary pathology as in the current case.

In conclusion, era for diagnosing endolymphatic hydrops by image analyses has started. This method is useful even in patients with profound hearing loss in whom ECoG cannot be performed. However, this tool of course cannot discriminate the secondary hydrops from Meniere's disease and should be used with careful attention in the diagnosis and treatment of inner ear diseases.

Acknowledgement

Part of this study was presented at the American Neurotology Society 45th Annual Spring Meeting in Las Vegas.

References

1. Yamakawa K. Uber die pathologish Veranderung bei einem Meniere-Kranken. J Otorhinolaryngol Soc Jpn 1938; 4: 2310-2.

2. Hallpike CS, Cairns H. Observation on the pathology of Meniere's syndrome. J Laryngol Otol 1938; 53: 625-55.

3. Kamakura T, Kitahara T, Horii A, Inohara H. Delayed facial nerve palsy after endolymphatic sac surgery. Int Adv Otol 2011; 7: 130-133.

4. Merchant SN, Adams JC, Nadol JB Jr. Pathophysiology of Meniere's syndrome: are symptoms caused by endolymphatic hydrops? Otol Neurotol 2005; 26: 74-81.

5. Nakashima T, Naganawa S, Sugiura M, Teranishi M, Sone M, Hayashi H et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. Laryngoscope 2007; 117: 415-20.

6. Naganawa S, Sugiura M, Kawamura M, Fukatsu H, Sone M, Nakashima T. Imaging of endolymphatic and perilymphatic fluid at 3T after intratympanic administration of gadolinium-diethylene-triamine pentaacetic acid. AJNR Am J Neuroradiol 2008; 29: 724-6.

7. Naganawa S, Nakashima T. Cutting edge of inner ear MRI. Acta Otolaryngol Suppl 2009; 560: 15-21.

8. Fukuoka H, Tsukada K, Miyagawa M, Oguchi T, Takumi Y, Sugiura M et al. Semi-quantitative evaluation of endolymphatic hydrops by bilateral intratympanic gadolinium-based contrast agent (GBCA) administration with MRI for Meniere's disease. Acta Otolaryngol 2010; 130: 10-6.

9. Nakashima T, Naganawa S, Pyykko I, Gibson W. P. R., Sone M, Nakata S. Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Otolaryngol Suppl 2009; 560: 5-8.

10. Horii A, Osaki Y, Kitahara T, Imai T, Uno A, Nishiike S et al. Endolymphatic hydrops in Meniere's disease detected by MRI after intratympanic administration of gadolinium: in comparison with sudden deafness. Acta Otolaryngol 131: 602-609, 2011

Int. Adv. Otol. 2011; 7:(1) 130-133

CASE REPORT

Delayed Facial Nerve Palsy after Endolymphatic Sac Surgery

Takefumi Kamakura, Tadashi Kitahara, Arata Horii, Hidenori Inohara

Department of Otorhinolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, Suita-city, Osaka, Japan. (TK, HI)
Department of Otolaryngology-Head and Neck Surgery, Osaka Rosai Hospital, Sakai-city, Osaka, Japan. (TK)
Department of Otolaryngology, Suita Municipal Hospital, Suita-city, Osaka, Japan. (AH)

Objective: Delayed facial nerve palsy (DFP) after otological and neurotological surgeries is always observed ipsilateral to the operated side, while it is rare in other types of ENT surgery including head and neck, suggesting that DFP may result from procedures selective to temporal bone surgery. Herein, we present a rare case of DFP after endolymphatic sac surgery, and review the pathogenesis and prevention of DFP after otological and neurotological surgeries.

Materials and Methods: The incidence of DFP after endolymphatic sac surgery from 1998 to 2008 at our hospital was 0.67% (1 out of 150 cases). A 44-year-old male with complaints of repeated vertigo attacks and cochlear symptoms such as persistent tinnitus and fluctuating hearing loss of the right ear. The patient received endolymphatic sac surgery on the right ear for treatment of intractable Meniere's disease, resulting in the onset of DFP.

Results: DFP onset occurred at post-operative day 8, with the House-Brackmann grade III. HSV and VZV serum tests were negative.

Conclusion: The later onset DFP observed in the present case after endolymphatic sac surgery might relate to the reactivation of a virus other than HSV and VZV in the geniculate ganglion induced by surgery.

Submitted : 02 July 2010 *Accepted : 05 December 2010*

Introduction

Delayed facial nerve palsy (DFP) can occasionally occur several days after temporal bone surgery, despite no direct contact with the facial nerve during operative procedures[1,2]. DFP was reported to actually occur after otologicical and neurotological surgeries including tympanoplasty with mastoidectomy, stapes surgery, and cochlear implant[1-13]. DPF only occurs on the same side as that operated, and is rare following other types of ENT surgery such as to the head and neck, suggesting a direct role of temporal bone surgery procedures. However, the underlying cause of DFP remains unclear. Herein, we report a novel case of DFP after endolymphatic sac surgery, and review the pathogenesis of DFP after otological and neurotological surgeries.

Case Report

The incidence of DFP after endolymphatic sac surgery from 1998 to 2008 at our hospital was 0.67% (1 out of 150 cases). A 44-year old male patient presented to our hospital in July, 2004 with complaints of repeated vertigo with cochlear symptoms including tinnitus and hearing loss in the right ear. He had been suffering from these symptoms since February, 2004, and had received medication at his former hospital without any affect. We diagnosed this case as intractable Meniere's disease and performed endolymphatic sac surgery on his right ear in September, 2004 to prevent from intractable vertigo attack and progressive sensorineural hearing loss.

The technical details of endolymphatic sac surgery (termed endolymphatic sac drainage and steroid-instillation surgery: EDSS) were previously reported [14-16]. In brief, a simple mastoidectomy was performed, clearly exposing the endolymphatic sac in the area between the sigmoid sinus and the inferior margin of the posterior semicircular canal (Figure 1A). The sac was opened with an L-shaped incision made along the posterior and distal margins of the lateral wall. The sac was then filled with a solid mass of 20 mg prednisolone powder (Figure 1B). While dissolving the mass in the sac, we prepared a bundle of absorbable gelatin films (approximately five 4×20×0.7 mm sheets) with fan- and stick-shaped ends (Figures 1C, 1D). These films were tied together with a

Corresponding address:
Takefumi Kamakura,
Department of Otorhinolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka Suita-city, Osaka, 565-0871, Japan.
Phone: +81-6-6879-3951; Fax: +81-6-6879-3959
E-mail: tkamakura@ent.med.osaka-u.ac.jp.

biochemical adhesive (human thrombin combined with human fibrinogen) at only the stick-shaped end in the same manner as for sac expanding surgery[17]. The fan-shaped end was then inserted into the sac, and small pieces of absorbable gelatin sponges soaked in a high concentration of dexamethasone (32 mg/4 ml) were placed inside and outside the sac lumen expanded with the bundle. The sponges containing dexamethasone placed outside the sac were coated with the adhesive to form a natural sustained-release vehicle for prolonged slow release of dexamethasone delivered into the sac. Using the same adhesive the stick-shaped end extending out of the sac was fixed to the front edge of the mastoid cavity to expand the incision into the sac for an adequate period of time after surgery. The mastoid cavity was filled with relatively large pieces of absorbable gelatin sponges dipped in antibiotic solution, after which the wound was closed with skin sutures.

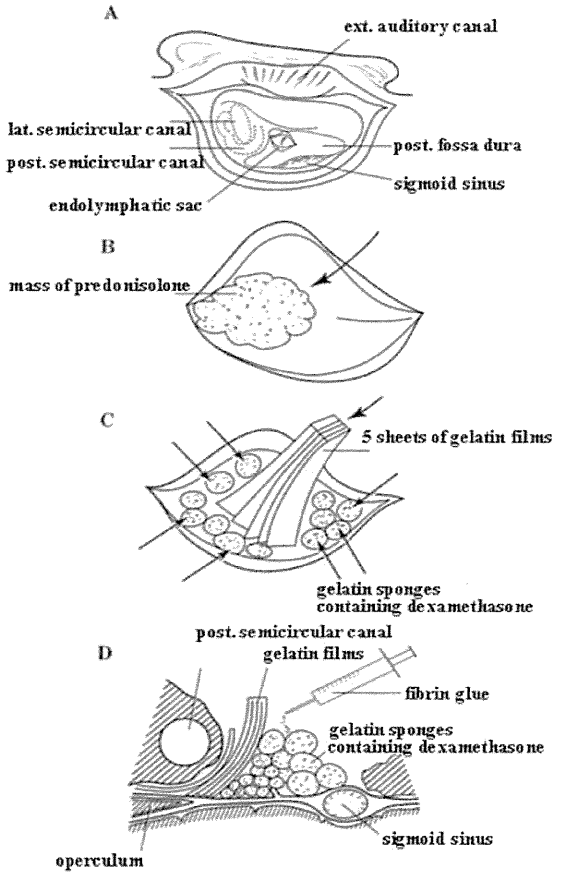


Figure 1. Schematic representation of endolymphatic sac drainage and steroid-instillation surgery.

DFP was observed at post-operative day eight (Figure 2). The House-Brackmann grade was III at DFP onset. Systemic steroid treatment was started immediately after DFP onset and was continued for one week. DFP had improved to grade II at eighteen days after onset. Two herpes serum tests, HSV and VZV, were completely negative. Four years after surgery, the patients' vertigo attack disappeared completely and his average hearing level in the right ear improved from 57.7dB to 40.0dB.

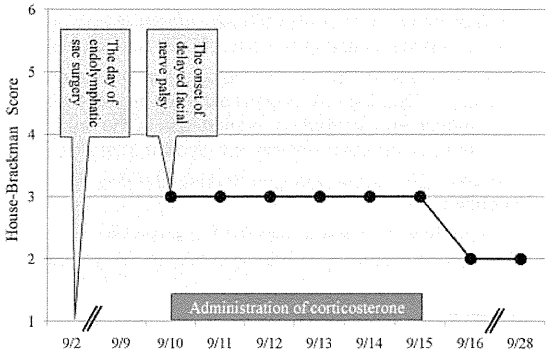


Figure 2. Time course of delayed facial nerve palsy after endolymphatic sac drainage and steroid-instillation surgery.

Discussion

The incidence of DFP after otological and neurotological surgeries was previously reported as 10—30% in acoustic neurinoma surgery[2,10,12] and vestibular neurectomy[13], 0.3—8.5% in tympanoplasty with mastoidectomy[1-3] and cochlear implant[4-6], and 0.2—0.5% in stapes surgery[7-9]. By comparison, the ratio of idiopathic facial nerve paresis such as Bell's palsy was reported to be lower by approximately 0.01—0.03% in Sweden, Ireland, England, Norway, United States, Colombia, and Japan[18], suggesting a greater effect of otological and neurotological surgeries on DFP than the idiopathic lesion.

Generally, the idiopathic facial nerve paresis, so-called Bell's palsy, is thought to occur due to intratubal facial nerve ischemia and/or edema under various kinds of stress[18]. In such a sense, all types of surgery could produce surgical stress to the patient and therefore be a potential cause of DFP on either side. Actually after otological and neurotological surgeries, DFP is always observed ipsilateral to the operated ear, and only rarely