Original Paper

Audiology & Neurotology

Audiol Neurotol 2014;19:49–56
DOI: 10.1159/000356386

Received: June 17, 2013
Accepted after revision: October 10, 2013
Published online: December 11, 2013

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

Shinya Morita Yuji Nakamaru Nobuyuki Obara Masayori Masuya
Satoshi Fukuda

Department of Otolaryngology – Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Key Words
Vogt-Koyanagi-Harada disease · Hearing loss · Audiogram · Prognosis · Corticosteroid

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.

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

KARGER

1420–3030/13/0191–0049$38.00/0

E-Mail karger@karger.com
www.karger.com/aud

Yuji Nakamaru, MD, PhD
Department of Otolaryngology – Head and Neck Surgery
Hokkaido University Graduate School of Medicine
Kita 15, Nishi 7, Kita-ku, Sapporo, Hokkaido 060-8638 (Japan)
E-Mail nmaru@med.hokudai.ac.jp

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]:

Table 1. Characteristics of patients with VKH disease and of controls

	Patients/controls		
	total subjects	≤50 years old	>50 years old
Number	85/85	49/49	36/36
Gender – male:female, n	37:48/37:48	22:27/22:27	15:21/15:21
Mean age ± SD, years	47.1±14.0/47.1±14.0	37.0±8.3/37.0±8.3	60.8±6.6/60.8±6.6
Mean duration from ocular symptom onset to initial treatment ± SD, days	8.2±5.9/–	8.4±5.8/–	8.0±5.9/–

(1) no impairment (the average of hearing thresholds at 500, 1,000, 2,000 and 4,000 Hz equates to a 25-dB hearing level, dB HL, or less); (2) mild (the average of hearing thresholds is 26–40 dB HL); (3) moderate (the average of hearing thresholds is 41–60 dB HL); (4) severe (the average of hearing thresholds is 61–80 dB HL); and (5) profound (the average of hearing thresholds is 81 dB HL or more).

The pattern of the pure tone audiogram was categorized into 4 types using the classification scheme of Mazzoli et al. [2003]. Low frequencies were defined as ≤500 Hz, mid frequencies as >500 and ≤2,000 Hz, and high frequencies as >2,000 and ≤8,000 Hz. The audiogram types were defined as follow: (a) low frequency, a >15-dB HL difference between the poorer low-frequency thresholds and those at higher frequencies; (b) mid frequency, a >15-dB HL difference between the poorest thresholds in the mid frequencies and those at higher and lower frequencies; (c) high frequency, a >15-dB HL difference between the mean of the 500- and 1,000-Hz thresholds and the mean of the 4,000- and 8,000-Hz thresholds; and (d) flat, a <15-dB HL difference between the mean of the 250- and 500-Hz thresholds, the mean of the 1,000- and 2,000-Hz thresholds, and the mean of the 4,000- and 8,000-Hz thresholds. Asymmetric hearing loss was defined as a loss of hearing sensitivity with a difference of ≥15 dB HL between the ears at ≥2 frequencies.

Distortion Product Otoacoustic Emissions

DPOAE measurements were performed using an ER-33 instrument (Rion). An acoustic probe enclosed in a soft rubber covering and containing a miniature microphone and a speaker was placed – but not hermetically sealed – in the distal portion of the external auditory canal. The stimuli applied were a 65-dB sound pressure level (dB SPL) tone of f_1 and a 55-dB SPL tone of f_2 ($f_2 > f_1$; $f_2/f_1 = 1.22$). The DPOAE response levels were measured at the frequency $2f_1–f_2$. The noise floor levels were also calculated at each frequency. DPOAE were recorded for 3 frequency pairs at 2,000, 3,000 and 4,000 Hz. The DPOAE response levels and the noise floor levels for each of the frequency pairs were used to assess pass-fail results. A 'DPOAE pass' result was defined as a DPOAE level for the 3 frequency pairs at least 6 dB SPL above the noise floor level.

Treatment Procedure

Patients with complete or incomplete VKH disease were treated with high-dose systemic corticosteroids. An initial daily dose of prednisolone (200 mg/day) was given by intravenous infusion for 2 days, and thereafter tapered off to 150, 100 and 80 mg/day for 2 days. Intravenous prednisolone was then changed to oral prednisolone (60 mg/day), which was also tapered off gradually over a period of 6 months or more by the treating ophthalmologists according to the severity of the ocular inflammation.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 12.0; SPSS Inc., Chicago, Ill., USA). Statistical differences were analyzed using the Mann-Whitney U test and the Kruskal-Wallis test, with $p < 0.05$ considered statistically significant.

Results

Subject Profiles

The patient and control profiles are summarized in table 1. The study population comprised 85 patients, consisting of 37 males and 48 females ranging in age from 18 to 70 years, with a mean age ± SD of 47.1 ± 14.0 years. The duration from the onset of ocular symptoms to initial treatment ranged from 1 to 23 days, with a mean duration ± SD of 8.2 ± 5.9 days. The patients were divided into groups of 50 years or under (n = 49) and over 50 years (n = 36). There were no differences in gender distribution or in duration from the onset of ocular symptoms to initial treatment between the two groups.

The control group comprised 85 subjects, consisting of 37 males and 48 females ranging in age from 18 to 70 years. They showed normal pure tone thresholds at all frequencies, normal tympanic membranes on otoscopic examination, normal peak amplitudes with –100 to +50 daPa tympanic peak pressure in response to impedance audiometry, and pass results for DPOAE.

Characteristics of Hearing Loss in VKH Patients

The characteristics of hearing loss in the VKH patients are summarized in table 2. Hearing loss was detected by audiometry in 76 (89.4%) of the 85 patients,

Table 2. Characteristics of hearing loss in Vogt-Koyanagi-Harada disease

	Total subjects	≤50 years old	>50 years old	p
Hearing loss detected by audiometry	76 (89.4%)	43 (87.8%)	33 (91.7%)	0.565
Symptoms				
Hearing loss	23 (27.1%)	13 (26.5%)	10 (27.8%)	0.565
Tinnitus	29 (34.1%)	15 (30.6%)	14 (38.9%)	0.565
Affected ear				
Bilateral	59 (77.6%)	31 (72.1%)	28 (84.8%)	0.189
Symmetry	50 (65.8%)	29 (67.4%)	21 (63.6%)	0.731
Asymmetry	9 (11.8%)	2 (4.7%)	7 (21.2%)	0.028
Unilateral	17 (22.4%)	12 (27.9%)	5 (15.2%)	0.189
Total number of affected ears	135	74	61	
Severity				
Normal-mild	107 (79.3%)	69 (93.2%)	38 (62.3%)	<0.001
Moderate	23 (17.0%)	4 (5.4%)	19 (31.1%)	<0.001
Severe	5 (3.7%)	1 (1.4%)	4 (6.6%)	0.112
Profound	0 (0%)	0 (0%)	0 (0%)	
Audiogram pattern				
High frequency	96 (71.1%)	44 (59.5%)	52 (85.3%)	0.001
Flat	36 (26.7%)	28 (37.8%)	8 (13.1%)	0.001
Low frequency	3 (2.2%)	2 (2.7%)	1 (1.6%)	0.678
Mid frequency	0 (0%)	0 (0%)	0 (0%)	
DPOAE	75	42	33	
Pass	17 (22.7%)	15 (35.7%)	2 (6.1%)	0.002
Fail	58 (77.3%)	27 (64.3%)	31 (93.9%)	0.002

Values denote numbers with percentages in parentheses unless specified otherwise. Statistical differences were analyzed using the Mann-Whitney U test to compare groups.

whereas 23 (27.1%) of the 85 patients complained of hearing loss and 29 (34.1%) complained of tinnitus. Among the total number of subjects, the rate of objective hearing loss was significantly higher than either that of subjective hearing loss ($p < 0.001$) or tinnitus ($p < 0.001$). Fifty-nine (77.6%) of the 76 patients presented with bilateral and 17 (22.4%) with unilateral hearing loss (9 involving the right ear and 8 the left ear), so that a total of 135 ears were diagnosed with VKH disease-associated hearing loss; 107 (79.3%) of the 135 ears showed normal hearing to mild hearing loss according to the WHO classifications of severity, with no patient showing profound hearing loss; 96 (71.1%) of the 135 ears indicated a high-frequency audiogram pattern, and 58 (77.3%) of 75 ears received a fail result for DPOAE.

Hearing Thresholds: Patients versus Controls

Figure 1 shows the mean pure tone thresholds ± SD for air conduction in the audiograms of the affected ears and of the control group. In both patient groups, we found that hearing thresholds in the affected ear were significantly higher than those in the control group at all frequencies ($p < 0.001$). In particular, the hearing thresholds were significantly elevated at high frequencies compared with those at low-to-mid frequencies ($p < 0.001$).

Hearing Loss Features: Patients Aged 50 Years or under versus Those over 50 Years

When we compared the features of auditory disturbance between the two groups of patients, the severity of hearing loss ($p < 0.001$), the rate of high-frequency audiogram patterns ($p < 0.001$) and DPOAE fail results ($p = 0.002$) were significantly higher in patients aged over 50 years than in those aged 50 years or under (table 2). When we compared hearing thresholds in the affected ear of both groups of patients, thresholds in the over-50-year-old group were found to be significantly higher than those in the group aged 50 years or under at all frequencies ($p < 0.01$).

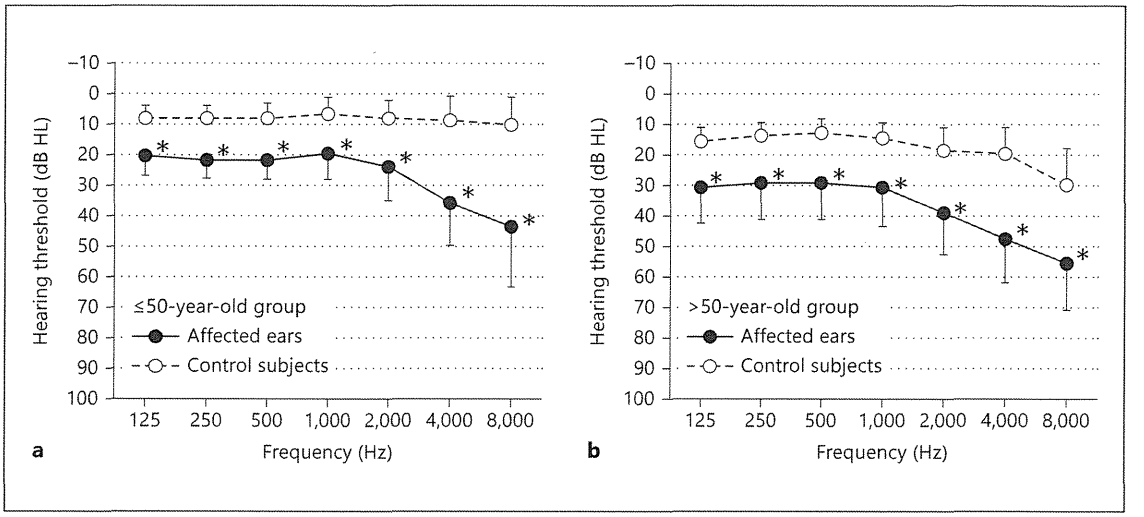

Fig. 1. Mean pure tone thresholds for air conduction in audiograms of the group 50 years of age and under (**a**) and of the group over 50 years of age (**b**) at initial presentation. Error bars: SD for each frequency. Statistical differences were analyzed using the Mann-Whitney U test. * $p < 0.001$.

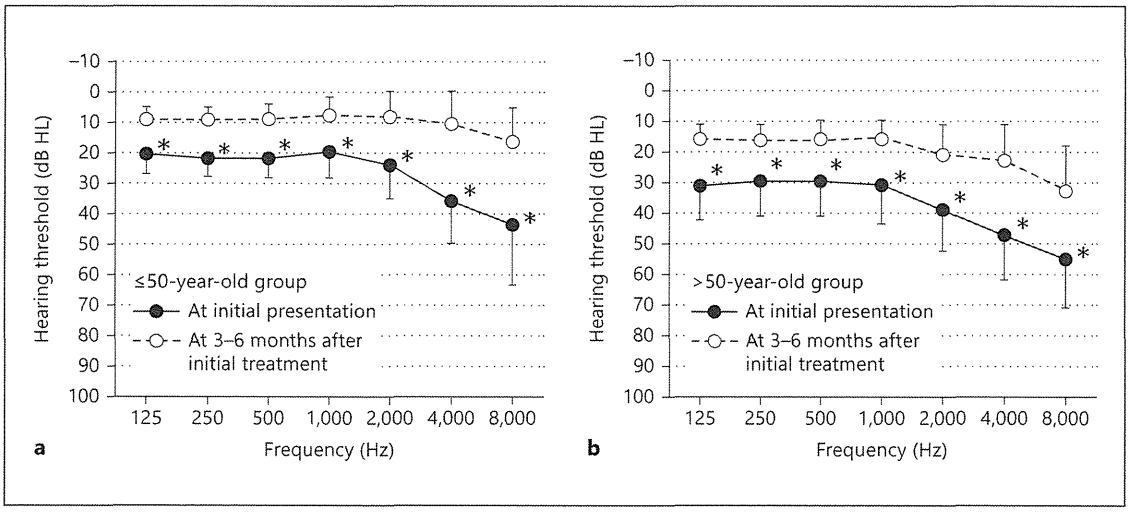

Fig. 2. Mean pure tone thresholds for air conduction in audiograms of the group 50 years of age and under (**a**) and of the group over 50 years of age (**b**) 3–6 months after the initial treatment. Error bars: SD for each frequency. Statistical differences were analyzed using the Mann-Whitney U test. * $p < 0.001$.

Efficacy of High-Dose Systemic Corticosteroid Therapy

Figure 2 shows the mean pure tone thresholds ± SD for air conduction in the audiograms of the affected ears 3–6 months after initial treatment. In both patient groups, we found that hearing thresholds at all frequencies after high-dose corticosteroid therapy were significantly better than those at initial presentation ($p < 0.001$).

The rate of recovery was 74.8% among the total subjects, 77.0% in the group aged 50 years or under, and 72.1% in the group aged over 50 years. The relationship between hearing outcome in VKH disease and each category was then assessed (table 3). Age, duration from onset of symptoms to initial treatment, and hearing threshold at initial presentation were significantly related to better hearing results ($p < 0.001$, $p = 0.008$ and $p = 0.001$).

Table 3. Factors related to hearing outcome in VKH disease

	Recovery (n = 101)	No recovery (n = 34)	p
Mean age ± SD, years	44.0±13.4	57.2±9.4	<0.001
Gender – male:female, n	44:57	16:18	0.724
Mean duration from symptom onset to initial treatment ± SD, days	6.6±4.2	11.4±6.5	0.008
Symptom of hearing loss, n	30 (29.7%)	8 (23.5%)	0.490
Symptom of tinnitus, n	38 (37.6%)	11 (32.4%)	0.582
Audiogram pattern, n			
High frequency	73 (72.3%)	23 (67.6%)	0.857[1]
Flat	26 (25.7%)	10 (29.4%)	
Low frequency	2 (2.0%)	1 (2.9%)	
DPOAE, n			
Pass	14 (13.9%)	3 (8.8%)	0.710[1]
Fail	42 (41.6%)	16 (47.1%)	
Mean hearing threshold at initial presentation ± SD, dB HL	28.8±11.7	36.5±10.0	0.001

Statistical differences were analyzed using the Mann-Whitney U test.
[1] Statistical differences in audiogram pattern and DPOAE were analyzed using the Kruskal-Wallis test.

Discussion

The clinical features of VKH disease include anterior uveitis, exudative retinal detachment and depigmented fundal lesions, as well as the presence of neurological, auditory or dermatologic manifestations. The diagnosis of VKH disease requires both ocular and extraocular symptoms and signs [Read et al., 2001]. However, only 20–40% of VKH patients develop neurological and auditory findings, such as meningismus and tinnitus, at the acute ophthalmic stage [Mondkar et al., 2000; Kitamura et al., 2005; Miyanaga et al., 2007]. The integumentary findings, such as alopecia, poliosis and vitiligo, usually appear in patients with VKH disease only in the convalescent stage, some 3–6 months after the onset of uveitis [Mondkar et al., 2000]. Therefore, with the present diagnostic criteria, accurate diagnosis of VKH disease in the acute ophthalmic stage is sometimes difficult, making physicians hesitant to begin high-dose systemic corticosteroid therapy. Although the diagnostic criteria include only tinnitus as an auditory finding, otologic complaints other than tinnitus, such as hearing loss and/or vertigo, have been reported [Kitamura et al., 2005; Ondrey et al., 2006].

The presence of age-related hearing loss must be excluded to accurately discuss hearing loss. Thus, we used the ISO 7029 standard [International Organization for Standardization, 2000], which provides age- and gender-specific normative data on hearing thresholds and takes into account age-related hearing loss across the population as a whole. It is useful for evaluating any degree of hearing loss, whether or not the loss is clinically relevant. In the current study, 89.4% of the total number of subjects were found to be suffering from hearing loss on the basis of audiometric findings, while only 34.1% complained of tinnitus. While hearing thresholds in the affected ear were significantly higher than those in the controls at all frequencies ($p < 0.001$), most of the patients showed only normal hearing to mild hearing loss based on the WHO classifications of severity [World Health Organization, 2003]. This might explain the higher rate of hearing loss detected by audiometry than either that of subjective hearing loss ($p < 0.001$) or tinnitus ($p < 0.001$). These results suggest that history taking alone is insufficient to detect auditory manifestations, and that some auditory examinations, other than for tinnitus, should be performed to evaluate this disease.

In patients aged over 50 years, a differential diagnosis between presbycusis and auditory manifestations associated with VKH disease is difficult. Presbycusis is the most common hearing problem in older people. In general, people aged over 50 years tend to lose their hearing slowly as they age. Presbycusis is estimated to effect 30–83% of adults aged 65 years and more [Helzner et al., 2005]. Most cases of presbycusis include high-frequency hearing loss and are typically a bilateral, symmetric phenomenon, although those affected do not always complain of hearing loss [Nelson and Hinojosa, 2006]. In the current study, hearing loss in patients with VKH disease was of-

ten mild, with bilateral symmetric high-frequency audiogram patterns. In particular, there was a strong tendency for bilateral high-frequency audiogram patterns to be observed in patients aged over 50 years. Similarly, most of these patients (61.1%) did not complain of audiological disturbances, although their hearing thresholds were significantly higher than those in patients aged 50 years or under at all frequencies ($p < 0.01$). These features appear to be similar to those of presbycusis and make it difficult to evaluate auditory manifestations associated with VKH disease.

We found that most VKH disease patients with hearing loss scored a fail result on the DPOAE, and hearing thresholds were significantly elevated at high frequencies compared with those of low-to-mid frequencies ($p < 0.001$), which may indicate more serious damage at the base of the cochlea than at the apex. In the cochlea, melanin or melanocytes are located in the stria vascularis, auditory receptors or hair cells, vestibular organ and endolymphatic sac [Barrenäs and Axelsson, 1992]. Although the functions of melanin and melanocytes in the inner ear remain unclear, it has been reported that melanin has semiconductive properties, responding to phonic, acoustic and electric stimulation, and the ability to convert energy states into molecular rotation and vibration, as well as the reverse [McGinness et al., 1974]. Furthermore, melanin in the cochlea functions as an intracellular calcium buffer and as a depot of essential metal ions that control the activity of various enzymes and metabolic processes [McGinness et al., 1974; Steel and Barkway, 1989]. Melanocytes also are required for the maintenance of normal function of the stria vascularis and cochlea, the development of endocochlear potentials, and the conservation of the ion and fluid gradients between endolymph and perilymph, all of which are critical for hair cell survival [Hilding and Ginzberg, 1977; Steel and Barkway, 1989]. Thus, melanin-containing cells in the inner ear are thought to protect the cochlea from various stresses such as loud noise, mechanical trauma and ototoxic drug administration [Steel and Barkway, 1989]. Meanwhile, reduced levels and/or activities of pigment cells may result in audiological abnormalities [Steel and Barkway, 1989; Barrenäs and Axelsson, 1992; Ardic et al., 1998]. Melanin-containing cells are considered to be concentrated more in the basal region than in the apical region, so the basal region is considered to be more vulnerable to various stresses in pigmentary abnormalities [Wästerström et al., 1986]. Several prominent cutaneous pigmentary abnormalities characterized by a loss of functional melanocytes have also demonstrated higher-frequency hearing loss [Ardic et al., 1998; Aydogan et al., 2006], which supports our present results on VKH disease.

Treatment of VKH disease is based on the early administration of high-dose systemic corticosteroids, followed by gradual tapering and maintenance for at least 6 months, and this regimen is associated with less intraocular inflammation, a decreased frequency of ocular recurrences and dermatologic features, and better visual outcomes [Rubsamen and Gass, 1991; Moorthy et al., 1995; Mondkar et al., 2000; Chee et al., 2009; Lai et al., 2009]. Clinicians should balance the benefits of uveitis control with the risk of side effects [Lai et al., 2009]. Although several reports have demonstrated the effectiveness of high-dose systemic corticosteroids for the ocular and neurologic manifestations of VKH disease [Solaro and Messmer Uccelli, 2000], no study has specifically examined the effectiveness of systemic steroids for the otologic manifestations. Their effectiveness has also been suggested in the treatment of hearing loss associated with other autoimmune inner ear diseases [Niparko et al., 2005], which may indicate that similar results can be expected for VKH disease. In the current study, we found that 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 pure tone thresholds at all frequencies was 74.8%. These results demonstrate that, as with autoimmune inner ear diseases, high-dose systemic corticosteroids are effective in the treatment of the auditory manifestations of VKH disease. As ophthalmologists make the decision whether to treat with high-dose systemic corticosteroids according to the severity of ocular inflammation, but not based on auditory findings in VKH patients, our study lacked a control group not receiving steroids. Although the rates of spontaneous recovery and recurrence remain clinical problems, as with ocular symptoms and signs, hearing loss associated with acute VKH disease is reversible and shows a relatively good short-term prognosis. In particular, young patients who presented with mild hearing loss and received early treatment showed significantly better hearing outcomes. Meanwhile, it is thought that presbycusis is exacerbated under the influence of hearing loss associated with VKH disease in patients aged over 50 years. However, some elderly patients showed an improvement in hearing after high-dose systemic corticosteroids therapy even when initially thought to be suffering from presbycusis. Thus, an accurate diagnosis of, and prognosis for, hearing loss associated with VKH disease in the elderly is difficult when using pure tone audiograms alone.

In conclusion, hearing loss associated with VKH disease was observed in a significantly larger number of patients than was tinnitus. Most of the patients showed mild hearing loss and a bilateral, symmetric high-frequency audiogram pattern, while exhibiting no auditory symptoms. Although the diagnostic criteria include only tinnitus, and not hearing loss, as an auditory sign, audiometry should be performed for the detection of asymptomatic hearing loss. High-dose systemic corticosteroids are thought to be effective for the auditory manifestations of VKH disease, which generally show a relatively good short-term prognosis. However, it is important to evaluate hearing loss in VKH disease at the acute ophthalmic stage and administer early treatment.

Disclosure Statement

We have no conflicts of financial interest to declare.

References

Ardiç FN, Aktan S, Kara CO, Sanli B: High-frequency hearing and reflex latency in patients with pigment disorder. Am J Otolaryngol 1998;19:365–369.

Aydogan K, Turan OF, Onart S, Karadogan SK, Tunali S: Audiological abnormalities in patients with vitiligo. Clin Exp Dermatol 2006; 31:110–113.

Barrenäs ML, Axelsson A: The development of melanin in the stria vascularis of the gerbil. Acta Otolaryngol 1992;112:50–58.

Chee SP, Jap A, Bacsal K: Prognostic factors of Vogt-Koyanagi-Harada disease in Singapore. Am J Ophthalmol 2009;147:154e1–161e1.

Gates GA, Mills JH: Presbycusis. Lancet 2005;366: 1111–1120.

Helzner EP, Cauley JA, Pratt SR, Wisniewski SR, Zmuda JM, Talbott EO, de Rekeneire N, Harris TB, Rubin SM, Simonsick EM, Tylavsky FA, Newman AB: Race and sex differences in age-related hearing loss: the Health, Aging and Body Composition Study. J Am Geriatr Soc 2005;53:2119–2127.

Hilding DA, Ginzberg RD: Pigmentation of the stria vascularis: the contribution of neural crest melanocytes. Acta Otolaryngol 1977;84:24–37.

International Organization for Standardization: Acoustics: statistical distribution of hearing thresholds as a function of age, ISO 7029. 2000. http://www.iso.org.

Kitamura M, Takami K, Kitaichi N, Namba K, Kitamei H, Kotake S, Ohno S: Comparative study of two sets of criteria for the diagnosis of Vogt-Koyanagi-Harada's disease. Am J Ophthalmol 2005;139:1080–1085.

Lai TYY, Chan RPS, Chan CKM, Lam DSC: Effects of the duration of initial oral corticosteroid treatment on the recurrence of inflammation in Vogt-Koyanagi-Harada disease. Eye (Lond) 2009;23:543–548.

Mazzoli M, van Camp G, Newton V, Giarbini N, Declau F, Parving A: Recommendations for the description of genetic and audiological data for families with nonsyndromic hereditary hearing impairment. Audiol Med 2003;1: 148–150.

McGinness J, Corry P, Proctor P: Amorphous semiconductor switching in melanins. Science 1974;183:853–855.

Miyanaga M, Kawaguchi T, Shimizu K, Miyata K, Mochizuki M: Influence of early cerebrospinal fluid-guided diagnosis and early high-dose corticosteroid therapy on ocular outcomes of Vogt-Koyanagi-Harada disease. Int Ophthalmol 2007;27:183–188.

Mondkar SV, Biswas J, Ganesh SK: Analysis of 87 cases with Vogt-Koyanagi-Harada disease. Jpn J Ophthalmol 2000;44:296–301.

Moorthy RS, Inomata H, Rao NA: Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol 1995;39:265–292.

Nelson EG, Hinojosa R: Presbycusis: a human temporal bone study of individuals with downward sloping audiometric patterns of hearing loss and review of the literature. Laryngoscope 2006;116:1–12.

Niparko JK, Wang NY, Rauch SD, Russell GB, Espeland MA, Pierce JJ, Bowditch S, Masuda A, Gulya AJ, Gantz BJ, Hughes GB, Brookhouser PE, Hannley MT, Telian SA, Harris JP, AIED Study Group: Serial audiometry in a clinical trial of AIED treatment. Otol Neurotol 2005; 26:908–917.

Ondrey FG, Moldestad E, Mastroianni MA, Pikus A, Sklare D, Vernon E, Nusenblatt R, Smith J: Sensorineural hearing loss in Vogt-Koyanagi-Harada syndrome. Laryngoscope 2006;116: 1873–1876.

Read RW, Holland GN, Rao NA, Tabbara KF, Ohno S, Arellanes-Garcia L, Pivetti-Pezzi P, Tessler HH, Usui M: Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. Am J Ophthalmol 2001;131: 647–652.

Rubsamen PE, Gass JD: Vogt-Koyanagi-Harada syndrome: clinical course, therapy and long-term visual outcome. Arch Ophthalmol 1991; 109:682–687.

Solaro C, Messmer Uccelli M: Intravenous methylprednisolone for aseptic meningitis in Vogt-Koyanagi-Harada syndrome. Eur Neurol 2000;44:129–130.

Steel KP, Barkway C: Another role for melanocytes: their importance for normal stria vascularis development in the mammalian inner ear. Development 1989;107:453–463.

Sugita S, Takase H, Taguchi C, Imai Y, Kamoi K, Kawaguchi T, Sugamoto Y, Futagami Y, Itoh K, Mochizuki M: Ocular infiltrating CD4+ T cells from patients with Vogt-Koyanagi-Harada disease recognize human melanocyte antigens. Invest Ophthalmol Vis Sci 2006;47: 2547–2554.

World Health Organization: Global burden of hearing loss in the year 2000. http://www.who.int/healthinfo/statistics/bod_hearingloss.pdf.

Wästerström SA, Bredberg G, Lindquist NG, Lyttkens L, Rask-Anderson H: Ototoxicity of kanamycin in albino and pigmented guinea pigs. I. A morphologic and electrophysiologic study. Am J Otol 1986;7:11–18.

Equilibrium Res Vol. 72(2) 97～106, 2013

原　著

前庭水管拡大症を伴う *SLC 26 A 4*, *ATP 6 V 1 B 1*, *SIX 1* 変異例の聴平衡覚所見の検討

野口　佳裕[1]・伊藤　卓[1)2)]・川島　慶之[1)3)]・西尾　綾子[1]
本田　圭司[1]・喜多村　健[1]

Audiovestibular findings in patients with enlargement of the vestibular aqueduct caused by mutations of *SLC 26 A 4*, *ATP 6 V 1 B 1* or *SIX 1*

Yoshihiro Noguchi[1], Taku Ito[1)2)], Yoshiyuki Kawashima[1)3)], Ayako Nishio[1],
Keiji Honda[1], Ken Kitamura[1]

[1]*Department of Otolaryngology, Tokyo Medical and Dental University*
[2]*Molecular Biology and Genetics Section, National Institute on Deafness and Other Communication Disorders, National Institutes of Health*
[3] *Department of Otolaryngology, Tsuchiura Kyodo General Hospital*

Enlargement of the vestibular aqueduct (EVA) is the most common malformation of the inner ear. EVA can be observed in various disorders including DFNB 4/Pendred syndrome, branchio-oto-renal/branchio-oto (BOR/BO) syndrome, and distal renal tubular acidosis (dRTA). Characteristic phenotypes of EVA include progressive, fluctuating hearing loss (HL), and repetitive vertigo. In this study, we compared the audiovestibular findings in patients with mutations of *SLC 26 A 4*, *ATP 6 V 1 B 1* or *SIX 1* to clarify whether the anatomical enlargement itself was related to the characteristic phenotypes. We enrolled five Pendred syndrome patients with *SLC 26 A 4* mutations, one dRTA patient with *ATP 6 V 1 B 1* mutations and two BO syndrome patients with a *SIX 1* mutation. One patient with a *SIX 1* mutation showed unilateral EVA, and the others had bilateral EVA. All five patients with *SLC 26 A 4* mutations had progressive HL, fluctuating HL and/or repetitive vertigo. A patient with *ATP 6 V 1 B 1* mutations also showed repetitive progression HL, fluctuating HL and repetitive vertigo. Fluctuating HL and repetitive vertigo were not recognized in two patients with *SIX 1* mutation, although one patient showed slight progression of HL. There were no significant positive associations in patients with *SLC 26 A 4* mutations between EVA widths and pure tone averages, and the widths and maximum slow phase velocities. These findings suggested that EVA itself had no relationship with either progressive, fluctuating HL, nor repetitive vertigo. The product of *SLC 26 A 4*, the Cl^-/HCO_3^- exchanger pendrin, and the product of the *ATP 6 V 1 B 1*, B 1-subunit of H^+-ATPase, can play a role in the maintainance of endolymph pH homeostasis. Therefore, a disruption of endolymph

pH homeostasis can be associated with the characteristic phenotypes.

Key words: enlargement of the vestibular aqueduct, *SLC 26 A 4, ATP 6 V 1 B 1, SIX 1*

はじめに

前庭水管拡大症（enlargement of the vestibular aqueduct，以下EVA）は，1978年にValvassoriとClemisが画像上の診断基準を提唱して以来，現在では頻度の高い内耳奇形として知られている[1]。EVAは，非症候群性難聴として孤発例[2][3]と常染色体劣性遺伝性難聴例[4]に認められる。症候群性のものとしては，Pendred症候群[5]，branchio-oto-renal/branchio-oto（以下，BOR/BO）症候群[6]，難聴を伴う遠位尿細管性アシドーシス（distal renal tubular acidosis：以下，dRTA）[7]，Waardenburg症候群[8]，CHARGE症候群[9]，Down症候群[10]などの多彩な疾患群に伴う。遺伝学的検査が行われ直接EVAとの関連が明らかになった原因遺伝子として，*SLC 26 A 4*（常染色体劣性非症候群性遺伝性難聴DFNB/Pendred症候群）[11)~13)]，*SIX 1*（BOR/BO症候群）[14]，*ATP 6 V 1 B 1*あるいは*ATP 6 V 0 A 4*（dRTA）[15][16]，*POU 3 F 4*（X連鎖性非症候群性遺伝性難聴DFNX 2）[17]がある。

遺伝学的知見が明らかになる前より，難聴の進行や変動，反復性の発作性回転性めまいなどがEVAの臨床的特徴として報告されてきた[2][3][18)~20)]。しかし，EVAを合併する疾患の中でDFNB/Pendred症候群の占める割合が高い[1]ため，前述の臨床的特徴はこれらの疾患の特徴を代表している可能性がある。今回われわれは，これらの臨床症状が前庭水管拡大という形態学的特徴に起因するものか否かを明らかにするため，原因遺伝子の異なるEVA例の聴平衡覚所見を検討した。

[1] 東京医科歯科大学耳鼻咽喉科
[2] Molecular Biology and Genetics Section, National Institute on Deafness and Other Communication Disorders, National Institutes of Health
[3] 土浦協同病院耳鼻咽喉科

対象と方法

難聴やめまいを主訴に当科を受診し，側頭骨CTにてEVAと診断され，遺伝学的検査にて原因遺伝子が同定された8例を対象とした（表1）。孤発例が5例であり，1例に常染色体劣性，2例に常染色体優性の遺伝形式が疑われた。EVAの診断は，前庭水管の中間部の径が1.5 mm以上もしくは開口部の径が2.0 mm以上のものとした[21]。7例が両側性，1例が片側性のEVAを示した。他の側頭骨奇形として，4例に両側のincomplete partition（incompletely partitioned cochlea：IP）を認めた。

遺伝学的検査は，当施設の倫理審査委員会の承認のもと文書による同意取得の後に行った。静脈血よりDNAを抽出し，各遺伝子の全エクソンおよびエクソン・イントロン境界領域をキャピラリー式自動シークエンサーにより解析した。全例に*SLC 26 A 4*の遺伝学的検査を行い，5例（症例1～5）にホモ接合あるいは複合ヘテロ接合による既知の*SLC 26 A 4*変異を同定した。5例全例に甲状腺腫大が認められ，Pendred症候群と診断した。甲状腺ホルモン検査では，症例1で遊離T3が軽度低下（1.76）していたが，残りの4例は正常であった。症例6～8は既に論文として報告している。症例6はdRTA例であり*ATP 6 V 1 B 1*の複合ヘテロ接合変異[22]，症例7，8はBO症候群例であり*SIX 1*変異[14][23]が同定された。症例6～8に*SLC 26 A 4*変異は認められなかった。

聴平衡覚の臨床症状は，診療録をもとに後ろ向きに行った。純音聴力検査では，初診時と最終診察時の4分法平均気導聴力レベルを評価した。平衡機能検査では，注視眼振検査所見，赤外線CCDカメラ下での頭位・頭位変換眼振検査所見，電気眼振計下での温度刺激検査（エアー；15℃，60秒，61／分）における最大緩除相速度（正常：20°／秒以上）を検討した。

*SLC 26 A 4*変異5例に対して，各耳の前庭水管径（中間部径，開口部径）と4分法平均聴力レ

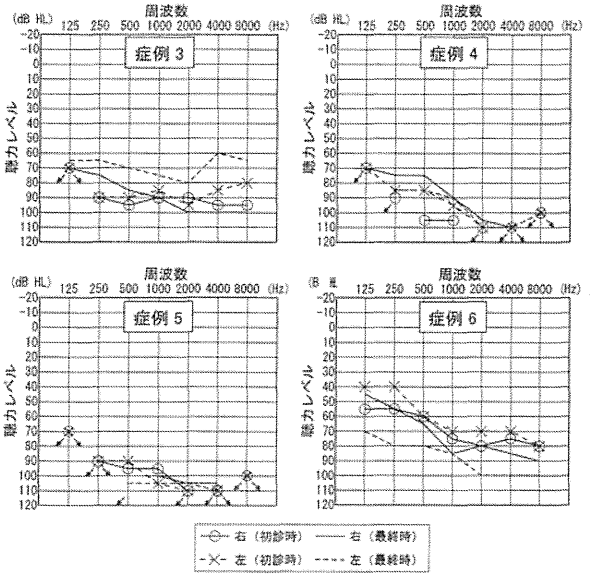

図1　平均聴力レベルの変化を認めた4例の気導オージオグラム

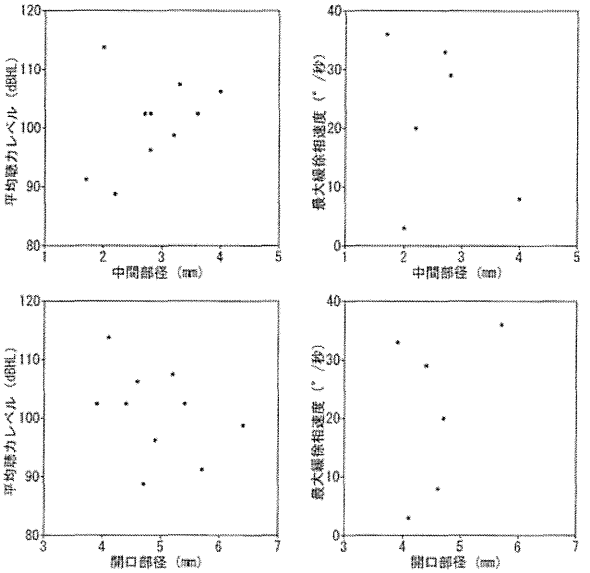

図2　前庭水管径と平均聴力レベル，最大緩徐相速度の関係

ベル（10耳）および最大緩徐相速度（6耳）との相関係数を求めた。統計処理は，統計解析ソフトJMP v.9.0.2を用いてスピアマンの順位相関係数の検定を行った。

結　果

1．聴覚所見（表2）

難聴を指摘された，あるいは自覚した時期は0～6歳であった。この中で，BO症候群の2例（症例7，8）は小学校就学前後の比較的遅い時期に指摘されていた。*SLC 26 A 4* 変異例の60%（5例中3例）が難聴の進行，80%（5例中4例）が変動を自覚していた。*ATP 6 V 1 B 1* 変異例も，難聴の進行や変動を自覚していた。一方，*SIX 1* 変異のある症例7は左のみEVAを認めたが，難聴の変動はなかったが，両難聴の進行を自覚した。症例8は，難聴の進行や変動の自覚は認められなかった。

純音聴力検査では，*SLC 26 A 4* 変異全例が初診時に両側の高度から重度難聴を示していた。経過観察期間中の聴力の変化は，10耳中7耳(70%)が5 dB以内であり，残りの3耳中2耳は回復，1耳は軽度悪化していた。*ATP 6 V 1 B 1* 変異例は，初診時に右高度難聴，左中等度難聴を呈したが，その後両難聴の変動を繰り返し約11年の経過観察期間中に右6.3 dB，左20.0 dBの聴力悪化を認めた。*SIX 1* 変異2例は，初診時に両中等度難聴を示した。両難聴の進行を自覚した症例7は，検査上は両側軽度の低音域の聴力悪化を認めたが，平均聴力レベルの変化は5 dB以内であった。症例8は，約11年の経過観察中に明らかな聴力の悪化は認められなかった。聴力の変動を認めた4例の気導オージオグラムを図1に示した。

2．平衡覚所見（表3）

めまいは *SLC 26 A 4* 変異例の80%（5例中4例）が自覚し，全例が回転性めまいを反復していた。*ATP 6 V 1 B 1* 変異例も反復性の回転性めまいを自覚した。一方，*SIX 1* 変異2例ではめまいの自覚はなかった。めまいを呈した5例は，難聴よりも後にめまいを生じていた。

SLC 26 A 4 変異例において，当科経過観察中にめまいの自覚があったのは症例2のみであった。この症例も診察中にめまいの訴えはなく，平衡機能検査はすべてめまい非発作時に行われた。注視眼振は全例で認められなかったが，80%（5例中4例）に頭位眼振もしくは頭位変換眼振が認められた。温度刺激検査を施行した3例中1例(33%)が異常を示したが，残りの2例は正常であった。*ATP 6 V 1 B 1* 変異例では，頭位・頭位変換眼振検査にて定方向性の水平もしくは水平性回旋性混合性眼振を認めたが，方向は左右いずれのときもあり，発作時の難聴増悪側との関係も明らかではなかった。方向交代性上向性の頭位眼振

表1　対象

症例	年／性	遺伝形式	前庭水管拡大（mm）			他の奇形	合併症	原因遺伝子	変異の種類
			側	中間	開口				
1	29／女	常劣	両 右	4.0	4.6	incomplete partition	甲状腺腫大（軽度低下）	*SLC 26 A 4*	[c.2169 A>G] + [c.2169 A>G]
			左	2.0	4.1				
2	26／女	孤発	両 右	2.7	3.9	incomplete partition	甲状腺腫大（機能正常）	*SLC 26 A 4*	[c.2169 A>G] + [IVS 15+5 G>A]
			左	2.8	4.4				
3	19／女	孤発	両 右	1.7	5.7		甲状腺腫大（機能正常）	*SLC 26 A 4*	[c.2169 A>G] + [IVS 15+5 G>A]
			左	2.2	4.7				
4	24／女	孤発	両 右	3.3	5.2	incomplete partition	甲状腺腫大（機能正常）	*SLC 26 A 4*	[c.1315 G>A] + [IVS 5+1 G>T]
			左	2.8	4.9				
5	24／女	孤発	両 右	3.2	6.4	incomplete partition	甲状腺腫大（機能正常）	*SLC 26 A 4*	[c.2169 A>G] + [c.1229 C>T]
			左	3.6	5.4				
6	12／男	孤発	両 右	1.8	5.1		遠位尿細管性アシドーシス	*ATP 6 V 1 B 1*	[c.756_770 del] + [c.1242 insC]
			左	2.4	4.6				
7	18／女	常優	左 右	0.4	0.9		先天性耳瘻孔	*SIX 1*	[p.Y 129 C]
			左	3	2.3				
8	21／女	常優	両 右	3.5	4.5		先天性耳瘻孔	*SIX 1*	[p.Y 129 C]
			左	1.5	1.8				

や座位への頭位変換時に右向きの水平性眼振を示すこともあった。温度刺激検査では，両側軽度低下していた。*SIX 1* 変異の1例は，明らかな注視・頭位・頭位変換眼振はなく，温度刺激検査でも正常であった。

3．難聴の増悪，めまい発症の誘因

3例が感冒（症例2，6）や頭部外傷（症例5，6）に伴う難聴の増悪やめまいを経験していたが，これらの誘因がなくても難聴の悪化やめまいが認められることもあった。

4．*SLC 26 A 4* 変異例における前庭水管径と平均聴力レベル，最大緩徐相速度との相関

表4に相関係数および p 値，図2に散布図を示した。前庭水管開口部径と平均聴力レベルの間には負の相関が認められたほか，明らかな相関は認められなかった。

考　察

EVAに認められる難聴の進行・変動の発生機構として，内リンパ嚢・内リンパ管拡大という解剖学的構造そのものが関与することが提唱されてきた。すなわち，比較的小さな頭部外傷おいても，頭蓋内圧の上昇により内リンパ嚢内の高濃度の内容液が蝸牛・前庭方向へ逆流し，ライスネル膜などの破綻に伴う外リンパと内リンパの混合が難聴の進行や変動を引き起こすというものである[2)3)]。実際，Wilsonら[24)]は，EVA6例7耳に対する内リンパ嚢充填術が聴力予後を改善したことを報告し，この逆流説を支持した。しかし，本論文の最後に，データの検討方法の不正確性を含めたSmithによる否定的なコメントが掲載されている[24)]。また，前庭水管拡大の程度と難聴の程度や温度刺激検査所見との相関はないとされている[18)19)25)]。本研究においても，*SLC 26 A 4* 変異例における前庭水管径と平均聴力レベルもしくは最大緩徐相速度との間には正の相関は認められなかった。さらに，過去の報告例を個々にみると，EVAが認められるにもかかわらず聴力が正常でめまいも示さない症例[19)]や片側性EVA例で非EVA側に難聴が認められる症例[4)]が存在する。従って，内リンパ嚢・内リンパ管拡大という解剖学的構造の

表2　聴覚所見

症例	難聴			経過観察期間		平均聴力レベル		聴力変化
	発症	進行	変動			初診時	最終時	
1	2歳	両	両	1カ月	右	106.3	108.8	5 dB 以内
					左	113.8	112.5	5 dB 以内
2	2歳	両	両	4年	右	102.5	105.0	5 dB 以内
					左	102.5	106.3	5 dB 以内
3	幼少時	両	両	5年5カ月	右	91.3	91.3	5 dB 以内
					左	88.8	75.0	13.8 dB 回復
4	1歳	なし	右	1年4カ月	右	107.5	90.0	17.5 dB 回復
					左	96.3	93.8	5 dB 以内
5	0歳	なし	なし	6年8カ月	右	98.8	105.0	6.2 dB 悪化
					左	102.5	105.0	5 dB 以内
6	3歳	左	両	10年9カ月	右	72.5	78.8	6.3 dB 悪化
					左	67.5	87.5	20.0 dB 悪化
7	5歳	両	なし	5年9カ月	右	42.5	46.3	5 dB 以内
					左	57.5	62.5	5 dB 以内
8	6歳	なし	なし	11年1カ月	右	43.8	42.5	5 dB 以内
					左	43.8	48.8	5 dB 以内

みでは，難聴の進行・変動を説明することは困難と考えられた。

今回，*SLC 26 A 4* 変異例では難聴の進行は60%，難聴の変動は80%，反復性めまいは80%と高率に認められ，*ATP 6 V 1 B 1* 変異例でもこれら全てを呈した。一方，*SIX 1* 変異の2例中1例で軽度の難聴の進行を自覚したが，2例とも難聴の変動や反復性めまいは認められなかった。*SLC 26 A 4*・*ATP 6 V 1 B 1* 変異例と *SIX 1* 変異例の臨床所見の相違には，診察時の年齢，EVA 以外の奇形の存在，変異の種類などが影響する可能性がある。診察時の年齢に関しては，乳幼児例では難聴の進行・変動，めまいなどの症状を示さない時期にあることや，症状が認められたとしても自ら訴えられないことが影響を及ぼしうる。しかし，今回の症例は全例が12歳以上であり，乳幼児例は含まれていなかった。また，EVA 以外の内耳奇形の存在そのものが臨床症状の程度に影響する可能性が考えられる。しかし，IP などの蝸牛奇形は，少なくとも難聴の程度には有意な影響を及ぼさないことが報告されている[26]。一方，変異の種類は，一般的に症状の有無や程度に関連しうる。例えば，非症候群性遺伝性難聴で最も頻度の高い原因遺伝子 *GJB 2* では，c.235 delC 変異例は p.V 37 I 変異例よりも難聴が重篤であることが報告されている[27]。*SLC 26 A 4* 変異に関しては，東アジア人に多く認められる p.H 723 R（c.2169 A>G）のアリル数と難聴の程度との関連が報告されている[28]。本報告では，p.H 723 R アリルを2つもつホモ接合による変異例，p.H 723 R アリルを1つもつ複合ヘテロ接合による変異例，p.H 723 R 以外の変異例の各群の難聴の程度を比較したが，有意な相関は認められなかった。従って，この問題を解決するには，今後広い変異スペクトラムを持った多数の各遺伝子変異例を集積し，遺伝型と表現型との関連を検討する必要がある。

表3　平衡覚所見

症例	めまい			注視眼振	頭位眼振	頭位変換眼振	最大緩徐相速度（°／秒）	
	発症	性質	反復					
1	12歳	回転性	あり	なし	左水平回旋混合性		右	8
							左	3
2	小学校	浮動性回転性	あり	なし	なし	下向き垂直回旋性（懸垂頭位）	右	33
							左	29
3		なし		なし	なし	右水平性（座位）	右	36
							左	20
4	6歳	回転性	あり	なし	左水平性			
5	7歳	回転性	あり	なし	なし			
6	4歳	回転性	あり	なし	水平～水平回旋混合性		右	14
					方向交代上向性	右水平性（座位）	左	17
7		なし						
8		なし		なし	なし	なし	右	51
							左	29

SLC 26 A 4 変異例では，難聴の進行は37.5～100%，変動は50～100%，回転性めまいは70.5～100%に認められることが報告されている[28]。今回の *SLC 26 A 4* 変異例の難聴は，自覚的に80%が進行もしくは変動を示したが，当科経過観察期間中の平均聴力レベルの変化は10耳中7耳が5 dB以内と比較的安定しているものが多かった。この理由として，今回の症例の年齢が当科受診時にすでに19歳以上と高く，初診時に10耳中9耳が90 dB以上の重度難聴を示していたことからすでに不可逆的な高度障害が内耳に生じていたことが考えられる。反復性回転性めまいは80%に認められた。めまいの発症時期が難聴よりも遅延している理由として，前庭の代償機構が働くこと，乳幼児期にはめまいを必ずしも訴えられないこと，運動失調や平衡失調として現れる[2)21)]ため周囲に見過ごされている可能性が考えられた。Sugiuraら[29]は，めまい発作中の診察が可能であった4例において，難聴増悪直後から数日以内に30分から1日持続する回転性めまいを発症し，その後も長いと不安定感が数日持続することを報告している。今回の症例では，病歴聴取にて症例1が難聴の増悪とともにめまいが発症し，長いと3日程度持続していた。

SLC 26 A 4 変異例の平衡機能検査所見については，めまい発作時に難聴増悪側向きの水平性もしくは水平性回旋性混合性眼振が認められ，その後眼振の向きが反対側に変わる例が報告されている[29]。また，原因遺伝子は不明であるが，EVA例が方向交代性の頭位眼振を示す例も報告されている[2]。今回の頭位・頭位変換眼振検査では，非発作時に80%に眼振が認められ，定方向性の水平性もしくは水平性回旋性混合性眼振のほか，懸垂頭位もしくは座位への頭位変換時に眼振を認める例も存在した。*SLC 26 A 4* 欠失マウスでは巨大化した異常形態の耳石が観察されており[30]，方向交代性眼振や頭位変換時の眼振は良性発作性頭位めまい症と同様の機序により発生する可能性は否定できない。温度刺激検査は，EVA例の80～87%で異常を示す[19)25)]が，めまいのない異常症例が存在する一方でめまいを反復する正常症例が存在する[2]。今回も，症例2が反復性めまいを示したが温度刺激検査は正常であった。約半数のメニエール病症例では正常の温度刺激反応を示すことが報

表4　前庭水管径と平均聴力レベル，最大緩徐相速度との相関

	平均聴力レベル（n＝10）	最大緩徐相速度（n＝6）
中間部径	0.37（p＝0.30）	−0.26（p＝0.62）
開口部径	−0.42（p＝0.22）	0.28（p＝0.62）

告[31]されているが，温度刺激検査で評価する限り*SLC 26 A 4*変異例の前庭機能は聴覚機能に比べ可逆性を示す可能性がある。

Berrettini ら[7]は，遺伝学的検査は行われていないがEVAを合併するdRTAの3例を報告した。めまいの自覚や前庭機能の異常はなかったが，3例全例に難聴の進行，1例に変動が認められた。Shinjo ら[32]も難聴の進行と回転性めまいを示す同様の1例を報告している。本症例は，その後当科にて*ATP 6 V 1 B 1*と*ATP 6 V 0 A 4*の遺伝学的検査を行ったが変異は同定されなかった。*ATP 6 V 1 B 1*変異が同定されたEVA合併のdRTA例はJoshua ら[33]により報告され，非対称性の進行性難聴を示したが難聴の変動やめまいについては記載されていない。今回の*ATP 6 V 1 B 1*変異例[22]は，両難聴の変動・進行と反復性めまい発作を示し，*SLC 26 A 4*変異例と同様の聴平衡覚所見を示した。その後報告された*ATP 6 V 1 B 1*変異の2例は中等度もしくは高度難聴を示したが，難聴の進行・変動，めまいの有無は不明である[16]。

BOR/BO症候群では，全体としてみると34%にEVAを合併する[34]。しかし，本症候群では約40%に*EYA 1*変異が同定され[35]，*SIX 1*変異によるものは約4%[36]と少ない。EVAを合併する*SIX 1*変異については，われわれが症例7を最初に報告[14]したが，その後今回の症例8[23]以外に2家系4例が報告[36]されている。2家系中1家系はミスセンス変異（c.328 C>T）による4世代にわたるBOR/BO症候群家系であるが，変異が同定される前に臨床報告[37]がなされており，画像検査を施行した8例中3例に片側もしくは両側EVAを合併している。聴力検査上難聴の進行を認める例がいるが，EVAの有無や側とは関連はなく変動は認められないようである。また，暗所での不安定感を訴える例がいるが，反復性めまい発作はない。別の1家系ではミスセンス変異（c.334 C>T）を有し，両EVAと非対称性の進行性感音難聴を示したが，詳細は不明である。従って，今回の症例も含めると，*SIX 1*変異例では進行性難聴を示す可能性があるが必ずしもEVAの有無とは関連がなく，難聴の変動やめまい発作は認められない。

今回の検討結果からは，*SLC 26 A 4*変異や*ATP 6 V 1 B 1*変異を認める症例と*SIX 1*変異例では難聴の変動やめまいの点で異なる臨床症状を示した。各遺伝子生成タンパクの機能からみると，*Six*遺伝子ファミリーは共発現する*Eya*遺伝子ファミリーなどとともに多数の組織に広く認められ，器官の発生を規制している。特に，内耳発生においては*Six 1*とEya 1の相互作用が重要であり[38]，*Six 1*欠失マウスでは内リンパ管・内リンパ嚢拡大が生じる[39]。一方，*SLC 26 A 4/Slc 26 a 4*がコードするpendrinは内耳ではCl^-/HCO_3^-交換体として働いている[1]。*ATP 6 V 1 B 1/Atp 6 v 1 b 1*は，H^+・ATPaseのサブユニットの1つをコードするH^+ポンプである。従って，*SLC 26 A 4/Slc 26 a 4*と*ATP 6 V 1 B 1/Atp 6 v 1 b 1*にはpH調節という点で，*Six 1*にはない共通項がある。内リンパのpHは，蝸牛や卵形嚢では7.5，内リンパ嚢では6.6–7.1と局所ごとのイオン輸送によりコントロールされている[40]。この内リンパpHホメオスタシスは聴覚およびその維持に重要であり，主にH^+とHCO_3^-によりコントロールされている。*Slc 26 a 4*欠失マウスでは胎生E15.5から成体に到るまで内リンパの酸性化が認められる[1]。この酸性化と内リンパ嚢，内リンパ管の拡張は，二次的にコルチ器と血管条の発達障害を引き起こす。血管条には内リンパ電位生成において酸化ストレスに対するネガティブフィードバック機構が想定されているが，この破綻が内リンパ電位の恒常性に影響し難聴の変動や進行を示すことが考えられている[1]。*ATP 6 V 1 B 1/Atp 6 v 1 b 1*変異が内リンパのpHをアルカリ化するか否かは

不明であるが，H^+ ポンプをコードし dRTA の原因となることを考えれば同様に内リンパ pH ホメオスタシスに関与する可能性がある[40]。従って，*SLC 26 A 4* 変異例や *ATP 6 V 1 B 1* 変異例では何らかの誘因によりこの pH ホメオスタシスに破綻が生じ，難聴の進行・変動を引き起こすことが考えられる。反復性めまいの原因は十分に検討されていないが，難聴悪化時にめまいを随伴することがあり[22][29]，同様の機序が関与する可能性がある。

今回，異なる3つの原因遺伝子に分類し EVA の臨床症状を検討したが，各遺伝子群の症例数は必ずしも十分とは言えない。従って，今回の結論を確実なものとするためには，特に報告の少ない *ATP 6 V 1 B 1* 変異や *SIX 1* 変異などの *SLC 26 A 4* 変異以外で EVA の原因となる症例をより多く収集することが必須である。さらに，今後はグリセロールテスト，フロセミドテスト，VEMP などの機能検査を追加することで，より詳細な EVA の病態を評価していく必要があると考えられる。

ま と め

EVA を合併する *SLC 26 A 4* 変異5例，*ATP 6 V 1 B 1* 変異1例，*SIX 1* 変異2例の聴平衡覚所見を検討した。難聴の進行・変動，反復性めまいは *SLC 26 A 4* 変異例と *ATP 6 V 1 B 1* 変異例に認められたが，*SIX 1* 変異例では1例に軽度の難聴の進行を認めたものの難聴の変動や反復性めまいは認められなかった。従来より EVA の臨床的特徴とされてきた難聴の変動，反復性めまいは，前庭水管の拡大という解剖学的異常所見とは無関係に発症する可能性が示唆された。

本論文の要旨は，6 th international symposium on Meniere's disease and inner ear disorders (2010年11月，京都) および第69回日本めまい平衡医学会 (2010年11月，京都) にて発表した。

文　献

1) Griffith AJ, Wangmann P: Hearing loss associated with enlargement of the vestibular aqueduct: Mechanistic insights from clinical phenotypes, genotypes, and mouse models. Hear Res 281: 11–17, 2011
2) Jackler RK, De La Cruz A: The large vestibular aqueduct syndrome. Laryngoscope 99: 1238–1243, 1989
3) Lenvenson MJ, Parisier SC, Jacobs M, et al.: The large vestibular aqueduct syndrome in children. Arch Otolaryngol Head Neck Surg 115: 54–58, 1989
4) Griffith AJ, Arts HA, Downs C, et al.: Familial large vestibular aqueduct syndrome. Laryngoscope 106: 960–965, 1996
5) Phelps PD, Coffey RA, Trembath RC, et al.: Radiological malformations of the ear in Pendred syndrome. Clin Radiol 53: 268–273, 1998
6) Chen A, Francis M, Ni L, et al.: Phenotypic manifestations of branchio-oto-renal syndrome. Am J Med Genet 58: 365–370, 1995
7) Berrettini S, Forli F, Franceschini SS, et al.: Distal renal tubular acidosis associated with isolated large vestibular aqueduct and sensorineural hearing loss. Ann Otol Rhinol Laryngol 111: 385–391, 2002
8) Madden C, Halsted MJ, Hopkin RJ, et al.: Temporal bone abnormalities associated with hearing loss in Waardenburg syndrome. Laryngoscope 113: 2035–2041, 2003
9) Bauer PW, Wippold FJ 2 nd, Goldin J, et al.: Cochlear implantation in children with CHARGE association. Arch Otolaryngol Head Neck Surg 115: 54–58, 1989
10) Blaser S, Propst EJ, Martin D, et al.: Inner ear dysplasia is common in children with Down syndrome (trisomy 21). Laryngoscope 116: 2113–2119, 2006
11) Everette LA, Glaser B, Beck JC, et al.: Pendred syndrome is caused by mutations in a putative sulphate transporter gene. Nat Genet 17: 411–422, 1997
12) Coyle B, Reardon W, Herbrick J-A, et al.: Molecular analysis of the PDS gene in Pendred syndrome (sensorineural hearing loss and goiter). Hum Mol Genet 7: 1105–1112, 1998
13) Usami S-I, Abe S, Weston MD, et al.: Nonsyndromic hearing loss associated with enlarged vestibular aqueduct is caused by PDS mutations. Hum Genet 104: 188–192, 1999
14) Ito T, Noguchi Y, Yashima T, et al.: SIX 1

mutation associated with enlargement of the vestibular aqueduct in a patient with Branchio-Oto syndrome. Laryngoscope 116: 796-799, 2006
15) Joshua B, Kaplan DM, Raveh E, et al.: Audiometric and imaging characteristic of distal renal tubular acidosis and deafness. J Laryngol Otol 122: 193-198, 2008
16) Andreucci E, Bianchi B, Carboni I, et al.: Inner ear abnormalities in four patients with dRTA and SNHL: clinical and genetic heterogeneity. Pediatr Nephrol 24: 2147-2153, 2009
17) Arellano B, Ramirez Camacho R, Garcia Berrocal JR, et al.: Sensorineural hearing loss and Mondini dysplasia caused by a deletion at locus DFN 3. Arch Otolaryngol Head Neck Surg 126: 1065-1069, 2000
18) Zalzal GH, Tomaski SM, Vezina LG, et al.: Enlarged vestibular aqueduct and sensorineural hearing loss in childhood. Arch Otolaryngol Head Neck Surg 121: 23-28, 1995
19) Yetiser S, Kertmen M, Ozkaptan Y, et al.: Vestibular disturbance in patients with large vestibular aqueduct syndrome (LVAS). Acta Otolaryngol 119: 641-646, 1999
20) 藤崎俊之, 佐藤　斎, 和田匡史, 他：前庭水管拡大に伴う難聴の長期経過. Audiol Jpn 43: 169-174, 2000
21) Madden C, Halsted M, Benton C, et al.: Enlarged vestibular aqueduct syndrome in the pediatric population. Otol Neurotol 24: 625-632, 2003
22) Yashima T, Noguchi Y, Kawashima Y, et al.: Novel ATP 6 V 1 B 1 mutations in distal renal tubular acidosis and hearing loss. Acta Otolaryngol 130: 1002-1008, 2010
23) Noguchi Y, Ito T, Nishio A, et al.: Audiovestibular findings in a branchio-oto syndrome patient with a SIX 1 mutation. Acta Otolaryngol 131: 413-418, 2011
24) Wilson DF, Hodgson RS, Talbot JM: Endolymphatic sac obliteration for large vestibular aqueduct syndrome. Am J Otol 18: 101-107, 1997
25) Berrettini S, Forli F, Bogazzi F, et al.: Large vestibular aqueduct syndrome: audiological, radiological, clinical, and genetic features. Am J Otolaryngol 26: 363-371, 2005
26) King KA, Choi BY, Zelewski C, et al.: SLC 26 A 4 genotype but not cochlear radiologic structure is correlated with hearing loss in ears with an enlarged vestibular aqueduct. Laryngoscope 120: 384-389, 2010
27) Oguchi T, Ohtsuka A, Hashimoto S, et al.: Clinical features of patients with GJB 2 (connexin 26) mutations: severity of hearing loss is correlated with genotypes and protein expression patterns. J Hum Genet 50: 76-83, 2005
28) Suzuki H, Oshima A, Tsukamoto K, et al.: Clinical characteristic and genotype-phenotype correlation of hearing loss patients with SLC 26 A 4 mutations. Acta Otolaryngol 127: 1292-1297, 2007
29) Sugiura M, Sato E, Nakashima T, et al.: Long-term follow-up in patients with Pendred syndrome: vestibular, auditory and other phenotypes. Eur Arch Otorhinolaryngol 262: 737-743, 2005
30) Everett LA, Belyantseva IA, Noben-Trauth K, et al.: Targeted disruption of mouse Pds provides insight about the inner-ear defects encountered in Pendred syndrome. Hum Mol Genet 10: 153-161, 2001
31) Dobie RA, Snyder JM, Donaldson JA: Electronystagmographic and audiologic findings in patients with Meniere's disease. Acta Otolaryngol 94: 19-27, 1982
32) Shinjo Y, Kaga K, Igarashi T: Distal renal tubular acidosis associated with large vestibular aqueduct and sensorineural hearing loss. Ann Otol Rhinol Laryngol 111: 385-391, 2002
33) Joshua B, Kaplan DM, Raveh E, et al.: Audiometric and imaging characteristics of distal renal tubular acidosis and deafness. J Laryngol Otol 122: 193-198, 2008
34) Kemperman MH, Koch SM, Joosten FB, et al.: Inner ear anomalies are frequent but non-

obligatory features of the branchio-oto-renal syndrome. Arch Otolaryngol Head Neck Surg 128: 1033–1038, 2002
35) Chang EH, Menezes M, Meyer NC, et al.: Branchio-oto-renal syndrome: the mutation spectrum in EYA 1 and its phenotypic consequences. Hum Mutat 23: 582–589, 2004
36) Kochhar A, Orten DJ, Sorensen JL, et al.: SIX 1 mutation screening in 247 branchio-oto-renal syndrome families: a recurrent missense mutation associated with BOR. Hum Mutat 29: 565, 2008
37) Stinckens C, Standaert L, Casselman JW, et al.: The presence of a widened vestibular aqueduct and progressive sensorineural hearing loss in the branchio-oto-renal syndrome. A family study. Int J Pediatr Otorhinolaryngol 59: 163–172, 2001
38) Zheng W, Huang L, Wei ZB, et al.: The role of Six 1 in mammalian auditory system development. Development 130: 3989–4000, 2003
39) Ozaki H, Nakamura K, Funahashi J, et al.: Six 1 controls patterning of the mouse otic vesicle. Development 131: 551–562, 2004
40) Lang F, Vallon V, Knipper M, et al.: Functional significance of channels and transporters expressed in the inner ear and kidney. Am J Physiol Cell Physiol 293: C 1187–1208, 2007

利益相反に該当する事項はない。
本研究の一部は，厚生労働省難治性疾患克服研究事業・遺伝学的手法における診断の効果的な実施体制に関する研究（H 22–難治–一般–014）の補助を受けた。

別刷請求先：野口佳裕

急性感音難聴

Acute sensorineural hearing loss

佐藤 宏昭

POINT

近年，急性感音難聴に対するステロイドの局所治療（鼓室内注入）は注目されつつあるが，まだ発展途上の治療であることも事実である。本稿で本治療法の現状について以下の事項について述べる。

- ステロイドの局所投与の利点
- ステロイド全身投与と局所投与の内耳移行の比較
- 原因の明らかな急性感音難聴に対する局所投与
- 原因不明の急性感音難聴に対する局所投与

はじめに

副腎皮質ステロイド（以下，ステロイドと略す）にはサイトカインの産生抑制による抗炎症作用，活性酸素種の産生を抑制する抗酸化作用，内耳虚血に対する保護効果，抗アポトーシス活性などさまざまな薬理作用があり，内耳炎による急性感音難聴や音響外傷，耳毒性薬剤などの活性酸素種の増加に起因する急性感音難聴，さらに原因不明の急性感音難聴である突発性難聴など，多くの急性感音難聴の治療に使用されている。ステロイドの薬理作用にはまだ不明な点もあるが，これらの薬理作用により内耳に対して保護効果を有することはよく知られている。

本稿では急性感音難聴に対するステロイド局所投与（鼓室内注入）について，全身投与と比較してどのような長所があるのか，またその治療効果と評価，および基礎実験段階の研究も含めた研究の現状について述べる。

局所投与の利点

動物実験により鼓室内に注入したさまざまな物質が内耳へ移行することは古くから知られており，この経路を利用した治療法として1950～60年代にはメニエール病に対する局麻薬やアミノ配当体系抗菌薬の注入，1970年代には慢性耳鳴に対する局麻薬の注入が試みられている。これらの薬剤と同様にステロイドも鼓室内注入により内耳に移行することが報告され[1]，その後の基礎実験で静注や経口などの全身投与に比べはるかに高濃度に移行することも明らかとなり，近年突発性難聴の新たな治療法として注目されている。正円窓膜の薬剤透過性を利用した鼓室内注入療法の長所としては，静注，経口などの全身投与に比べはるかに少ない投与量で内耳へ高濃度に薬剤を移行させることができ，投与薬剤の副作用を低減しうる点が挙げられる。特に糖尿病を有する急性感音難聴などステロイドの全身投与を避けたい例にはきわめて有用な投与法である。

さとう ひろあき：岩手医科大学耳鼻咽喉科教室（〒020-8505 岩手県盛岡市内丸19-1）

0914-3491/13/¥500/論文/JCOPY

表 1　ステロイド鼓室内注入による鼓室階外リンパへの移行濃度

報告者	対象	測定法	曝露時間	外リンパ濃度
野村（1982） Dex	モルモット $n=3$	HPLC	15 分	1.3 μg/mL
佐藤（1989） Dex	モルモット $n=7$	RIA	3 時間	2.6 μg/mL
Parnes（1999） Dex	モルモット $n=6$	HPLC	30 分	1.55 μg/mL
Chandrasekhar（2000） Dex	モルモット $n=15$	RIA	15,30,60 分	0.13～0.22 μg/mL
Bachmann（2001） PSL	モルモット $n=9$	HPLC	15 分～16 時間 （採取時間）	18.7～952 μg/mL
Bird（2007） MPSL	ヒト $n=39$	HPLC	0.3～2.2 時間	6.7 μg/mL

（文献 2 より引用）

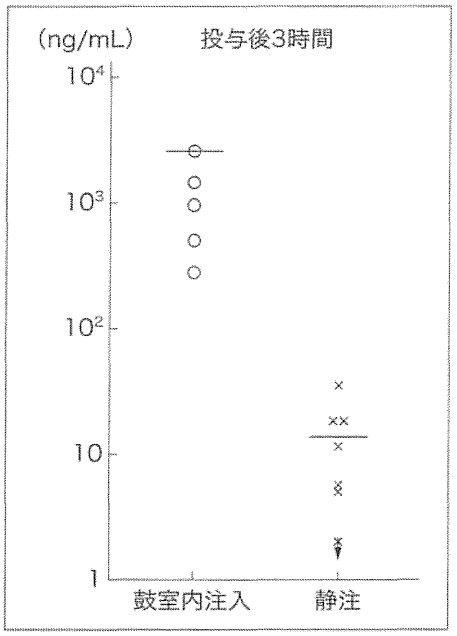

図 1　静注と鼓室内注入のモルモット鼓室階外リンパ中デキサメタゾン濃度の比較
デキサメタゾンの鼓室内注入量は 100 ng (0.05 mL), 静注は 250～450 ng (1 mg/kg)
（文献 3 より引用）

表 2　鼓室内注入と静注との鼓室階外リンパ移行濃度の比較

報告者/ 静注投与量	静注	鼓室内注入	移行 濃度比
佐藤（1989） Dex 1 mg/kg	0.013 μg/mL （3 時間）	2.6 μg/mL （3 時間）	189.6 倍
Parnes（1999） Dex 8 mg/kg	0.063 μg/mL （4 時間：peak 値）	1.55 μg/mL （0.5 時間：1時間後 peak 値）	24.7 倍
Chandrasekhar（2000） Dex 0.45 mg/kg	0.05 μg/mL （1 時間）	0.22 μg/mL （1 時間）	4.4 倍
Bachmann（2001） PSL 60 mg/kg	14.7 μg/mL （2.5 時間後 peak 値）	952 μg/mL （3 時間後 peak 値）	64.8 倍
Bird（2007） MPSL 10 mg/kg	0.053 μg/mL （0.3～2.2 時間）	6.7 μg/mL （0.3～2.2 時間）	126.4 倍

（文献 2 より引用）

ステロイド鼓室内注入と静注との移行濃度の比較

鼓室内に注入したステロイドの鼓室階外リンパへの移行を調べた報告を**表 1** に示した。鼓室階外リンパでは採取できる検体が微量であるため，移行濃度の測定には高速液体クロマトグラフィー（HPLC）ないしラジオイムノアッセイ（RIA）が用いられる。報告によりステロイドの種類，注入から検体採取までの時間（曝露時間）がさまざまなため単純な比較は困難だが，モルモットではデキサメタゾンで 0.22～2.6 μg/mL，プレドニゾロンで 952 μg/mL，ヒトではメチルプレドニゾロンで 6.7 μg/mL の移行濃度が得られている。これまでのさまざまな動物実験で鼓室内注入後の鼓室階外リンパへのステロイドの移行濃度は，静注や経口による全身投与に比べ 4.4～189.6 倍とはるかによいことが明らかとなっている[2,3]（**図 1, 表 2**）。