学位論文

Nationwide Epidemiological Survey of Delayed Endolymphatic Hydrops in Japan

遅発性内リンパ水腫に関する全国疫学調査

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Contents

Overall introduction

Delayed endolymphatic hydrops (DEH) is a very rare disease and its actual clinical status is still unknown. Therefore, I attempted to clarify the epidemiological characteristics of DEH through two nationwide epidemiological surveys in Japan. In one survey, a questionnaire was administered to hospitals with otorhinolaryngology departments throughout Japan to estimate the number of patients with DEH in Japan and to determine the prevalence of DEH. In the other survey, clinical information on patients with DEH was collected from several base hospitals over a period of many years and their epidemiological characteristics and trends were statistically analyzed.

This doctoral dissertation is based on the following two papers [1, 2].

[1] Ito S, Takakura H, Akaogi K, et al. Estimated Number and Prevalence of Patients with Delayed Endolymphatic Hydrops in Japan: A Nationwide Survey. Acta Otolaryngol. 2022;published online.

[2] Ito S, Takakura H, Akaogi K, et al. A 14-year nationwide epidemiological analysis of delayed endolymphatic hydrops in Japan. Acta Otolaryngol. 2022;142(7-8):568-574.

Chapter 1

Estimated Number and Prevalence of Patients with Delayed Endolymphatic Hydrops in Japan : A Nationwide Survey

Abstract

Background: Delayed endolymphatic hydrops (DEH) is a rare disease, and the actual number of patients in Japan remains unknown.

Objective: To investigate the number and prevalence of patients with DEH in Japan.

Methods: In total, 781 departments of otorhinolaryngology in Japan were selected for survey by stratified random sampling according to the total number of hospital beds. I sent questionnaires to the target departments and collected data regarding the number of patients with DEH who visited those departments in 2019.

Results: The overall response rate was 68.0% (531 departments). The estimate number of patients with DEH in Japan was 962, and the prevalence was calculated to be 0.8 per 100,000 population.

Conclusion: Patients with DEH were extremely rare in Japan.

Significance: This may be the first nationwide epidemiological study on the number and prevalence of patients with DEH in Japan or in the world.

Keywords: delayed endolymphatic hydrops, nationwide survey, prevalence

Introduction

Delayed endolymphatic hydrops (DEH) is a disease that is preceded by severe sensorineural deafness and followed by vertigo attacks such as those of Meniere's disease (MD) or hearing fluctuations in the contralateral ear several years to decades later. DEH was proposed by Schuknecht in 1978 and is classified into ipsilateral and contralateral types [1]. Ipsilateral DEH is defined as a disease of recurrent rotatory vertigo secondary to endolymphatic hydrops (EH) in the ipsilateral ear with preceding severe deafness, whereas contralateral DEH is defined as the formation of EH in the contralateral ear, resulting in fluctuating sensorineural hearing loss [1]. From a pathological point of view, Schuknecht proposed the following as the mechanism of DEH: the resorptive mechanism of the ipsilateral or contralateral inner ear, probably the rugose epithelium of the endolymphatic sac, is injured during preceding deafness and eventually disrupts the balance between secretion and resorption of endolymph, resulting in progressive EH that causes attacks of auditory and/or vestibular systems [2].

In Japan, the diagnostic criteria for DEH were proposed by the Japan Society for Equilibrium Research in 1987 [3], and DEH has been treated as a clinical entity distinct from MD. Furthermore, in 2015, DEH was selected as a designated intractable disease in Japan (meaning an intractable disease for which the number of patients has not reached the number of people specified by Order of the Ministry of Health, Labour and Welfare in Japan, by which certain standards are established from objective indicators with regard to the diagnosis of the intractable disease, and which has high necessity to ensure high-quality and appropriate medical care for patients with the intractable disease judging from the situation in which the patients is put). Legislation has been established to allow patients with severe DEH to receive specific medical expenses. The Japanese criteria for

designated intractable diseases are as follows: (1) rarity (affecting less than 0.1% of the population in Japan), (2) unknown etiology, (3) lack of effective treatment, (4) necessity of long-term treatment, and (5) existence of objective diagnostic criteria [4]. In this regard, the diagnostic criteria for DEH were revised in 2017, and a severity classification was added [5]. The number and prevalence of patients with DEH in Japan have been estimated based on the results of previous nationwide surveys of MD [6], which report the estimated number of DEH patients to be about one-tenth that of MD [7]. However, exact data based on a nationwide epidemiological survey of DEH remain unknown. Thus, I conducted a nationwide epidemiologic survey to estimate the number of patients with DEH in the Japanese population in 2019 and to calculate the prevalence of DEH in Japan.

Methods

Nationwide epidemiologic survey

I conducted a nationwide epidemiological survey targeting hospitals with a department of otorhinolaryngology to estimate the number of patients with DEH in the Japanese population. This nationwide epidemiologic survey was conducted from December 2020 to March 2021 in accordance with the Nationwide Epidemiologic Survey Manual issued by the Research Committee on the Epidemiology of Intractable Diseases in Japan [8].

A stratified random sampling method was applied to estimate the number of patients with DEH by which the targets were selected from all departments of otorhinolaryngology in Japan according to the number of hospital beds, and 781 departments were selected for analysis. The target hospitals were stratified into the following seven categories (with their respective sampling proportions): university hospitals (100%), general hospitals with ≥ 500 beds (100%), 400-499 beds (80%), 300-

399 beds (40%), 200-299 beds (20%), 100-199 beds (10%), ≤ 99 beds (5%).

The questionnaire was sent to each sampled department in December 2020, requesting answers to the following: 1) the number of all patients with DEH who visited the department between January 1 and December 31, 2019 (both initial and follow-up visits) and 2) the number of males among them. Two and three months after the initial mailing, I mailed reminder letters to those departments that had not yet responded. The deadline for collection of responses to the questionnaire was set at March 22, 2021.

This study was approved by the Ethics Committee of Toyama University Hospital, Toyama, Japan (Approval number: R2018178).

Statistical analysis

The total number of patients in Japan was estimated by multiplying the reported patient numbers by the reciprocal of the sampling rate and survey response rate for each category and summing them [8]. The overall prevalence rates in the Japanese population were calculated based on the Japanese population on 1 October 2019 [9].

Results

In total, 781 departments were sampled in this study through stratified random sampling from all departments of otorhinolaryngology in Japan, and the overall response rate was 68.0% (531/781 departments). The response rate by category of hospitals was highest for university hospitals (87.9%), follow by general hospitals with ≥ 500 beds (69.6%) (Table 1).

Finally, a total of 589 patients with DEH were reported, among whom 241 were male (40.9%). The number of DEH patients was highest in university hospitals (65.2%),

whereas they were rare in general hospitals with less than 300 beds (Table 1).

Table 1. Response rates to the survey on patients with delayed endolymphatic hydrops according to hospital category.

Categories of hospitals	Sampling rate (%)	Sampled departments	Responding departments	% response	Number of patients	%	Number of male patients	%
University hospitals	100	132	116	87.9	384	65.2	163	67.6
≥ 500 beds	100	227	158	69.6	123	20.9	48	19.9
400 - 499 beds	80	175	109	62.3	46	7.8	16	6.6
300 - 399 beds	40	136	84	61.8	22	3.7	6	2.5
200 - 299 beds	20	55	29	52.7	8	1.4	7	2.9
100 - 199 beds	10	46	30	65.2	6	1.0	1	0.4
≤ 99 beds	5	10	5	50.0	0	0.0	0	0.0
Total		781	531	68.0	589	100	241	100

The estimated numbers of patients with DEH by category of hospitals are shown in Table 2. There were estimated to be 962 patients with DEH (95% confidence interval: 811–1,114) in Japan, with the largest number of patients visiting university hospitals (45.3%). The calculated prevalence was 0.8 per 100,000 population based on the mid-year population of Japan in 2019 [9].

Table 2. Estimated number of patients in Japan with delayed endolymphatic hydrops according to hospital category.

Categories of hospitals	Estimated number of patients	95% CI
University hospitals	436	374–500
≥ 500 beds	176	131–223
400 - 499 beds	92	59–126
300 - 399 beds	89	26–152
200 - 299 beds	75	11–141
100 - 199 beds	92	6–178
≤ 99 beds	0	0
Total	962	811–1114

CI: confidence interval.

Discussion

I conducted a nationwide epidemiological survey to estimate the number of patients with DEH in Japan in 2019. The present study revealed that there were 962 patients with DEH throughout Japan in 2019 and that the prevalence of DEH was 0.8 per 100,000 population. This is the first nationwide survey to estimate the number of patients with DEH and to calculate prevalence of DEH in Japan. As far as I are aware, this is the first study in the world to report the number of patients with DEH and its prevalence in a given region.

The study was designed in accordance with a manual developed by the Research Committee on the Epidemiology of Intractable Diseases in 2017 with the aim of unifying the methodology of nationwide epidemiological surveys for intractable diseases in Japan. The survey was limited to hospitals with a department of otorhinolaryngology as the main symptoms of DEH are hearing loss and vertigo, and it is presumed that most treatments for patients with DEH are provided by otorhinolaryngologists in Japan.

In Japan, even though university hospitals account for only about 7% of all hospitals with otorhinolaryngology departments, it was estimated that about half of the patients with DEH visited university hospitals in this survey. As indicated by the present study, DEH is a rare disease, and it is expected that some patients will visit a more specialized university hospital because they cannot be diagnosed or are difficult to treat in general hospitals. In addition, the higher response rate from university hospitals in the survey compared to other general hospital categories may have affected the estimates of the number of patients.

In this study, I statistically estimated the prevalence of DEH in Japan to be 0.8 per 100,000 population. There are only a few reports referring to the prevalence of DEH in Japan and no statistical reports on the prevalence of DEH in the overall population in

Japan. The prevalence of DEH was reported to be one-twelfth that of MD by Kudo et al. [10] and to be one-seventh by Watanabe et al. [11], although these estimates were based on the number of patients with DEH and MD at a single institution. In a multicenter study, Watanabe et al. reported a prevalence of DEH of one-tenth that of MD based on the number of patients with DEH and MD at seven institutions [7]. Considering that the reported prevalence of MD in Japan is 34.5 per 100,000 population [12], the prevalence of DEH calculated in the present study is extremely low compared to previous expectations. All of the preceding reports are based on the number of patients visiting a university hospital. This study revealed that patients with DEH tend to more frequently visit university hospitals, indicating that previous studies may have overestimated the number of patients with DEH.

Regarding the sex of DEH patients, 241 (40.9%) of the 589 reported patients were male, confirming a slight female predominance, a result consistent with previous studies [13,14]. With respect to patient sex, MD tends to be more common in females than males [12,15,16], and a Japanese survey reported that 62.4% of the patients were females [17], indicating a similar trend in patient sex in DEH as in MD.

There are several limitations to this study. First, it is possible that patients who visited more than one hospital were counted as duplicates. If such patients were included, the number of patients with DEH would be even smaller. Second, although the survey was limited to departments of otorhinolaryngology, it is possible that there are patients with DEH who were treated in other departments. In particular, patients with the ipsilateral type of DEH can have previous deafness for several years, but the only new symptom that appears after the onset of DEH is vertigo, which does not preclude the possibility of patients visiting other departments in Japan, such as internal medicine. Third, it is possible

that some patients with the contralateral type of DEH who do not have vertigo may not be diagnosed as having DEH because it is difficult to distinguish from bilateral progressive hearing loss. If a large number of such patients exist, I may have underestimated the number of patients with DEH.

In conclusion, I conducted a nationwide survey to estimate the number and prevalence of patients with DEH in Japan in 2019. The number of patients with DEH in Japan was estimated to be 962, and the prevalence was calculated to be 0.8 per 100,000 population. This report may not only be the first nationwide epidemiological study on the number and prevalence of patients with DEH in Japan but also in the world.

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Abbreviations

DEH: delayed endolymphatic hydrops; EH: endolymphatic hydrops; MD: Meniere's disease

Disclosure statement

The authors have no funding, financial relationships, or conflicts of interest to disclose.

References

[1] Schuknecht HF. Delayed endolymphatic hydrops. Ann Otol Rhinol Laryngol. 1978;87(6 Pt 1):743-748.

[2] Schuknecht HF. Neurolabyrinthitis. Viral infections of the peripheral auditory and vestibular systems. In: Nomura Y, editor. Hearing loss and dizziness. Tokyo: Igaku-Shoin; 1985.

[3] Komatsuzaki A, Harada Y, Hozawa J, et al. Delayed endolymphatic hydrops. The guideline for standardization of diagnostic criteria in vertiginous diseases. The Committee for Standardization of Diagnostic Criteria in 16 Vertiginous Diseases. Equilib Res. 1988;47(2):249-250.

[4] Kanatani Y, Tomita N, Sato Y, et al. National Registry of Designated Intractable Diseases in Japan: Present Status and Future Prospects. Neurol Med Chir. 2017;57(1):1-7.

[5] Ikezono T, Ito A, Takeda N, et al. Documents for standards in diagnostic criteria for dizziness. Equilib Res. 2017;76:233-241.

[6] Shojaku H, Takakura H, Tsubota M, et al. 2014 reports of epidemiological study of Meniere's disease and delayed endolymphatic hydrops. Research comittee on Intractable Equilibrium Dysfunction, Health, Labour and Welfare Research Grants for Intractable Disease Policy Research Project. Ministry of Health, Labour and Welfare, Japan. 2015. p. 105–109.

[7] Watanabe Y, Shojaku H, Ueda Y, et al. Multicenter case study of delayed endolymphatic hydrops. 1998 reports of the Peripheral Vestibular Disorder Research Committee of Japan. 1998. p. 54-56.

[8] Nakamura Y, Hirota Y, Kawamura T, et al. Manual of nationwide epidemiological survey for understanding the patient number and clinical epidemiology for the rare diseases, 3rd ed. Research committee of continuous epidemiological data collection and analysis of rare diseases, Health, Labour and Welfare Sciences Research Grants, the Ministry of Health, Labour and Welfare, Japan. 2017. [cited 2022 Jun 4]. Available from: https://www.jichi.ac.jp/dph/nanbyou/manual_2017.pdf.

[9] Portal Site of Official Statistics of Japan (e-stat). Ministry of Internal Affairs and Communications. Population Estimates as of 1 October 2019. Statistics Bureau of Japan, Japan. 2019. [cited 2022 June 4]. Available from: https://www.e-stat.go.jp/dbview?sid=0003412313

[10] Kudo Y, Senba T, Futaki T. Delayed endolymphatic hydrops. Diagnosis and treatment. Pract Otorhinolaryngol. 1986;Suppl 8:208-216.

[11] Watanabe Y, Aso S, Mizukoshi K. Clinical findings of delayed endolymphatic hydrops -Characteristics of contralateral cases-. Equilib Res. 1989;48:152-157.

[12] Shojaku H, Watanabe Y, Fujisaka M, et al. Epidemiologic characteristics of definite Meniere's disease in Japan. A long-term survey of Toyama and Niigata prefectures. ORL J Otorhinolaryngol Relat Spec. 2005;67(5):305-309.

[13] Shojaku H, Watanabe Y, Takeda N, et al. Clinical characteristics of delayed endolymphatic hydrops in Japan: A nationwide survey by the Peripheral Vestibular Disorder Research Committee of Japan. Acta Otolaryngol. 2010;130(10):1135-1140.

[14] Albera A, Canale A, Boldreghini M, et al. Contralateral delayed endolymphatic hydrops: Clinical features and long term outcome. J Otol. 2021;16(4):205-209.

[15] Harris JP, Alexander TH. Current-day prevalence of Meniere's syndrome. Audiol Neurotol. 2010;15(5):318-322.

[16] Basura GJ, Adams ME, Monfared A, et al. Clinical Practice Guideline: Meniere's Disease. Otolaryngol Head Neck Surg. 2020;162(2 suppl):S1-S55.

[17] Shojaku H, Watanabe Y, Yagi T, et al. Changes in the characteristics of definite Meniere's disease over time in Japan: a long-term survey by the Peripheral Vestibular Disorder Research Committee of Japan, formerly the Meniere's Disease Research Committee of Japan. Acta Otolaryngol. 2009;129(2):155-160.

Chapter 2

A 14-Year Nationwide Epidemiological Analysis of Delayed Endolymphatic Hydrops in Japan

Abstract

Background: Delayed endolymphatic hydrops (DEH) is an inner ear disease that causes recurrent vertigo in the ipsilateral ear or fluctuating hearing in the contralateral ear due to endolymphatic hydrops secondary to preceding deafness. There are few reports of large, multicentre studies investigating the clinical-epidemiological characteristics of DEH.

Objective: This study aimed to clarify the characteristics of DEH in Japan.

Methods: Clinical data on 662 patients with DEH were analysed by nationwide, multicentre surveys conducted by the Peripheral Vestibular Disorders Research Group of Japan.

Results: The proportion of ipsilateral DEH (IDEH) was slightly higher than that of contralateral DEH (CDEH) at 55.4%. The time delay between onset of precedent deafness and onset of DEH was significantly longer for CDEH than for IDEH. The most common cause of precedent deafness was a disease of unknown cause with onset in early childhood (33.1%). Epidemiological characteristics were not significantly different between CDEH with and without vertigo.

Conclusion: DEH appearing to be caused by viral labyrinthitis has a high rate of onset within 40 years of precedent deafness. Clinical and epidemiological characteristics of IDEH, CDEH with vertigo, and CDEH without vertigo were very similar.

Significance: The clinical-epidemiological characteristics of DEH in Japan were clarified.

Keywords: delayed endolymphatic hydrops, ipsilateral, contralateral, epidemiological characteristics, Japanese nationwide survey

Introduction

Delayed endolymphatic hydrops (DEH) is an inner ear disease that causes recurrent rotatory vertigo in the ipsilateral ear or fluctuating hearing changes in the contralateral ear due to endolymphatic hydrops (EH) secondary to a preceding severe sensorineural hearing loss [1,2]. In 1971, Kamei et al. reported for the first time in the world that Meniere's disease-like vertigo attacks occur sequentially in patients with juvenile unilateral deafness of unknown cause [3]. In 1975, Wolfson and Leiberman [4] and Nadol et al. [5] separately reported that patients with unilateral severe hearing loss other than juvenile unilateral deafness also have a delayed onset of similar sequential attacks of vertigo and that the disease might be caused by EH. In 1978, Schuknecht first proposed the concept of DEH, which occurs in patients who have sustained a profound hearing loss in one ear, usually from infection or trauma, and then after a prolonged period of time develop either episodic vertigo from the same ear (ipsilateral DEH: IDEH) or fluctuating hearing loss, also sometimes with episodic vertigo, in the opposite ear (contralateral DEH: CDEH) [1]. This disease concept has largely continued to the present. Since the publication of this literature, many studies [6,7] have been conducted on the clinical and epidemiological features of DEH. However, most have been single-centre studies, and the small number of cases of DEH compared to those of Meniere's disease has made significant statistical analysis difficult. In Japan, the Meniere's Disease Research Group was organized by the Ministry of Health, Labour and Welfare in 1974 and reorganized into the Peripheral Vestibular Disorders Research Group in 1980. Then, nationwide multi-centre epidemiological surveys of DEH were conducted by the Peripheral Vestibular Disorders Study Group in 1998, 2001, and annually since 2006, and data on DEH cases have accumulated. The diagnostic criteria for DEH were proposed by the

Japan Society for Equilibrium Research (JSER) in 1987 and have been used for many years [8]. These criteria were developed for what was reported by Schuknecht to be the IDEH. However, it was noted that the diagnosis of CDEH does not completely distinguish Meniere's disease that develops in the good ear independently of preceding severe hearing loss, especially in patients with vertigo [9].

In 2010, Shojaku et al. reported a review of clinical characteristics regarding DEH using data from 198 cases collected in the first 5 years of these nationwide surveys according to these diagnostic criteria of DEH. They compared demographic characteristics, distribution of diagnosis of the precedent deafness, and time delay (TD) between the onset of precedent deafness and that of DEH between IDEH and CDEH and found no significant difference between them [10]. However, the insufficient number of cases of CDEH accumulated made it impossible to investigate whether a difference exists in clinical and epidemiological characteristics between CDEH with and without vertigo.

Thus, I examined the clinical and epidemiological characteristics of patients with IDEH and CDEH on an unprecedented scale, using data from a nationwide multicentre survey of DEH patients enrolled over the past 14 years by adding another 9 years of data to the initial 5 years of data comprising 198 cases reported by Shojaku et al. in 2010. For CDEH, patients were divided into two groups, those with and without vertigo, and differences in characteristics between the two patient groups were examined.

Methods

This study was approved by the Ethics Committee of Toyama University Hospital, Toyama, Japan (Approval number: R20180219).

Nationwide surveys were conducted in 1998, 2001, and from 2006 to 2017 by the

Vestibular Disorder Research Group of the Ministry of Health, Labour and Welfare in Japan, which enrolled patients with DEH from 21 public and private university hospitals. The diagnostic criteria for IDEH and CDEH were based on the following criteria developed by the JSER in 1987 [8]. Medical history includes (1) severe hearing loss or total deafness in one or both ears (pre-existing inner ear disorder is suspected); (2) development of Meniere's disease-like vestibular symptoms after many years (usually several years to several decades after the onset of hearing loss); or (3) absence of cochlear symptoms, especially auditory fluctuations, during attacks of vertigo. Examination reveals (1) severe sensorineural hearing loss or total deafness in one or both ears by pure tone audiometry; (2) a reduced nystagmus response in the hearing-impaired ear by Caloric test; (3) spontaneous horizontal rotatory nystagmus during vertigo attacks or evidence of evoked nystagmus; and (4) absence of neurological symptoms except for those of the VIIIth cranial nerves, and especially symptoms related to cranial nerves [8]. Although no clear diagnostic criteria were given for CDEH, the main points of the diagnosis were described as follows [8]: (1) severe (sensorineural) hearing loss or total deafness in one ear (previously present) and new hearing impairment in the other ear (good hearing ear) (It is presumed that the hearing was normal on this side until the time of impairment); (2) fluctuation of hearing in the good ear (at the same time, various features of sensorineural hearing loss may be present); (3) occasional Meniere's disease-like vestibular symptoms (depending on the case); (4) demonstration of vestibular dysfunction, which is not abolished, in the good hearing ear; (5) the presence of spontaneous horizontal rotatory nystagmus or evoked nystagmus during attacks in patients with vertigo; (6) absence of neurological symptoms; and (7) performance of a glycerol test or electrocochleogram as an ancillary inspection.

All data for the 14-year nationwide surveys were stored and analysed in the database software of the Department of Otorhinolaryngology, Head and Neck Surgery, University of Toyama. In this study, I divided the DEH patients into three groups, those with IDEH, CDEH with vertigo (CDEHwV), and CDEH without vertigo (CDEHwoV).

The following outcome measures were analysed between the three groups: age and sex distribution, ratio of patients, numbers, diagnosis of the precedent hearing loss, onset age of the precedent hearing loss, onset age of DEH, and TD between the onset of precedent deafness and the onset of DEH. The TD was evaluated according to three time periods: 0–19 years, 20–39 years, and ≥40 years.

Statistical analysis

Quantitative variables of patient characteristics and outcome measures are presented as means ± standard deviation (SD). Comparisons between the three groups were performed with one-way ANOVA or the Kruskal-Wallis test depending on the distribution of variables according to the Shapiro-Wilk test and the homogeneity of variances according to Levene's test.

Categorical variables are presented as numbers with percentages and were compared using the chi-square test or Fisher's exact test, as appropriate. If the results of either test were significant, a residual analysis or multiple comparisons with Bonferroni correction were performed as post hoc tests, respectively.

A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics 26.0 software (IBM Corporation, Chicago, IL).

Results

Based on the diagnostic criteria of the JSER proposed in 1987, in total, 662 DEH patients were enrolled in the study over the 14-year period comprising 1998, 2001, and 2006 to 2017. There were 367 cases of IDEH, 209 of CDEHwV, and 86 of CDEHwoV, as shown in Table 1. The mean patient age (years) was 50.1 ± 18.6 for IDEH, 52.2 ± 19.1 for CDEHwV, and 52.0 ± 19.4 for CDEHwoV, with no statistically significant difference between them ($p = 0.371$). The female ratio was 53.7% for IDEH, 57.4% for CDEHwV, and 59.3% for CDEHwoV, all with a slight female predominance, and no statistically significant differences were observed between the three groups ($p = 0.447$). There was no statistically significant difference between the three DEH groups with respect to the affected ear side ($p = 0.459$). With respect to onset age of precedent deafness, the number of patients with a clear description was 328 for IDEH, 184 for CDEHwV, and 71 for CDEHwoV, and their mean ages (years) were 21.7 ± 22.0, 19.0 ± 21.7, and 17.2 ± 20.6, respectively, with no statistically significant differences ($p = 0.171$). Regarding onset age of DEH, the number of patients with a clear description was 272 for IDEH, 146 for CDEHwV, and 42 for CDEHwoV, and their mean ages (years) were 43.9 ± 19.4, 45.3 ± 19.8, and 49.7 ± 18.1, respectively, with no statistically significant differences ($p = 0.187$). As for the TD between the onset of precedent deafness and DEH, the valid sample size was 278 cases for IDEH, 149 cases for CDEHwV, and 43 cases for CDEHwoV. The years until onset were 22.1 ± 15.4, 25.8 ± 17.5, and 29.7 ± 19.6, respectively, and were significantly different ($p = 0.003$). Post hoc tests with Bonferroni correction showed statistically significant differences between IDEH and CDEHwV and between IDEH and CDEHwoV.

Table 1. Characteristics of the patients with DEH

	IDEH	CDEHwV	CDEHwoV	p-Value
Total no. of patients	367	209	86	
Mean age, years	50.1 ± 18.6	52.2 ± 19.1	52.0 ± 19.4	.371*
Sex				
Male	169 (46.0%)	88 (42.1%)	34 (39.5%)	.447**
Female	197 (53.7%)	120 (57.4%)	51 (59.3%)	
Unknown	1 (0.3%)	1 (0.5%)	1 (1.2%)	
Affected side				
Right	156 (42.5%)	84 (40.2%)	44 (51.2%)	.459**
Left	192 (52.3%)	117 (56.0%)	39 (45.3%)	
Unknown	19 (5.2%)	8 (3.8%)	3 (3.5%)	
Onset age of precedent deafness				
No. of valid samples	328	184	71	
Mean age, years	21.7 ± 22.0	19.0 ± 21.7	17.2 ± 20.6	.171*
Onset age of DEH				
No. of valid samples	272	146	42	
Mean age, years	43.9 ± 19.4	45.3 ± 19.8	49.7 ± 18.1	.187*
Time delay between onset age of precedent deafness and onset age of DEH				
No. of valid samples	278	149	43	
Mean, years	21.1 ± 15.4[a,b]	25.8 ± 17.5[a]	29.7 ± 19.6[b]	.003*

DEH: delayed endolymphatic hydrops; IDEH: ipsilateral DEH; CDEHwV: contralateral DEH with vertigo; CDEHwoV: contralateral DEH without vertigo.

* Kruskal-Wallis test.

** Fisher's exact test.

[a] Significant result of post-hoc test with Bonferroni correction between IDEH and CDEHwV.

[b] Significant result of post-hoc test with Bonferroni correction between IDEH and CDEHwoV.

Table 2 shows the distribution of diagnoses of diseases causing precedent deafness in each DEH group. Of the 367 patients with IDEH, diagnoses of precedent deafness were unknown in 228 (62.1%), sudden deafness in 80 (21.8%), mumps deafness in 40 (10.9%), and others in 19 (5.2%). Of the 209 patients with CDEHwV, the causal diagnoses of precedent deafness were unknown in 126 (60.3%), sudden deafness in 44 (21.1%), mumps deafness in 18 (8.6%), and others in 21 (10.0%). Of the 86 CDEHwoV patients, the diagnoses causing precedent deafness were unknown cause in 49 (57.0%), sudden deafness in 17 (19.8%), mumps deafness in 10 (11.6%), and others in 10 (11.6%). There was no significant difference in the distribution of diagnoses of diseases causing precedent deafness among the three types of DEH (p = 0.263). The main diagnoses of precedent deafness were deafness of unknown cause (with onset in early childhood as the most common diagnosis), sudden deafness, and mumps deafness.

Table 2. Diagnoses of diseases causing precedent deafness in DEH

Diagnosis	IDEH	CDEHwV	CDEHwoV	p-Value
Unknown cause	228 (62.1%)	126 (60.3%)	49 (57.0%)	.263*
Onset in early childhood	118 (32.2%)	71 (34.0%)	30 (34.9%)	
Onset age ≥ 5 years	73 (19.9%)	34 (16.3%)	7 (8.1%)	
Onset unknown	37 (10.1%)	21 (10.0%)	12 (14.0%)	
Sudden deafness	80 (21.8%)	44 (21.1%)	17 (19.8%)	
Mumps deafness	40 (10.9%)	18 (8.6%)	10 (11.6%)	
Others	19 (5.2%)	21 (10.0%)	10 (11.6%)	
Otitis media and mastoiditis	15 (4.1%)	12 (5.7%)	6 (7.0%)	
Meningitis	2 (0.5%)	4 (1.9%)	1 (1.2%)	
Trauma	1 (0.3%)	1 (0.5%)	1 (1.2%)	
Inner ear malformation	0	2 (1.0%)	1 (1.2%)	
Acoustic tumor	0	1 (0.5%)	1 (1.2%)	
Drug-induced hearing loss	1 (0.3%)	1 (0.5%)	0	
Total	367 (100.0%)	209 (100.0%)	86 (100.0%)	

DEH: delayed endolymphatic hydrops; IDEH: ipsilateral DEH; CDEHwV: contralateral DEH with vertigo; CDEHwoV: contralateral DEH without vertigo.

* By chi-square test.

The onset age of precedent deafness and that of DEH, and the TD between the onset of these two conditions among the three main causes of precedent deafness can be compared for each DEH group in Table 3. The results of statistical analyses revealed that in common among the three types of DEH, the onset age of precedent deafness due to 'unknown cause with onset in early childhood' was significantly younger than that of 'sudden deafness' and 'mumps deafness'. The results of statistical analyses further revealed that in IDEH and CDEHwV, but not in CDEHwoV, the onset age of DEH after the development of 'sudden deafness' was significantly older than that of 'unknown cause with onset in early childhood' and 'mumps deafness'. Finally, in regard to the TD between the onset of precedent deafness and that of IDEH, statistical analyses showed that in common among the three types of DEH, the TD between the onset of 'sudden deafness' and that of DEH was significantly shorter than the TD between the onset of 'unknown cause with onset in early childhood' and that of DEH.

Table 4 shows the distribution of the number of cases for each category of TD between onset of precedent deafness and that of DEH among three main diagnoses of precedent deafness. The chi-square test showed that these distributions of the TD were significantly different between the three main causes of the precedent deafness. A post-hoc test with residual analysis showed that the frequency of patients with TD 0–19 years was significantly smaller and that of patients with TD ≥20 years was significantly larger for 'unknown cause with onset in early childhood'. Notably, the frequency of patients with TD ≥40 years was significantly larger for 'unknown cause with onset in early childhood' and significantly smaller for 'sudden deafness' and 'mumps deafness'.

Table 3. Onset ages of precedent deafness and DEH, and time delay between the onset of precedent deafness and that of DEH for the three main diagnoses of precedent deafness in each DEH group.

	IDEH	CDEHwV	CDEHwoV
Onset age of precedent deafness, years			
Unknown cause with onset in early childhood	2.4 ± 1.5[a,b]	2.3 ± 1.4[a,b]	2.4 ± 1.4 [a,b]
Sudden deafness	43.9 ± 14.9[b,c]	47.9 ± 14.4[b,c]	40.4 ± 12.9 [b]
Mumps deafness	13.4 ± 12.9[a,c]	6.5 ± 5.6[a,c]	5.4 ± 2.1 [a]
p-Value*	1.79e-41	1.19e-22	7.58e-11
Onset age of DEH, years			
Unknown cause with onset in early childhood	30.7 ± 15.7[b]	36.0 ± 16.1[b]	41.1 ± 15.4
Sudden deafness	57.4 ± 15.0[b,c]	59.2 ± 12.3[b,c]	50.3 ± 14.3
Mumps deafness	32.3 ± 14.0[c]	26.1 ± 8.7[c]	37.3 ± 24.2
p-Value*	1.51e-17	1.06e-10	.219
Time delay between the onset of precedent deafness and that of DEH, years			
Unknown cause with onset in early childhood	28.9 ± 15.3[a,b]	34.5 ± 16.4[a,b]	38.6 ± 15.5[b]
Sudden deafness	12.2 ± 8.3[b]	11.6 ± 8.9[b]	11.7 ± 11.7[b]
Mumps deafness	17.9 ± 15.4[a]	19.1 ± 11.1[a]	31.5 ± 22.4
p-Value*	8.02e-13	3.44e-10	.003

DEH: delayed endolymphatic hydrops; IDEH: ipsilateral DEH; CDEHwV: contralateral DEH with vertigo; CDEHwoV: contralateral DEH without vertigo.

* By Kruskal-Wallis test.

[a] Significant result of post hoc test with Bonferroni correction between 'unknown cause with onset in early childhood' and 'mumps deafness'.

[b] Significant result of post hoc test with Bonferroni correction between 'unknown cause with onset in early childhood' and 'sudden deafness'.

[c] Significant result of statistical post hoc test with Bonferroni correction between 'sudden deafness' and 'mumps deafness'.

Table 4. Distribution of time delay between onset of precedent deafness and that of DEH for the three main diagnoses of precedent deafness.

Time delay (years)	Unknown cause with onset in early childhood	Sudden deafness	Mumps deafness	p-Value
0–19	38[b] (23.8%)	94[a] (77.7%)	27 (50.9%)	1.17e-20*
20–39	70[a] (43.8%)	25[b] (20.7%)	24 (45.3%)	
≥40	52[a] (32.5%)	2[b] (1.7%)	2[b] (3.8%)	
Total	160 (100%)	121 (100%)	53 (100%)	

* By chi-square test.

[a] Cells with observed counts significantly larger than expected counts in the residual analysis.

[b] Cells with observed counts significantly smaller than expected counts in the residual analysis.

Table 5. Distributions of time delay between the onset of precedent deafness and that of DEH for the three main diagnoses of precedent deafness in each DEH group.

	Years	IDEH	CDEHwV	CDEHwoV	p-Value
Unknown cause with onset in early childhood	0–19	27 (29.0%)	10 (18.9%)	1 (7.1%)	.172
	20–39	40 (43.0%)	25 (47.2%)	5 (35.7%)	
	≥40	26 (28.0%)	18 (34.0%)	8 (57.1%)	
	Total	93 (100%)	53 (100%)	14 (100%)	
Sudden deafness	0–19	53 (73.6%)	30 (81.1%)	11 (91.7%)	.037
	20–39	19 (26.4%)	6 (16.2%)	0 (0.0%)	
	≥40	0* (0.0%)	1 (2.7%)	1* (8.3%)	
	Total	72 (100%)	37 (100%)	12 (100%)	
Mumps deafness	0–19	20 (57.1%)	6 (42.9%)	1 (25.0%)	.248
	20–39	14 (40.0%)	8 (57.1%)	2 (50.0%)	
	≥40	1 (2.9%)	0 (0.0%)	1 (25.0%)	
	Total	35 (100%)	14 (100%)	4 (100%)	

DEH: delayed endolymphatic hydrops; IDEH: ipsilateral DEH; CDEHwV: contralateral DEH with vertigo; CDEHwoV: contralateral DEH without vertigo.

* Statistically significant difference based on multiple comparisons (Fisher's exact test).

Table 5 shows the distributions of the TD between the onset of precedent deafness and the onset of DEH among the three DEH groups for the three main three diagnoses of precedent deafness. In case groups in which the precedent deafness was ‘unknown cause with onset in early childhood’ and ‘mumps deafness’, the distribution of the TD was not statistically different between the three types of DEH ($p = 0.172$ for ‘unknown causes with onset in early childhood’ and $p = 0.248$ for ‘mumps deafness’). In the case group in which the precedent deafness was ‘sudden deafness’, analysis showed a significant difference in distribution of the TD among the three DEH groups ($p = 0.037$). Multiple comparisons with Bonferroni correction showed a significant difference only between IDEH and CDEHwoV for a TD ≥40 years.

Discussion

In Japan, the diagnostic criteria for DEH were proposed by the JSER in 1987 and have been used for many years [8]. In 2017, the diagnostic criteria for DEH were revised by the JSER, and a severity classification for DEH was added [11]. The Japanese diagnostic criteria for DEH stipulate IDEH and are not clearly defined for CDEH. In this context, the 1987 diagnostic criteria described the main points for the diagnosis of CDEH. In the present study, the 1987 diagnostic criteria for DEH were used as this is a national survey of DEH patients in Japan in 1998, 2001 and from 2006 to 2017.

Of the 662 cases enrolled in the present study, 367 (55.4%) were of IDEH and 295 (44.6%) were of CDEH, with a slightly larger proportion of IDEH than CDEH. In the 2010 report by Shojaku et al., the proportion of CDEH was slightly larger, but IDEH was larger in the present study due to the additional accumulation of cases. The proportion of female patients showed a slight female predominance of 55.6% (368/662 cases), a result

consistent with that of previous studies [10,12]. Among those with CDEH, the ratio of CDEHwV patients (70.8%, 209 patients) to CDEHwoV patients (29.2%, 86 patients) was greater. Albera et al. reported a 46% rate of CDEH with vertigo [12], which was small compared to my results. In the 2010 study by Shojaku et al. [10], however, the ratios of the CDEHwV and CDEHwoV groups were 82.7% and 17.3%, respectively. Although the ratio for CDEHwV was lower in the present study than that in the Shojaku et al. study, the trend was similar, with CDEHwV being more common than CDEHwoV.

None of the comparisons among the three groups of DEHs showed statistically significant differences with respect to age, sex ratio, affected side, onset age of precedent deafness, and onset age of DEH (Table 1). Contrastingly, with regard to TD between onset of precedent deafness and DEH, the differences were significant, with the post hoc test revealing significantly shorter TD in IDEH than in CDEH with or without vertigo (Table 1). The diagnosis of CDEH does not completely distinguish Meniere's disease that develops in the good ear independently of the preceding severe hearing loss, especially in patients with vertigo [9,11]. Furthermore, the peak age of onset of Meniere's disease is reported to be in the 50s for men and 60s for women [13]; the significantly longer TD in CDEH compared to IDEH may be due to the inclusion of such cases.

Among the causes of the precedent deafness, idiopathic hearing loss of unknown cause was the most predominant disease with 403 cases (60.9%) overall, of which 219 (33.1%) were of unknown cause with onset in early childhood (Table 2). Other types of hearing loss included sudden deafness in 141 cases (21.3%) and mumps deafness in 68 cases (10.3%) (Table 2). In 2010, Shojaku et al. reported that 61.6% of cases were of unknown cause, of which 43.9% were of unknown cause with onset in early childhood, 12.6% were of sudden deafness, and 12.5% were of mumps deafness [10]. Although the

ratio of sudden deafness tended to be higher in the present study, these same three diseases were the three main causes of the precedent deafness. Huang and Lin reported a retrospective review of 105 IDEH cases, 54 CDEH cases, and 1 bilateral DEH case. Among the diseases causing the precedent deafness in the 105 IDEH cases, 35 (33.3%) had an unknown cause that occurred in childhood, 12 (11.4%) had sudden hearing loss, and mumps and viral labyrinthitis accounted for 10 cases (9.5%) [7]. In the 54 CDEH cases, however, 18 patients (33.3%) had an unknown cause that occurred in childhood, 4 (7.4%) had sudden hearing loss, and 5 (9.3%) had mumps [7]. These results were generally consistent with my results, except that sudden deafness occurred less frequently than in the present study.

A comparison among IDEH, CDEHwV, and CDEHwoV with respect to the distribution of diseases causing the precedent deafness showed no significant difference, similar to the previous Shojaku et al. study [10]. Although that study did not examine whether the distribution of diseases causing the precedent deafness differs in CDEH with and without vertigo, my results indicated that there is no difference in the distribution of the diseases causing the precedent deafness between CDEHwV and CDEHwoV (Table 2).

In common among the three DEH types, disease with unknown cause at onset in early childhood had a significantly longer mean TD than that for sudden deafness, whereas there was no significant difference in TD between sudden deafness and mumps deafness (Table 3). This result was also reported by Shojaku et al. [10]. In the present study, although I classified CDEH into CDEHwV and CDEHwoV, the result was not different between the two, suggesting that the mechanism of DEH development after a disease of unknown cause at onset in early childhood may differ from those after sudden deafness

and mumps deafness, as described by Shojaku et al. [10]. Comparing the TD between the onset of precedent deafness and that of DEH for each disease, the group with deafness of unknown cause at onset in early childhood tended to have a longer TD than the groups with sudden deafness or mumps deafness, with a significantly higher ratio of TD over 40 years (Table 4). When the distribution of TD length was compared among the DEH types for each disease, the distribution was almost the same (Table 5). These results are consistent with those reported by Shojaku et al. [10] and represent a significantly longer TD when deafness of unknown cause at onset in early childhood is the cause of precedent deafness in DEH, regardless of the type of DEH.

As a mechanism for the development of DEH, Schuknecht proposed the following: some viral insult causes viral labyrinthitis in one ear that results in the precedent deafness and disruption of the resorptive mechanisms of the ipsilateral or contralateral inner ear, possibly the rugose epithelium of the endolymphatic sac. This leads to eventual decompensation in the balance between endolymph secretion and resorption, thus resulting in progressive EH [14]. Because viral infection is considered the primary cause of sudden deafness [15], Shojaku et al. concluded that the homogeneity of the epidemiological characteristics of DEH after both sudden and mumps deafness was due to the fact that the impaired endolymphatic sac reabsorption due to viral infection proposed by Schuknecht was the primary factor in both types of DEH. Furthermore, they proposed the hypothesis that the group of patients with deafness of unknown cause at onset in early childhood would include many patients with Meniere's disease (most of them in their 50s or 60s at the time of onset) or EH secondary to factors other than viral labyrinthitis that happen to be completely unrelated to the precedent deafness [10]. The results of the present study may also be based on that hypothesis because I used the same

diagnostic criteria as in those in Shojaku et al. [10] and significantly increased the number of DEH cases; consequently, the epidemiological characteristics were almost the same as those in the previous study.

Recently, 3 Tesla magnetic resonance imaging (3T-MRI) after intratympanic or intravenous injection of gadolinium has enabled the visualization of EH in patients with EH disease including DEH [16,17]. These studies suggest that vestibular EH on the side of the precedent deafness in IDEH and cochlear EH in the ear opposite the precedent deafness in CDEH are highly prevalent, indicating that EH may be involved in the onset of DEH symptoms. As well, there are reports of a high frequency of bilateral EH in IDEH [16,18], and in idiopathic sudden hearing loss, EH was positive in 66% of the cochleae and 41% of the vestibules in the affected ear and in 52% and 38%, respectively, in the unaffected ear [18]. This suggested that asymptomatic EH is observed in the contralateral ear with high frequency in patients with IDEH and sudden deafness.

Iwasa et al. reported that they performed 3T-MRI after bilateral intratympanic injection of gadodiamide in 19 patients with DEH and that all 11 IDEH patients and the 8 CDEH patients had vestibular EH in the ear with precedent deafness and cochlear EH in the better hearing ear, respectively, indicating results compatible with the concept of DEH [17]. They also found that bilateral-type EH is common in CDEH (5/8 cases, 62.5%), but in 5 patients with CDEHwV, there were 2 cases of positive vestibular EH on the side of the preceding deafness, 2 cases on the affected ear, and 1 case of no EH, and in 3 patients with CDEHwoV, 1 case positive for vestibular EH on the side of the preceding deafness, 1 case on the affected ear, and 1 case of bilateral vestibular EH, suggesting that the relationship between vertigo and vestibular EH in CDEH is very complex and with no consistent trend. Several papers describe the existence of three

different types of EH: degenerative hydrops with paralytic nystagmus, which is found in the impaired inner ear; irritative hydrops, which causes clinical symptoms of Meniere's disease due to increased endolymphatic pressure and is associated with irritative nystagmus in the early stages of attacks; and retention hydrops, in which endolymphatic pressure is not increased and not associated with nystagmus [19,20]. The mode of onset of DEH (IDEH, CDEHwV, or CDEHwoV) may be determined by which site (cochlear or vestibular, ipsilateral or contralateral) develops symptomatic EH in a unilateral or bilateral EH formed after the precedent deafness. I believe that the present results, in which the epidemiological characteristics of the three types of DEH were almost identical, can be explained by this mechanism of DEH occurrence.

There are several limitations to this study. First, some of the participating centres differed from year to year, which may have affected the characteristics of the patient population enrolled. Second, the study could not assess differences in functional or imaging characteristics of the three types of DEH patients due to insufficient data collection of audiological, electrophysiological, 3T-MRI, and other laboratory data from year to year. Further research is needed in this regard.

In conclusion, I accumulated clinical and epidemiological data on 662 patients with DEH in Japan and analysed their characteristics through a 14-year, multicentre study. The TD between onset of precedent deafness and DEH in patients with CDEH whether with or without vertigo, was significantly longer than that in patients with IDEH, but the three types of DEH were nearly homogeneous with respect to other epidemiological characteristics. The most common cause of precedent deafness was disease of unknown cause, accounting for approximately 60% of all three types of DEH, with the most common diagnosis of 'unknown cause with onset in early childhood (<5 years of age)'

accounting for more than 30% of all cases, and the other two main causes being sudden deafness and mumps deafness. The TD between onset of disease of unknown cause in early childhood and onset of DEH was significantly longer than that for sudden deafness or mumps deafness, especially in the proportion of patients with TD ≥40 years. There were no significant differences in epidemiological characteristics between CDEHwV and CDEHwoV.

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Abbreviations: CDEH: contralateral delayed endolymphatic hydrops; CDEHwoV: CDEH without vertigo; CDEHwV: CDEH with vertigo; DEH: delayed endolymphatic hydrops; EH: endolymphatic hydrops; IDEH: ipsilateral delayed endolymphatic hydrops; JSER: Japan Society for Equilibrium Research; SD: standard deviation; TD: time delay

Disclosure statement

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References

[1] Schuknecht HF. Delayed endolymphatic hydrops. Ann Otol Rhinol Laryngol. 1978;87(6 Pt 1):743–748.

[2] Schuknecht HF, Suzuka Y, Zimmermann C. Delayed endolymphatic hydrops and its relationship to Meniere's disease. Ann Otol Rhinol Laryngol. 1990;99(11):843–853.

[3] Kamei T, Noro H, Yabe T, et al. Statistical observation of unilateral total deafiiess and characteristic unilateral total deafness among young children with tendency towards occurrence of dizziness. Jibiinkoka. 1971;43:349–358.

[4] Wolfson RJ, Leiberman A. Unilateral deafness with subsequent vertigo. Laryngoscope. 1975;85(10):1762–1766.

[5] Nadol JB Jr, Weiss AD, Parker SW. Vertigo of delayed onset after sudden deafness. Ann Otol Rhinol Laryngol. 1975;84(6):841–846.

[6] LeLiever WC, Barber HO. Delayed endolymphatic hydrops. J Otolaryngol. 1980;9(5):375–380.

[7] Huang TS, Lin CC. Delayed endolymphatic hydrops: study and review of clinical implications and surgical treatment. Ear Nose Throat J. 2001;80(2):76–78, 81–82, 84 passim.

[8] Komatsuzaki A, Harada Y, Hozawa J, et al. Delayed endolymphatic hydrops. The guideline for standardization of diagnostic criteria in vertiginous diseases. The Committee for Standardization of Diagnostic Criteria in 16 Vertiginous Diseases. Equilib Res. 1988;47(2):249–250.

[9] Takeda N, Koizuka I, Nishiike S, et al. Clinical features in patients with delayed endolymphatic hydrops. J Otolaryngol Jpn. 1998;101:1385–1389.

[10] Shojaku H, Watanabe Y, Takeda N, et al. Clinical characteristics of delayed endolymphatic hydrops in Japan: A nationwide survey by the Peripheral Vestibular Disorder Research Committee of Japan. Acta Otolaryngol. 2010;130(10):1135–1140.

[11] Ikezono T, Ito A, Takeda N, et al. Documents for standards in diagnostic criteria for dizziness. Equilib Res. 2017;76:233–241.

[12] Albera A, Canale A, Boldreghini M, et al. Contralateral delayed endolymphatic hydrops: Clinical features and long term outcome. J Otol. 2021;16(4):205–209.

[13] Shojaku H, Watanabe Y, Yagi T, et al. Changes in the characteristics of definite Meniere's disease over time in Japan: a long-term survey by the Peripheral Vestibular Disorder Research Committee of Japan, formerly the Meniere's Disease Research Committee of Japan. Acta Otolaryngol. 2009;129(2):155–160.

[14] Schuknecht HF. Neurolabyrinthitis. Viral Infections of the peripheral auditory and vestibular systems. In: Nomura Y, editor. Hearing loss and dizziness. Tokyo: Igaku-Shoin; 1985.

[15] Merchant SN, Durand ML, Adams JC. Sudden deafness: is it viral? ORL J Otorhinolaryngol Relat Spec. 2008;70(1):52–60; discussion 60–62.

[16] Nonoyama H, Tanigawa T, Tamaki T, et al. Evidence for bilateral endolymphatic hydrops in ipsilateral delayed endolymphatic hydrops: preliminary results from examination of five cases. Acta Otolaryngol. 2014;134(3):221–226.

[17] Iwasa Y, Tsukada K, Kobayashi M, et al. Bilateral delayed endolymphatic hydrops evaluated by bilateral intratympanic injection of gadodiamide with 3T-MRI. PLoS One. 2018;13(12):e0206891.

[18] Okazaki Y, Yoshida T, Sugimoto S, et al. Significance of endolymphatic hydrops in

ears with unilateral sensorineural hearing loss. Otol Neurotol. 2017;38(8):1076–1080.

[19] Wittmaack K. Die Oroth- und Pathobiologie des Labyrinthes. Stuttgart: Georg Thieme Verlag; 1956.

[20] Takeda N. History of Meniere's disease based on Meniere's original publications. Equilib Res. 2018;77(3):131–135.

Summary

In this study, the clinical epidemiological characteristics of DEH were clarified through two nationwide epidemiological surveys. In the first epidemiological survey, I estimated the number of DEH patients in Japan to be 962, with a prevalence rate of 0.8 per 100,000 population. In the second epidemiological survey, I obtained the following findings: 1) the proportion of IDEH was slightly higher than that of CDEH; 2) approximately 70% of CDEH cases were accompanied by vertigo; 3) women tended to be slightly more common; 4) the most common diagnosis of precedent deafness was deafness of unknown cause with onset in early childhood; 5) the TD was significantly longer for CDEH than for IDEH. Furthermore, I have shown that there were no significant differences in the clinical epidemiological characteristics between IDEH, CDEHwV, and CDEHwoV. This is the first large-scale and precise investigation in the world and the data could be valuable in the clinical setting of DEH. I consider that the findings that the clinical characteristics of IDEH and CDEH are epidemiologically homogenous will contribute to the future revision of the medical care system for patients with designated intractable diseases.