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ORIGINAL ARTICLE

# 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

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**Abstract**

*Conclusion.* The incidence of new cases of Meniere's disease (MD) in elderly patients aged 60 years or more was found to have increased over time after correction for age distribution in the overall population. Job- and care-related fatigue may be involved in the recent increase in elderly-onset cases because physical and mental fatigue can induce onset of the disease. *Objectives.* Changes over time in the epidemiologic characteristics of MD in Japan were analyzed. *Materials and methods.* Between 1975 and 2006, four nationwide, multi-center surveys of MD were conducted by the Meniere's Disease Research Committee of Japan (1975–1976) and the Peripheral Vestibular Disorders Research Committee of Japan (1982–1984, 1990, and 2001–2006). Information was collected by the committee members on a total of 1368 de novo cases of definite MD, 520 reported in the first survey, 290 in the second survey, 148 in the third survey, and 410 in the fourth survey. *Results.* Clear changes were seen over time in the population-adjusted sex distribution of the disease and population-adjusted age at onset. The number of definite MD cases in females increased over time relative to the number of cases in males. The proportion of cases in which onset occurred at 60 years of age or more increased over time when the number of cases in each age group was adjusted for changes in age distribution of the population over time. From the time of the third survey, there was a slight increase in the proportion of cases with bilateral involvement.

**Keywords:** *Meniere's disease (definite), onset age, sex distribution, aging*

## Introduction

Basic demographic characteristics of Meniere's disease (MD) have been reported from many places worldwide [1–7]. Most such reports present epidemiologic data representing a single brief period, without addressing secular trends. The Meniere's Disease Research Committee of Japan was organized by the Ministry of Health and Welfare of Japan in 1974 and continued after reorganization in 1980 as the Peripheral Vestibular Disorders Research Committee. Between 1974 and the end of 1990, the committee conducted three nationwide, multi-center surveys to investigate the epidemiologic and clinical characteristics of MD, surveying patients admitted to hospitals with which members of the committee were affiliated [8–10]. Because the same diagnostic criteria have been used consistently [8], these epidemiologic surveys provide a unique opportunity to evaluate long-term trends in the epidemiologic characteristics of MD. We analyzed basic epidemiologic characteristics of MD as found in the fourth nationwide survey of Japan conducted from

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2001 to 2006 and compared the recent data with data from the three previous surveys.

## Materials and methods

The first nationwide survey was conducted from April 1975 to December 1976 by 17 committee members at 14 university and 3 general hospitals located in various districts or areas of Japan [8–10]. Data collected from 520 patients with definite MD included age, sex, and occupation; mode of onset; and whether symptoms were bilateral or unilateral. The second nationwide survey was conducted from January 1982 to December 1984 by 24 committee members in 22 university and 2 general hospitals [9,10]. Data similar to those collected in the first survey were collected from 290 patients with definite MD. The third survey was conducted from January to December 1990 by 16 committee members at 13 university and 3 general hospitals [9,10]. Data similar to those collected in the first and second surveys were collected from 148 patients with definite MD. The fourth survey was conducted in 2001 and from January 2004 to December 2006 by 14 committee members at 14 university hospitals. Data were collected from 410 patients with definite de novo MD (i.e. patients who had undergone their first medical examination for definite MD symptoms) and were similar to data collected in the three previous surveys.

The diagnostic criteria for MD, decided on in 1976 by the committee conducting the first survey, are as follows: (1) repeated attacks of whirling vertigo; (2) fluctuating cochlear symptoms synchronized with attacks of vertigo; and (3) exclusion of central nervous system involvement, eighth nerve tumor, and other cochleovestibular diseases [8]. Cases fulfilling all 3 criteria were diagnosed as cases of definite MD, whereas cases fulfilling only criteria 1 and 3 or criteria 2 and 3 were considered cases of suspected MD. In 1991, the committee decided on diagnostic criteria for MD with bilateral fluctuant hearing loss as follows: (1) repeated attacks of whirling vertigo; (2) fluctuating bilateral cochlear symptoms synchronized with attacks of vertigo; and (3) exclusion of central nervous system involvement, eighth nerve tumor, and other cochleovestibular diseases [11]. Because the cochlear symptoms sometimes fluctuate, and the severity of symptoms is not the same in each ear, some patients complain of severe unilateral, not bilateral, symptoms. Cases fulfilling all three criteria were diagnosed as cases of definite bilateral MD. Use of the glycerol test and/or frequently repeated pure tone audiometry is highly recommended to diagnose bilateral involvement more precisely. Only patients who had undergone their first medical examination for MD symptoms were surveyed. All of the cooperating committee members were ear, nose, and throat physicians.

Survey data were stored and analyzed by database software at the Department of Otolaryngology at the University of Toyama. Data from the fourth survey on the sex distribution of definite MD, unilateral vs bilateral involvement, and age at onset per sex were analyzed. The distribution of bilateral involvement and of age at onset per sex was compared between the four surveys to investigate changes over time. The sex ratio and onset age for definite MD from the first, second, and third surveys were adjusted for sex and age ratios of the general population calculated with the use of denominators interpolated from census data between census years. Data from the national census for 1980, 1985, 1990, and 2005 were used to correct the data from the first, second, third, and fourth survey, respectively. For statistical analysis, chi-squared tests were performed on a personal computer with StatView for Windows (version 4.5, Abacus Concepts, Berkeley, CA, USA). Some of the data in this study were analyzed in previous studies [8–10].

## Results

At the time of the first survey, nearly equal numbers of males and females, i.e. 259 males (49.8%) and 261 females (50.2%), were diagnosed with definite MD (Table I). The second to fourth surveys showed a progressive increase with time in the proportion of definite MD cases occurring among females. At the time of the fourth survey, 256 females (62.4%) and only 154 males (37.6%) were diagnosed with definite MD. The percentage of females in the population of Japan did not change between 1975 and 2005; it was 50.8% in 1975 and 51.2% in 2005, according to national census data. The population-adjusted proportion of female patients in the fourth survey was significantly greater than that in the first survey ($p < 0.01$; Table II).

Proportions of cases with bilateral involvement during the time of each survey are shown in Table III. At the time of the first survey, 48 of the 520 cases of definite MD (9.2%) were diagnosed as bilateral.

Table I. Sex distribution of definite MD per survey period.

| | 1975–76 | 1982–84 | 1990 | 2001–2006 |
|---|---|---|---|---|
| Males | 259 (49.8) | 126 (43.4) | 63 (42.6) | 154 (37.6) |
| Females | 261 (50.2) | 164 (56.6) | 85 (57.4) | 256 (64.4) |
| Total patients | 520 (100) | 290 (100) | 148 (100) | 410 (100) |

Number (and percentage) of patients are shown.

Table II. Population-adjusted sex distribution of definite MD per survey period.

| | 1975–76 | 1982–84 | 1990 | 2001–2006 |
|---|---|---|---|---|
| Males | 257 (49.4) | 125 (43.1) | 63 (42.6) | 154 (37.6) |
| Females | 263 (50.6) | 165 (56.9) | 85 (57.4) | 256 (64.4) |
| Total patients | 520 (100) | 290 (100) | 148 (100) | 410 (100) |

Number (and percentage) of patients are shown.

The proportion of cases showing bilateral involvement fluctuated over time, declining slightly from the first to the second (7.9%) survey, then increasing between the early surveys and the third (16.2%) and fourth (13.8%) surveys. The proportions of definite bilateral MD cases reported during the third and fourth surveys were significantly greater than those in the first and second surveys ($p < 0.01$).

Age at onset of definite MD peaked in the fourth decade in males and in the third decade in females at the time of the first survey (Tables IV and V). At the time of the second survey, age at onset peaked in the third decade in males and in the fifth decade in females. At the time of the third survey, onset age peaked in the fourth decade in males and in the third decade in females. At the time of the fourth survey, onset age peaked in the fifth decade in males and in the sixth decade in females. Population-adjusted onset age peaked in the fourth decade in males and the fifth decade in females at the time of the first survey and in the fifth decade in males and the sixth decade in females at the time of the fourth survey (Tables VI and VII).

The population-adjusted proportion of patients with definite MD for whom age at onset was 60 years or more increased slightly from the first to the fourth survey (Tables VI and VII, and VIII). During the time of the first survey, the percentage of male patients with onset age of 60 years or more was 15.7%, the percentage of female patients was 12.7%, and the percentage of total patients for whom onset age was 60 years or more was 13.5%; these values increased to 20.1% in males, 31.1% in females, and 26.9% in total by the time of the fourth survey. Differences between the first survey and fourth survey in population-adjusted age at onset of 60 years or more among female patients and among the total patients were significant ($p < 0.05$).

Table III. Unilateral and bilateral involvement of definite MD per survey period.

| | 1975–76 | 1982–84 | 1990 | 2001–2006 |
|---|---|---|---|---|
| Unilateral | 472 (90.8) | 267 (92.1) | 124 (83.8) | 343 (86.2) |
| Bilateral | 48 (9.2) | 23 (7.9) | 24 (16.2) | 55 (13.8) |
| Total | 520 (100) | 290 (100) | 148 (100) | 398 (100) |
| Unclear | 0 | 0 | 0 | 12 |

Number (and percentage) of patients are shown.

Table IV. Onset age in males with definite MD per survey period.

| Age (years) | 1975–76 | 1982–84 | 1990 | 2001–2006 |
|---|---|---|---|---|
| ≤19 | 12 (4.7) | 5 (4.1) | 1 (1.7) | 6 (3.9) |
| 20–29 | 36 (14.1) | 13 (10.7) | 4 (6.7) | 17 (11.0) |
| 30–39 | 65 (25.5) | 32 (26.2) | 14 (23.3) | 32 (20.8) |
| 40–49 | 88 (34.5) | 31 (25.4) | 20 (33.3) | 27 (17.5) |
| 50–59 | 34 (13.3) | 28 (23.0) | 17 (28.3) | 41 (26.6) |
| 60–69 | 15 (5.9) | 10 (8.2) | 4 (6.7) | 23 (14.9) |
| ≥70 | 5 (2.0) | 3 (2.5) | 0 (0.0) | 8 (5.2) |
| Total | 255 (100) | 122 (100) | 80 (100) | 154 (100) |
| Unclear | 4 | 4 | 3 | 0 |

Number (and percentage) of patients are shown.

## Discussion

In this study, changes over time in the sex ratio, proportion of unilateral vs bilateral definite MD, and age at onset of definite MD were examined on the basis of data collected during four nationwide, multi-center surveys conducted by the Peripheral Vestibular Disorders Research Committee of Japan (formerly the Meniere's Disease Research Committee of Japan) between 1975 and 2006. Clear changes were seen over time in the population-adjusted sex distribution of the disease and population-adjusted age at onset. The number of definite MD cases in females increased over time relative to the number of cases in males. The proportion of cases in which onset occurred at 60 years of age or more increased over time when the number of cases in each age group was adjusted for changes in age distribution of the population over time. From the time of the third survey, there was a slight increase in the proportion of cases with bilateral involvement.

The sex distribution of patients with MD has varied among other such regional surveys. In Scandinavian countries, the majority of cases of MD have been reported in females. Stahle et al. [1] found in a year-long 1973 survey that 60% of MD patients in the Uppsala region and the county of Skane in

Table V. Onset age in females with definite MD per survey period.

| Age (years) | 1975–76 | 1982–84 | 1990 | 2001–2006 |
|---|---|---|---|---|
| ≤19 | 15 (5.9) | 7 (4.5) | 3 (3.6) | 2 (0.8) |
| 20–29 | 34 (13.3) | 19 (12.2) | 11 (13.1) | 29 (11.4) |
| 30–39 | 72 (28.2) | 29 (18.6) | 23 (27.4) | 43 (16.9) |
| 40–49 | 64 (25.1) | 43 (27.6) | 20 (23.8) | 45 (17.7) |
| 50–59 | 52 (20.4) | 38 (24.4) | 19 (22.6) | 56 (22.0) |
| 60–69 | 16 (6.3) | 13 (8.3) | 8 (9.5) | 64 (25.2) |
| ≥70 | 2 (0.8) | 7 (4.5) | 0 (0) | 15 (5.9) |
| Total females | 255 (100) | 156 (100) | 84 (100) | 254 (100) |
| Unclear | 6 | 8 | 1 | 2 |

Table VI. Population-adjusted onset age among males with definite MD.

| Age (years) | 1975–76 | 1982–84 | 1990 | 2001–2006 |
|---|---|---|---|---|
| ≤19 | 7 (2.6) | 3 (2.5) | 1 (1.2) | 6 (3.9) |
| 20–29 | 23 (9.2) | 11 (9.4) | 4 (6.1) | 17 (11.0) |
| 30–39 | 56 (21.9) | 27 (22.1) | 15 (25.3) | 32 (20.8) |
| 40–49 | 73 (28.7) | 26 (20.9) | 16 (26.2) | 27 (17.5) |
| 50–59 | 56 (21.9) | 32 (26.6) | 20 (33.1) | 41 (26.6) |
| 60–69 | 27 (10.5) | 17 (13.6) | 5 (8.4) | 23 (14.9) |
| ≥70 | 13 (5.2) | 6 (4.9) | 0 (0.0) | 8 (5.2) |
| Total males | 255 (100) | 122 (100) | 80 (100) | 154 (100) |

Table VIII. Population-adjusted onset age among all patients with definite MD 4 Surveys.

| Age (years) | 1975–76 | 1982–84 | 1990 | 2001–2006 |
|---|---|---|---|---|
| ≤19 | 15 (3.0) | 7 (2.7) | 3 (2.0) | 8 (2.0) |
| 20–29 | 46 (9.0) | 28 (10.1) | 13 ( 9.3) | 48 (11.3) |
| 30–39 | 119 (23.4) | 51 (15.5) | 39 (27.2) | 75 (18.4) |
| 40–49 | 127 (25.0) | 61 (21.9) | 31 (21.5) | 72 (17.6) |
| 50–59 | 133 (26.0) | 76 (27.3) | 42 (29.2) | 97 (22.0) |
| 60–69 | 52 (10.3) | 35 (12.4) | 16 (11.1) | 87 (25.2) |
| ≥70 | 17 (3.2) | 20 (7.2) | 0 (0.0) | 23 (5.9) |
| Total patients | 510 (100) | 279 (100) | 144 (100) | 408 (100) |

Sweden were females. Havia et al. [6] found in a 2005 survey that 67% of definite MD patients in the Helsinki University hospital area in Finland were females. In 2007, Klockars et al. [7] reported that 70% of MD patients in Finland were females. According to surveys conducted in Italy and the United States, however, the proportion of MD cases in males and females has been almost equal. After a year-long 1992 survey in the region of Tuscany in Italy, Nuti et al. [5] reported that 53.9% of MD patients were females. In a 13-year survey (1973–1985) of southeastern Latium, the adjusted sex distribution was found to be almost equal (males, 48.9%; females, 51.1%) [4]. In the United States, Wladislavosky-Waserman et al. [2] reported changes in the sex distribution of MD between 1951 and 1980 in Rochester, Minnesota. In the first decade, a slight but not significant preponderance of female patients was observed. In the following two decades, the number of female MD patients declined over time, and the number of male MD patients exceeded the number of female patients, although not significantly, in the third decade.

In Japan before 1965, MD occurred more frequently in males than in females. In 1973, Naito reported that the male:female ratio was about 1.5 from 1934 to 1960, although after that time, the number of female patients with MD increased more rapidly than the number of male patients, and the difference between the two sexes almost disappeared [12]. Most of the subsequent Japanese surveys showed a preponderance of female patients [9,10,13,14]. In a year-long 1991 survey, 68.4% of MD patients in Toyama prefecture were found to be females [13], and in a 1994 survey, 79.2% of MD patients in the Hida district of Gifu prefecture were found to be females [10]. The sex distribution of definite MD was almost equal in our committee's first survey, but there was a preponderance of female cases of MD in the subsequent surveys. In recent times, the number of cases of definite MD has been greater among females than among males in Japan.

Table VII. Population-adjusted onset age among females with definite MD.

| Age (years) | 1975–76 | 1982–84 | 1990 | 2001–2006 |
|---|---|---|---|---|
| ≤19 | 9 (3.4) | 4 (2.8) | 2 (2.4) | 2 (0.8) |
| 20–29 | 22 (8.8) | 17 (10.7) | 9 (11.2) | 29 (11.4) |
| 30–39 | 63 (24.8) | 24 (15.7) | 24 (26.5) | 43 (16.9) |
| 40–49 | 55 (21.5) | 35 (22.5) | 15 (18.1) | 45 (17.7) |
| 50–59 | 73 (28.8) | 43 (27.9) | 22 (26.5) | 56 (22.0) |
| 60–69 | 27 (10.4) | 18 (11.5) | 12 (13.8) | 64 (25.2) |
| ≥70 | 6 (2.3) | 14 (9.0) | 0 (0.0) | 15 (5.9) |
| Total females | 255 (100) | 156 (100) | 84 (100) | 254 (100) |

In the present study, the proportion of MD cases with bilateral involvement was significantly higher at the time of the third and fourth surveys than at the time of the first and second surveys. The Peripheral Vestibular Disorders Research Committee of Japan prepared a draft of the diagnostic criteria for bilateral MD between 1988 and 1990 and published the criteria in 1991 [11]. The establishment and spread of the diagnostic criteria for bilateral MD may have influenced the reported incidence of bilateral involvement starting at the time of the third survey in 1990. A patient with bilateral MD often does not notice the bilateral fluctuant cochlear symptoms, and thus the physician in charge sometimes thinks that the patient is suffering from unilateral MD. Use of the unilateral glycerol test or frequently repeated pure tone audiometry is recommended for accurate diagnosis of bilateral involvement.

MD was once considered to be quite rare in the elderly [12]. However, in 1984, Wladislavosky-Waserman et al. [2] reported a high annual incidence of MD in the elderly in the United States. In 2002, Ballester et al. [15] pointed out that MD is not at all uncommon in the elderly. Several investigations have revealed that cases of MD in the elderly constitute between 10.8% and 37.8% of the total number of MD cases [1–3,13,16]. Because MD is not usually a life-threatening disease, cases of MD in the elderly comprise both long-standing cases that are reactivated and de novo cases. One may therefore think that the increased number of elderly MD

patients is associated with recent increases in lifespan. However, we found that the proportion of MD cases in which onset age was 60 years or more during the time of the fourth survey was greater than in previous surveys when we corrected for age distribution of the overall population. This nationwide trend is similar to the increase in elderly-onset MD found in a recent regional survey [17]. In Japan, it appears that the recent increase in de novo MD cases exceeds the increase in the elderly population.

Elderly individuals are healthier now than those of previous generations. According to the 2005 census, 22.2% of elderly persons in Japan are working. This percentage is higher than that in France (1.2%), Italy (2.5%), Finland (2.7%), Germany (3.3%), and the United States (15.1%) in 2005 [18]. The larger population of working elderly persons in recent years might explain the trend in MD in Japan. Ikeda and Watanabe [19] reported 11 patients who had their first vertiginous attack after the age of 69 years (9 males, 2 females). Six of the nine elderly male patients with de novo MD were working. Four of them had managerial jobs. Only one male patient was out of work, and employment status was unclear in two male patients. Two female patients were housewives. Because physical and mental fatigue can induce onset of the disease [10], job-related fatigue may be involved in the recent increase in elderly-onset cases.

Today, 33% of the population is aged 65 years or more. In 2004, the number of persons aged 65 years or older was 24.88 million, the number of persons aged 65 years or older certified as requiring long-term care or support was 3.94 million [20]. Such individuals are generally looked after at home mainly by a family member, usually a female or someone aged 60 years or older. Care-related fatigue may also be involved in the increase in elderly-onset cases of MD. Ikeda and Watanabe [19] reported three elderly patients aged 69 years or older with de novo MD who had looked after a sick, elderly family member. Two of them were housewives and one was a man out of work.

Compared with other countries, the rate of the elderly populations of Japan increased rapidly. In such a rapidly aging society as Japan, elderly persons often experience various stressful events. Investigation of the variety and grade of the stress among the patients with MD may be useful for clarifying the reason why the elderly-onset MD cases have increased recently in Japan.

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# Recurrence Rate of Idiopathic Sudden Low-Tone Sensorineural Hearing Loss Without Vertigo: A Long-Term Follow-Up Study

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**Objective:** Among the types of idiopathic sudden sensorineural hearing loss, low-tone type without vertigo has attracted attention for its recurrence and progression to Ménière's disease. The purpose of this article is to characterize the recurrent type of sudden low-tone sensorineural hearing loss without vertigo using neuro-otologic examination.
**Study Design:** Retrospective.
**Setting:** Tertiary referral center.
**Interventions:** Diagnostic and prognostic.
**Methods:** Long-term follow-up of 82 patients diagnosed at the university hospital with idiopathic sudden low-tone sensorineural hearing loss without vertigo. The recurrence rate was determined according to results of electronystagmography (ENG) and electrocochleography (ECochG) tests at the onset of the first episode of hearing loss.
**Results:** Forty percent of the patients experienced recurrent hearing loss. Among the patients who experienced recurrence, 45% had a recurrence within 6 months from the first episode of hearing loss. The recurrence rate varied largely according to the results of the ENG and ECochG tests. In patients with an elevated ratio of the summating potential to the action potential and spontaneous nystagmus on ENG, the recurrence rate was 78.6%. However, in those with a normal ratio of the summating potential to the action potential and without spontaneous nystagmus, the recurrence rate was 31.8%.
**Conclusion:** Our results indicate that idiopathic sudden low-tone sensorineural hearing loss without vertigo has a high recurrence rate when vestibular alteration and endolymphatic hydrops are detected on initial examination. A combination of nystagmus detection and ECochG test well characterizes the pathophysiology of sudden low-tone sensorineural hearing loss without vertigo. **Key Words:** Acute low-tone sensorineural hearing loss—Electronystagmography—Endolymphatic hydrops—Idiopathic sudden low-tone sensorineural hearing loss—Ménière's disease—Vestibular alteration.
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Idiopathic sudden sensorineural hearing loss of low-tone type with preservation of high-tone hearing and without episodes of vertigo may be distinct from other audiometric types of sudden sensorineural hearing loss of unknown origin. Its unique clinical features are as follows. The prototype category for the disease entity was first introduced by Abe in 1982 (1), characterized as a good prognostic group (acute low-tone sensorineural hearing loss). As the follow-up periods increased, it was revealed that the sudden low-tone sensorineural hearing loss without vertigo has a relatively high incidence of subsequent hearing loss and/or progression to definite Ménière's disease (2,3). The rates of recurrence and progression to Meniere's disease in these patients when followed up long-term were 27 and 11%, respectively (2). Previous studies using electrocochleography (ECochG) and glycerol tests suggest that the pathophysiology of acute low-tone sensorineural hearing loss may be attributable to endolymphatic hydrops confined to the cochlea (2,4,5).

We recently found that patients with sudden sensorineural hearing loss with recurrent episodes tend to have endolymphatic hydrops, whereas those without recurrent episodes do not (6). The average SP/AP ratio (the ratio of the summating potential to the action potential) of ECochG was higher for patients with recurrent episodes than for those with a single episode, although there was no statistically significant difference in the average SP/AP ratio between low-tone and high-tone types (6). This result suggests that sudden low-tone sensorineural hearing loss characterized only by a single episode is more likely to be attributable to some other cause rather than endolymphatic hydrops.

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We now recommend vestibular tests for patients with idiopathic sudden sensorineural hearing loss to predict its prognosis. We observed that approximately half of the patients with idiopathic sudden sensorineural hearing loss had subclinical vestibular dysfunction, even those who had not noticed vestibular symptoms at the first visit (7). Among the patients with spontaneous nystagmus at initial electronystagmography (ENG), approximately 50% showed subsequent hearing loss (7). The patients who developed Ménière's disease had spontaneous nystagmus at initial ENG. In contrast, none developed Ménière's disease when spontaneous nystagmus was absent (7). In the present study, we used a combination of ECochG and ENG tests to obtain an accurate prognosis of patients with sudden low-tone sensorineural hearing loss without vertigo.

## MATERIALS AND METHODS

Medical records of 1,334 patients who were diagnosed with idiopathic sudden sensorineural hearing loss from 1985 to 2003 were retrospectively reviewed. Idiopathic sudden sensorineural hearing loss is defined as a hearing loss for which the sum of the hearing levels at 3 consecutive audiometric frequencies is 70 dB or more, developed within 24 hours or less, and is not attributable to any commonly identifiable event (7). The low-tone type is defined as a hearing loss for which the average hearing level at 125, 250, and 500 Hz is at least 10 dB worse than that at 2, 4, and 8 kHz, and there is less than 10-dB difference in hearing level at 1 kHz in comparison with that at both the adjacent frequencies (500 Hz and 2 kHz) (7).

In the current study, 82 patients with idiopathic sudden low-tone sensorineural hearing loss and without vertigo who met all the following inclusion criteria were examined: 1) no past hearing loss, 2) no past history of ocular or vestibular disease, 3) medical treatment received within 30 days of onset, and 4) patient availability for long-term follow-up. Of 82 patients, 35 met the audiometric definition of acute low-tone sensorineural hearing loss proposed by the Study Group for Acute Profound Deafness Research Committee of the Ministry of Health, Labour, and Welfare of Japan, as follows: the sum of the hearing levels at low frequencies of 125, 250, and 500 Hz was 70 dB or more, and the sum of the hearing levels at high frequencies of 2, 4, and 8 kHz was 60 dB or less. The remaining 47 patients had sudden low-tone sensorineural hearing loss with age-related high-tone deterioration, which was excluded by the previously proposed definition of acute low-tone sensorineural hearing loss. In most patients, corticosteroids were administered intravenously as an initial treatment.

**TABLE 1.** *Recurrence rate of hearing loss*

| | | SP/AP ratio | |
|---|---|---|---|
| | | Normal | Elevation |
| SN | Absence | 31.8% (7 of 22) | 57.1% (4 of 7) |
| | Presence | 47.1% (8 of 17) | 78.6% (11 of 14) |

An elevation in the SP/AP ratio to a value greater than 0.37 was considered indicative of endolymphatic hydrops.

SN indicates spontaneous nystagmus; SP/AP ratio, the ratio of the summating potential to the action potential.

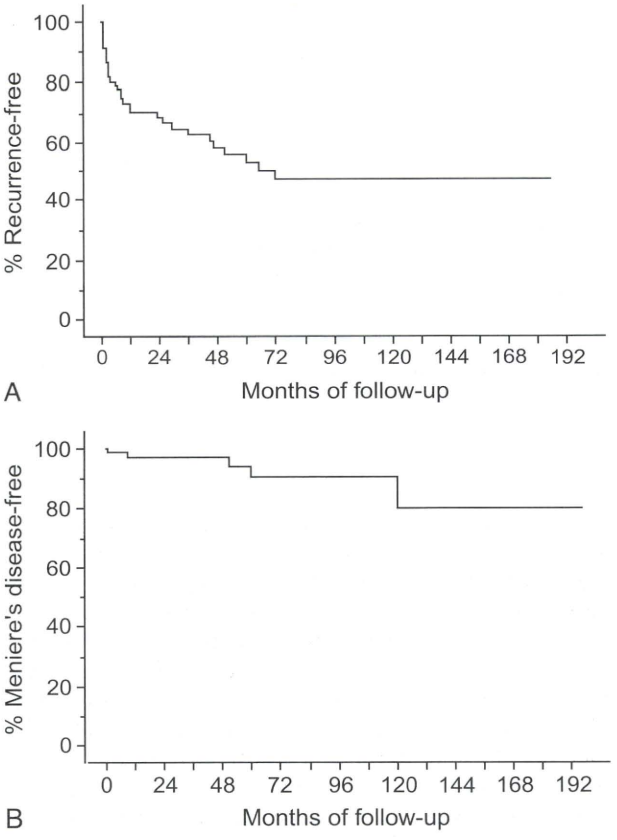


**FIG. 1.** Kaplan-Meier plots of 82 patients with sudden low-tone sensorineural hearing loss and without vertigo, indicating the rate and timing of relapses (*A*) and development of Ménière's disease (*B*). Forty percent of patients had recurrent hearing loss. Forty-five percent of the patients with recurrence experienced a recurrence within 6 months from the first episode of hearing loss.

The recurrence rate of hearing loss and the progression rate to definite Ménière's disease were assessed. We defined recurrence as a second attack of hearing loss with or without vertiginous symptoms. Meniere's disease was diagnosed according to the criteria proposed by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology–Head and Neck Surgery (8). The follow-up period varied from 6 to 196 months with a mean of 56 months.

Computer analysis of ENG was routinely performed for patients with idiopathic sudden sensorineural hearing loss as part of a battery of clinical neurologic examinations at our university. Eye movements were recorded by the ENG technique and sampled at 100 Hz with an A-D converter on a PC (7). For detection of spontaneous nystagmus, subjects were seated in an upright position with their eyes closed for the first 30 seconds and were instructed to perform simple calculations during the time period. Electrocochleography was performed using the transtympanic approach with a reference electrode on the ipsilateral earlobe and the ground on the forehead. An elevated SP/AP ratio greater than 0.37 was considered indicative of endolymphatic hydrops (9). Electronystagmography and ECochG tests were performed in most of these patients within 2 weeks of initial diagnosis.

Statistical evaluations were performed using the $\chi^2$ test. A difference was considered statistically significant at $p < 0.05$.

**TABLE 2.** *The rate of progression to definite Ménière's Disease*

| | | SP/AP ratio | |
|---|---|---|---|
| | | Normal | Elevation |
| SN | Absence | 0.0% (0 of 22) | 0.0% (0 of 7) |
| | Presence | 11.8% (2 of 17) | 21.4% (3 of 14) |

An elevation in the SP/AP ratio to a value greater than 0.37 was considered indicative of endolymphatic hydrops.

SN indicates spontaneous nystagmus; SP/AP ratio, the ratio of the summating potential to the action potential.

Bonferroni correction was performed in adjusting for multiple comparisons (Table 1).

## RESULTS

The 82 patients comprised 31 men and 51 women aged 17 to 73 years (mean, 41.6 yr, SD, 13.8 yr). Of the 82 patients, 33 had recurrent hearing loss. The cumulative recurrence rate was 29% at 1 year and 47% at 5 years (Fig. 1A). Among the patients who experienced recurrence, 45% had a recurrence within 6 months from the first episode of hearing loss. There was no significant difference in prognosis between patients who met the definition for acute low-tone sensorineural hearing loss and those who did not. Of the 82 patients, 5 developed Ménière's disease. The cumulative rate of progression to Ménière's disease was 3% at 1 year and 10% at 5 years (Fig. 1B).

Both ENG and ECochG tests were performed in 60 patients. Thirty-five percent of these patients showed an elevated SP/AP ratio on ECochG. Spontaneous nystagmus at initial ENG was found in 51.7% of patients. The patients were divided into 4 groups based on the findings of SN and ECochG. The group with an elevated SP/AP ratio and spontaneous nystagmus had a recurrence rate of approximately 80% compared with a rate of approximately 30% in the group with normal SP/AP ratio and without spontaneous nystagmus (Table 1). There was a statistically significant difference in recurrence between the 2 groups.

In groups with spontaneous nystagmus at the initial ENG, the progression rate to definite Ménière's disease was approximately 10% with a normal SP/AP ratio and approximately 20% with an elevated SP/AP ratio (Table 2). In groups without spontaneous nystagmus, none developed Ménière's disease. There was a statistically significant difference in the progression rate of Ménière's disease between the groups with and without spontaneous nystagmus.

## DISCUSSION

Idiopathic sudden low-tone sensorineural hearing loss without vertigo has been described as acute low-tone sensorineural hearing loss in Japan (1–4,10,11), but it has not been well documented in the European or North American literature. The incidence of acute low-tone sensorineural hearing loss is estimated to be approximately 40 to 60/100,000 based on regional surveys (12). The frequent chief complaint is aural fullness, followed by hearing impairment, tinnitus, autophony, and hyperacusis (12). Audiometric definitions of acute low-tone sensorineural hearing loss remain controversial and have been described variously in extents of hearing levels at the 3 low frequencies and the 3 high frequencies (1–4,11).

Our data indicate that the recurrence rate in idiopathic sudden low-tone sensorineural hearing loss without vertigo differs according to initial ECochG and ENG findings. The recurrence rate reached almost 80% when endolymphatic hydrops on ECochG and vestibular alterations on ENG were detected. The progression rate to definite Ménière's disease was approximately 15% when vestibular alterations were detected. For the "endolymphatic hydrops (+) and vestibular alteration (+)" patient group, subsequent severity and extent of endolymphatic hydrops within the inner ear may determine whether they develop definite Ménière's disease or present with recurrent hearing loss without subjective vertigo. Immune responses were found in patients with acute low-tone sensorineural hearing loss and Ménière's disease (13).

The recurrence rate was 30% when the SP/AP ratio was normal and spontaneous nystagmus was absent. When spontaneous nystagmus was absent on ENG recordings, none of the patients developed Ménière's disease. It is possible that the "endolymphatic hydrops (−) and vestibular alteration (−)" patient group may be similar to other audiometric types of sudden sensorineural hearing loss of unknown origin.

Idiopathic sudden low-tone sensorineural hearing loss with endolymphatic hydrops and vestibular alterations has a high recurrence rate. A combination of nystagmus detection and ECochG test could improve the accuracy of both prognosis and treatment planning in patients with sudden low-tone sensorineural hearing loss and without vertigo.

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ORIGINAL ARTICLE

# Clinical characteristics of delayed endolymphatic hydrops in Japan: A nationwide survey by the Peripheral Vestibular Disorder Research Committee of Japan

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**Abstract**

*Conclusion:* Similarly to almost all delayed endolymphatic hydrops (DEH) cases with both precedent sudden deafness and mumps deafness, two-thirds of DEH cases with precedent deafness of unknown cause with onset in early childhood developed DEH symptoms within 40 years after the precedent deafness. In spite of the diagnosis of precedent deafness, viral labyrinthitis may build up the late endolymphatic hydrops in most DEH cases up to four decades. *Objective:* To clarify the characteristics of DEH in Japan. *Methods:* Clinical information on 198 DEH cases was collected by nationwide, multicenter surveys conducted by the Peripheral Vestibular Disorders Research Committee of Japan. *Results:* The incidence of the ipsilateral type of DEH was 47.5%, which was almost equal to that of the contralateral type. In both types of DEH, the most common diagnosis of precedent deafness was deafness of unknown cause with onset in early childhood: 43.9% in both types of DEH. Sudden deafness and mumps deafness were the subsequent diagnoses of precedent deafness. The distribution of time delay of the onset between precedent deafness of unknown cause with onset in early childhood and DEH was different from that between precedent sudden and mumps deafness and DEH.

**Keywords:** *Ipsilateral, contralateral, cause of profound hearing loss, onset age, Time delay of onset between precedent deafness and DEH*

## Introduction

Clinical characteristics of delayed endolymphatic hydrops (DEH) have been reported from around the world [1–16]. Most such reports are derived from clinical records at a single facility, and do not employ statistical analysis because DEH is relatively rare compared with Meniere's disease. The Meniere's Disease Research Committee of Japan was organized by the Ministry of Health and Welfare of Japan in 1974 and continued after reorganization in 1980 as the Peripheral Vestibular Disorders Research Committee. To investigate the epidemiologic and clinical characteristics of DEH, the committee conducted nationwide, multicenter surveys of patients admitted to the hospitals where members of the committee were affiliated five times in 1998, 2001, and 2006–2008.

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DEH is classified into ipsilateral and contralateral types. The diagnostic criteria for DEH in Japan were proposed by the committee of the Japan Society for Equilibrium Research in 1987 [17]. The criteria used for the diagnosis of the ipsilateral type of DEH are as follows: (1) a precedent event characterized by profound sensorineural hearing loss in one ear (precedent deafness); (2) delayed development of episodic attacks of vertigo without fluctuating hearing loss in the opposite ear; and (3) exclusion of central nervous system lesions, eighth nerve tumors, and other cochleovestibular diseases such as syphilitic labyrinthitis. The criteria used for the diagnosis of the contralateral form of DEH are as follows: (1) precedent deafness in one ear; (2) delayed development of fluctuating hearing loss in the opposite ear that is sometimes associated with episodic attacks of vertigo; and (3) exclusion of central nervous system lesions, eighth nerve tumors, and other cochleovestibular diseases like syphilitic labyrinthitis. Profound hearing loss was defined as a pure tone average of greater than 90 dB over the 500, 1000, and 2000 Hz frequencies.

In 5 nationwide, multicenter surveys, the same diagnostic criteria have been used consistently and data for 198 patients with DEH were collected. In the present study, the rate of ipsilateral versus contralateral type of DEH, the sex ratio, diagnosis of precedent deafness, age at the onset of precedent deafness, age at the onset of DEH, and time delay of the onset between precedent deafness and DEH were analyzed.

## Material and methods

The first nationwide survey was conducted from June to November 1998 by seven committee members at seven university hospitals in Japan. Data were collected from 60 patients with DEH. The second nationwide survey was conducted from January to December 2001 by 11 committee members in 11 university hospitals. The third to the fifth surveys were conducted annually from January 2006 to December 2008 by 18 committee members at 1 private and 13 university hospitals. From the 5 nationwide, multicenter surveys, data from a total of 198 patients with DEH were assembled.

Survey data were stored and analyzed by database software at the Department of Otolaryngology at the University of Toyama. Data from the five surveys on the age and sex distribution of DEH, the rate of ipsilateral versus contralateral type of DEH, the diagnosis of the precedent deafness, age at onset of precedent deafness, age at onset of DEH, the time delay of onset between preceding deafness and onset of DEH were analyzed. For statistical analysis, Student's *t* tests and chi-square tests were performed with StatView for Windows (version 4.5, Abacus Concepts, Berkeley, CA, USA).

## Results

According to the criteria proposed by the committee of the Japan Society for Equilibrium Research, 198 patients with DEH were diagnosed as 94 cases (47.5%) of the ipsilateral type of DEH, and as 104 cases (52.5%) of the contralateral type of DEH. The number of patients with each type of DEH was almost equal (Table I). Among the patients with the contralateral type of DEH, 18 (17.3%) complained of fluctuating hearing loss in the opposite ear to the precedent deafness without vertigo, while 86 cases (82.7%) complained of fluctuating hearing loss in the opposite ear to the precedent deafness with vertigo.

A slight female predominance was observed in both types of DEH (Table I). For the ipsilateral type of DEH, there were 43 males (45.7%) and 51 females (54.3%) and for the contralateral type of DEH there were 39 males (37.5%) and 64 females (61.5%).

Among the 94 patients with the ipsilateral type of DEH, the diagnosis of precedent deafness was deafness of unknown cause in 57 cases (60.6%), sudden deafness in 15 cases (16.0%), and mumps in 9 cases (9.6%) (Table II). Deafness of unknown cause was found early in childhood (i.e. deafness of unknown cause with onset in early childhood) in 41 cases (43.6%). Among the 104 patients with the contralateral type of DEH, the diagnosis of precedent deafness

Table I. Sex ratio and symptoms of delayed endolymphatic hydrops (DEH).

| Parameter | Ipsilateral type | Contralateral type | Total |
|---|---|---|---|
| Total no. of patients | 94 | 104 | 198 |
| Males | 43 (45.7%) | 39 (37.5%) | 82 (41.4%) |
| Females | 51 (54.3%) | 64 (61.5%) | 115 (58.1%) |
| Unknown | – | 1 (1.0%) | 1 (0.5%) |
| Fluctuating hearing loss with vertigo | – | 86 (82.7%) | – |
| Fluctuating hearing loss without vertigo | – | 18 (17.3%) | – |

Table II. Diagnosis of precedent deafness in DEH.

| Parameter | Ipsilateral type | Contralateral type | Total |
|---|---|---|---|
| Cause unknown | 57 (60.6%) | 65 (62.5%) | 122 (61.6%) |
| Onset in early childhood | 41 (43.6%) | 46 (44.2%) | 87 (43.9%) |
| Onset age ≥ 5 years | 10 (10.6%) | 15 (14.4%) | 25 (12.6%) |
| Onset unknown | 6 (6.4%) | 4 (3.9%) | 10 (5.1%) |
| Sudden deafness | 15 (16.0%) | 10 (9.6%) | 25 (12.6%) |
| Mumps deafness | 9 (9.6%) | 15 (14.4%) | 24 (12.5%) |
| Otitis media and mastoiditis | 8 (8.5%) | 8 (7.7%) | 16 (8.1%) |
| Streptomycin injection | 1 (1.1%) | 1 (1.0%) | 2 (1.0%) |
| Meningitis | 1 (1.1%) | 1 (1.0%) | 2 (1.0%) |
| Surgery | 0 | 2 (1.9%) | 2 (1.0%) |
| Measles | 1 (1.1%) | 0 | 1 (0.5%) |
| High fever | 1 (1.1%) | 0 | 1 (0.5%) |
| Head trauma | 1 (1.1%) | 0 | 1 (0.5%) |
| Inner ear abnormality | 0 | 1 (1.0%) | 1 (0.5%) |
| Meniere's disease | 0 | 1 (1.0%) | 1 (0.5%) |
| Total no. of patients | 94 | 104 | 198 |

was deafness of unknown cause in 65 cases (62.6%), sudden deafness in 10 cases (9.6%), and mumps deafness in 15 cases (14.4%) (Table II). Deafness of unknown cause with onset in early childhood was found in 46 cases (44.2%). In both types of DEH, the three main diagnoses of the precedent deafness were deafness of unknown cause, sudden deafness, and mumps deafness. For deafness of unknown cause, deafness of unknown cause with onset in early childhood was the most common diagnosis.

In the ipsilateral type of DEH, the mean age at the onset of precedent deafness was 1.8 years in cases with deafness of unknown cause with onset in early childhood, 44.9 years in cases with sudden deafness, and 4.0 years in cases with mumps deafness (Table III). In the contralateral type of DEH, the mean age at the onset of precedent deafness was 2.3 years in cases with deafness of unknown cause with onset in early childhood, 31.6 years in cases with sudden deafness, and 5.5 years in cases with mumps deafness (Table IV). In both types of DEH, age at the onset of precedent deafness in cases with sudden deafness was significantly older than that with deafness of unknown cause with onset in early childhood and mumps deafness.

In the ipsilateral type of DEH, the mean age at the development of DEH was 28.1 years in cases with precedent deafness of unknown cause with onset in early childhood, 57.6 years in cases with precedent sudden deafness, and 24.1 years in cases with precedent mumps deafness (Table III). In the contralateral

Table III. Time delay of onset between precedent deafness and DEH in patients with the ipsilateral type of DEH among the three main diagnoses of precedent deafness.

| Parameter | No. of patients | Age at onset of precedent deafness (years) | Age at onset of DEH (years) | Time delay of onset between precedent deafness and DEH (years) |
|---|---|---|---|---|
| Total no. of patients | 94 | 14.5 (19.9) | 38.9 (19.8) | 23.9 (15.2) |
| Cause unknown with onset in early childhood | 41 | 1.8 (1.5)* | 28.1 (14.8)* | 26.4 (14.8)* |
| Sudden deafness | 15 | 44.9 (16.5)*+ | 57.6 (15.0)*+ | 13.7 (10.8)* |
| Mumps deafness | 9 | 4.0 (2.6)+ | 24.1 (9.9)+ | 19.9 (8.8) |

Results are shown as mean (SD).
*+$p < 0.01$.

Table IV. Time delay of onset between precedent deafness and DEH in patients with the contralateral type of DEH among the three main diagnoses of precedent deafness.

| Parameter | No. of patients | Age at onset of precedent deafness (years) | Age at onset of DEH (years) | Time delay of onset between precedent deafness and DEH (years) |
|---|---|---|---|---|
| Total no. of patients | 104 | 11.1 (15.9) | 39.2 (17.8) | 26.7 (16.9) |
| Cause unknown with onset in early childhood | 46 | 2.3 (1.3) | 31.9 (16.3)† | 29.7 (16.3)* |
| Sudden deafness | 10 | 31.6 (16.9)* | 48.8 (10.2)*† | 16.8 (11.1)*† |
| Mumps deafness | 15 | 5.5 (4.4)* | 22.7 (9.2)* | 17.2 (10.2)† |

Results are shown as mean (SD).
*$p < 0.01$.
†$p < 0.05$.

type of DEH, the mean age at the development of DEH was 31.9 years in cases with precedent deafness of unknown cause with onset in early childhood, 48.8 years in cases with precedent sudden deafness, and 22.7 years in cases with precedent mumps deafness (Table IV). In both types of DEH, age at the development of DEH in cases with precedent sudden deafness was significantly older than that with precedent deafness of unknown cause with onset in early childhood and mumps deafness.

In the ipsilateral type of DEH, the mean time delay of the onset between precedent deafness and DEH was 26.4 years in cases with deafness of unknown cause with onset in early childhood, 13.7 years in cases with sudden deafness, and 19.9 years in cases with mumps deafness (Table III). In the contralateral type of DEH, the mean time delay of the onset between precedent deafness and DEH was 29.7 years in cases with deafness of unknown cause with onset in early childhood, 16.8 years in cases with sudden deafness, and 17.2 years in cases with mumps deafness (Table IV). In both types of DEH, the time delay of the onset between precedent deafness and DEH in cases with deafness of unknown cause with onset in childhood was significantly longer than that with precedent sudden deafness.

The distribution of the time delay of the onset between precedent deafness and DEH in cases with deafness of unknown cause with onset in early childhood, sudden, and mumps deafness is shown in Table V. A chi-square test showed that the distribution of the time delay of the onset between precedent deafness and DEH in cases with unknown cause with onset in early childhood was different from that with sudden and mumps deafness (vs sudden deafness $p < 0.01$; vs mumps deafness $p < 0.05$). However, in 58 of 87 (72.8%) cases with precedent deafness of unknown cause with onset in early childhood, in 24 (96%) of 25 cases with precedent sudden deafness, and in 24 cases (100%) with precedent mumps deafness, DEH symptoms developed up to 40 years. Thus, two-thirds of DEH cases with precedent deafness of unknown cause with onset in early childhood developed DEH symptoms up to 40 years after precedent deafness, like almost all DEH cases with both precedent sudden and mumps deafness.

Table V. Distribution of time delay of onset between precedent deafness and DEH among the three main diagnoses of precedent deafness.

| Time delay (years) | Cause unknown with onset in early childhood | Sudden deafness | Mumps deafness |
|---|---|---|---|
| 0.9 | 3 (2.4%) | 8 (32%) | 4 (16.7%) |
| 10–19 | 24 (27.6%) | 9 (36.0%) | 9 (37.5%) |
| 20–29 | 16 (18.4%) | 5 (20.0%) | 8 (33.3%) |
| 30–39 | 15 (17.2%) | 2 (8.0%) | 3 (12.5%) |
| 40–49 | 5 (5.7%) | 1 (4.0%) | 0 |
| 50–59 | 17 (19.5%) | 0 | 0 |
| ≥60 | 7 (8.0%) | 0 | 0 |
| Total | 87 | 25 | 24 |

Chi-square test showed the difference of the distribution of time delay of onset between unknown cause with onset in early childhood and sudden deafness ($p < 0.01$) or mumps deafness ($p < 0.05$).

## Discussion

A total of 549 cases with unilateral DEH were previously reported [1–16]. Before the first publication of the criteria for the contralateral type of DEH by Schuknecht [4], 116 cases with the ipsilataral type of DEH had been reported. After Schuknecht's study, a total of 439 cases with DEH were documented, including 293 cases with the ipsilateral type of DEH and 140 cases with the contralateral type of DEH. The morbidity that causes vertigo is the same in both types of DEH. The discrepancy in the proportion of the contralateral type of DEH among the previous studies was likely caused by differences in the diagnostic criteria for the contralateral type of DEH used in each study, rather than by regional differences. In the contralateral type of DEH, the hearing level of the opposite better-hearing ear fluctuates for a long time after the onset of precedent profound deafness [4]. Some patients with the contralateral type of DEH suffered from fluctuating hearing loss with vertigo, others did not experience the symptom. In previous studies including patients both with and without vertigo [6,7,9,10,13,14], the mean rate of the contralateral type of DEH was 40.5%. However, in previous studies that included only patients with vertigo [5,8,11,12,15,16], the mean rate of the contralateral type of DEH was 25.2%. In the present study, because the contralateral type of DEH was diagnosed in patients with and without vertigo according to the criteria proposed by the Committee of the Japan Society for Equilibrium Research, the rate of the contralateral type of DEH was increased to 52.3%. Among them, 82.7% of patients were with vertigo and 17.3% of patients were without vertigo.

In the previous studies [1–16], the diagnoses of precedent deafness in a total of 549 cases with DHE were as follows: in the ipsilateral type of DEH, the diagnosis of precedent deafness was deafness of unknown cause with onset in early childhood in 198 cases (32.3%), sudden deafness in 58 cases (14.2%), and mumps in 63 cases (13.4%). In the contralateral type of DEH, the diagnosis of precedent deafness was deafness of unknown cause with onset in early childhood in 63 cases (45.0%), sudden deafness in 14 cases (10%), and mumps in 7 cases (5.0%). In the present study, the diagnosis of the precedent deafness of the ipsilateral type of DEH was deafness of unknown cause with onset in early childhood in 41 cases (43.6%), sudden deafness in 15 cases (16.0%), and mumps deafness in 9 cases (9.6%). The diagnosis of the precedent deafness of the contralateral type of DEH was deafness of unknown cause with onset in early childhood in 46 cases (44.2%), sudden deafness in 10 cases (9.6%), and mumps deafness in 15 cases (14.4%). The present findings demonstrated that in both types of DEH, the most common diagnosis of the precedent deafness was deafness of unknown cause with onset in early childhood, and that sudden and mumps deafness are the two main subsequent diagnoses of precedent deafness, which was consistent with the previous reports.

In both types of DEH, the mean age at the onset of precedent deafness in cases with sudden deafness was significantly older than that in cases with both deafness of unknown cause with onset in early childhood and mumps deafness (Tables III and IV). Therefore, the mean age at the development of DEH in cases with precedent sudden deafness was significantly older than in cases with precedent deafness of unknown cause with onset in early childhood and mumps deafness (Tables III and IV).

In the present study, in both types of DEH, the mean time delay of the onset between precedent sudden deafness and DEH did not differ from that between precedent mumps deafness and DEH (Tables III and IV). In contrast, the mean time delay of the onset between precedent deafness of unknown cause with onset in early childhood and DEH was significantly longer than that between precedent sudden deafness and DEH. These findings suggest that the mechanism of the development of DEH after deafness of unknown cause with onset in early childhood is different from that after sudden and mumps deafness. In 1985, Schuknecht [18] proposed a mechanism for the development of DEH: viral labyrinthitis damages the endolymph resorptive system during precedent deafness, resulting in endolymphatic hydrops long after the onset of precedent deafness. Since viral labyrinthitis has been supposed as an etiology of sudden deafness [19], in cases with precedent sudden and mumps deafness, DEH may develop under the mechanism proposed by Schuknecht. In fact all DEH cases, with the exception of one case with precedent sudden and mumps deafness, developed DEH symptoms within 40 years after the precedent deafness (Table V).

Distribution of time delay of the onset between precedent deafness of unknown cause with onset in early childhood and DEH was significantly different from that between precedent sudden and mumps deafness and DEH. However, like almost all DEH cases with both precedent sudden and mumps deafness, two-thirds of DEH cases with precedent deafness of unknown cause with onset in early childhood developed DEH symptoms within 40 years of the precedent deafness (Table V). Since viral labyrinthitis has been supposed as an etiology of deafness of unknown cause with onset in early childhood [1,10], the present findings suggest that, in spite of

the diagnosis of precedent deafness, the viral labyrinthitis may build up the late endolymphatic hydrops in most DEH cases up to four decades.

The pathogenesis of Meniere's disease is idiopathic endolymphatic hydrops. Based on the nationwide surveys from 2001 to 2006 conducted by the Peripheral Vestibular Disorders Research Committee in Japan [20], age at onset of Meniere's disease peaked in the fifth decade in males and the sixth decade in females. In the present study, the remaining one-third of DEH cases with precedent deafness of unknown cause with onset in early childhood developed DEH symptoms over 40 years after the precedent deafness. The development of DEH symptoms in such cases at more than 40 years old may be associated with the occasional Meniere's disease.

DEH is one of the secondary endolymphatic hydrops. Several etiologic factors other than viral infection have been reported in the generation of the endolymphatic hydrops [21–23]. Suzuki et al. [23] reported that 5 (28%) of 18 cases with deafness of unknown cause with onset in early childhood, 1 (100%) case with ipsilateral type of DEH, and 6 (75%) of 8 cases with the contralateral type of DEH showed the presence of autoantibody against inner ear protein. The wider distribution of the time delay of the onset between precedent deafness of unknown cause with onset in early childhood and DEH than that between precedent sudden and mumps deafness and DEH might be related to another etiologic factor, such as the autoimmune response.

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**ORIGINAL ARTICLE**

# Correlation between canal paresis and spontaneous nystagmus during early stage of acute peripheral vestibular disorders

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**Abstract**

*Conclusions:* This study demonstrates that the resolution period of spontaneous nystagmus (SN) may provide an indication of vestibular dysfunction on a particular day in the primary care setting. *Objective:* We aimed to predict canal paresis using fundamental observations of SN during the early stage of acute peripheral vestibular disorders. *Methods:* The study involved 87 patients who had recently experienced their first episode of acute spontaneous vertigo and direction-fixed horizontal nystagmus. Although they did not exhibit any other neurological deficits, they had been hospitalized with severe acute symptoms between 2004 and 2007. A correlation between the resolution period of SN and the results of laboratory caloric testing was reviewed. *Results:* The receiver operating characteristic analysis showed that the resolution period of SN may be a predictive indicator of unilateral vestibular hypofunction in the acute stage. In about half of the patients, SN disappeared on the third day after their initial visit. However, in 20% of the patients SN still persisted on the eighth day. Among the patients with SN, the prevalence of canal paresis increased with the increase in the resolution period of SN. When SN was observed on the fifth day, the prevalence was approximately 70%.

**Keywords:** *Acute peripheral vestibulopathy, acute isolated vertigo, vestibular neuritis*

## Introduction

In acute peripheral vestibular disorders, patients usually suffer from acute symptoms of severe vertigo that persist longer than several hours, accompanied by intense nausea and vomiting. Almost all patients experience the onset of the disease as a surprise and are anxious [1]. The head thrust test or post-head-shaking nystagmus is known to be useful in predicting a significant unilateral vestibular hypofunction at the bedside of the patient [2]. However, it would be better to perform these dynamic vestibular tests in the sub-acute stage of the disease or later after spontaneous nystagmus (SN) and nausea/vomiting are reduced. During the early stage of acute peripheral vestibular disorder, oculomotor examination typically reveals nystagmus due to static vestibular imbalance by showing the mixed horizontal-torsional and direction-fixed SN that does not change direction with gaze and is suppressed with fixation, in the absence of other neurological symptoms or signs [2,3]. This study aimed to predict canal paresis (CP) using fundamental observations of SN during the early stage of acute peripheral vestibular disorders to help primary care providers and their patients.

## Material and methods

This study reviewed the data of patients who were admitted to the otolaryngology ward of the university hospital and its affiliates between 2004 and 2007 for severe vertigo, nausea and/or vomiting, and gait impairment. The patients were referred primarily to

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either an emergency physician or an otolaryngologist, depending on the time of the patient's visit. Acute peripheral vestibular disorder was defined based on clinical features that suggested a possibly acute isolated vertigo of peripheral origin and was independent of the results of caloric testing subsequently performed. The criteria for inclusion were as follows: (1) a single episode of spontaneous vertigo that persisted for several hours, (2) the presence of a direction-fixed and horizontal SN that did not change direction with gaze and was suppressed with fixation compared with when Frenzel glasses were in place (we have included both mixed horizontal-torsional type and horizontal type); (3) no history of inner ear disease; (4) no cochlear symptoms; (5) no headache; and (6) no central nervous system involvement, as measured by neurological physical examination and urgent brain CT.

In clinical practice, central vestibular disorders occasionally present with features of peripheral vestibular nystagmus and a negative neurologic examination at the onset of a vertigo attack [3]. Patients were excluded from this study if they revealed central nervous system disorders on subsequent brain MRIs and neurological examinations during their course of hospitalization. They were also excluded if they exhibited unilateral sensorineural hearing loss on pure-tone audiometry. Finally, 87 patients were included in the study (33 men and 54 women aged 25–89 years; 31 patients at the university hospital and 56 patients at affiliates; Table I). SN was assessed daily in the morning at the bedside. Patients were administered anti-vertiginous and anti-emetic drugs without corticosteroids for several days to obtain relief from intense vertigo and nausea.

Table I. Summary of patients with acute peripheral vestibular disorder.

| Parameter | Value |
|---|---|
| Subjects ($n$ = 87) | |
| Sex (male/female) | 33/54 |
| Age (years) | 61.5 ± 14.3 |
| Acute symptoms | |
| Vertigo sensation ($n$ = 87) | 6.9 ± 7.6 days |
| Nausea and/or vomiting ($n$ = 79) | 3.1 ± 2.9 days |
| Difficulty in walking ($n$ = 76) | 3.0 ± 1.8 days |
| Findings | |
| Bedside test | |
| Nystagmus duration ($n$ = 87) | 5.3 ± 5.7 days |
| Laboratory vestibular test | |
| CP in caloric test | 48.60% (35/72) |
| DP in rotational test | 30.30% (10/33) |

CP, canal paresis; DP, directional preponderance.

After nausea and vomiting were resolved, the patients were examined through routine laboratory evaluation of oculomotor-vestibular functions, which consisted of (1) spontaneous, positional, and gaze-evoked nystagmus; (2) pursuit, optokinetic system; and (3) caloric testing in sequence. The patients were also routinely evaluated using the sinusoidal rotational testing, galvanic body sway testing, and vestibular evoked myogenic potential testing in sequence [4]. Eye movements were recorded by the electronystagmographic (ENG) technique and sampled at 100 Hz with an A-D converter on a PC. Caloric stimuli consisted of alternate irrigation for 60 s with 6 L/min of cold and hot air, 24°C and 50°C, respectively. Asymmetry of vestibular function was calculated using the Jongkees formula. Significant CP corresponding to the evidence of unilateral vestibular dysfunction was defined as a response difference of 20% or more between the ears (laboratory-specific normal limits). The sinusoidal rotational test was performed with the patient's eyes closed in the dark with the head anteflexed to 30°. The patient was subjected to 0.1 Hz sinusoidal oscillations with a peak angular velocity of 75.4°/s. Directional preponderance (DP) was defined as a response difference of 10% or more between the ears (laboratory-specific normal limits).

In the present study, we aimed to predict the prevalence of unilateral vestibular hypofunction on a particular day in patients with SN using the resolution period of bedside SN (counted from the first visit) in patients with peripheral vestibules. First, receiver operating characteristic (ROC) analysis was performed to determine the predictability of the resolution period measures of SN; CP on laboratory caloric test was regarded as the gold standard. The area under the ROC curve (AUC) was estimated by the trapezoidal rule. An AUC > 0.60 was considered a highly predictive indicator. Second, the cumulative percentage of patients with SN in the early stage was examined. Third, among the patients with SN, the prevalence of CP with respect to a hospital stay was examined.

The duration of subjective symptoms was also examined. The relationship between the resolution of subjective symptoms and bedside SN was analyzed using Pearson's product-moment correlation coefficient. A correlation coefficient between 0.20 and 0.40 was considered mild correlation and 0.40–0.70 moderate correlation. A difference with a $p$ value of $< 0.05$ was considered statistically significant.

## Results

The visit was during the daytime (9:00 am to 5:00 pm) in 42% of the patients, during the evening or night (5:00 pm to 3:00 am) in 46%, and during the early morning (3:00 am to 9:00 am) in 12%. ROC analysis was performed to determine the predictability of the resolution period measures of SN (Figure 1). We found that the resolution period of SN could be a predictive indicator of unilateral vestibular hypofunction in the acute stage (AUC 0.63).

Figure 2A shows the cumulative percentage of patients with SN in the early stage. In about half of the patients, SN disappeared on the third day after the initial visit. However, in 20% of the patients SN still persisted on the eighth day. The prevalence of CP among the patients with SN is shown in Figure 2B. The prevalence increased with the increase in the duration of SN. For instance, when SN was observed on the third day, the prevalence was approximately 60%, and when SN was observed on the fifth day, the prevalence was approximately 70%. The duration of bedside SN did not correlate properly with DP in the subsequent laboratory rotational test (AUC 0.55).

Of the acute symptoms, nausea and/or vomiting and gait impairment resolved relatively quickly in most patients, but the resolution period of the vertigo

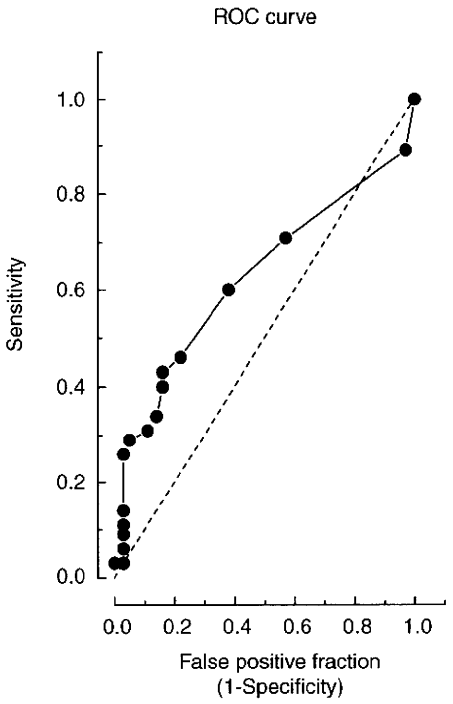


Figure 1. The receiver operating characteristic (ROC) curve indicates that the resolution period of spontaneous nystagmus in the acute stage may be a predictor of canal paresis (CP) in the caloric test. The area under the ROC curve was 0.63.

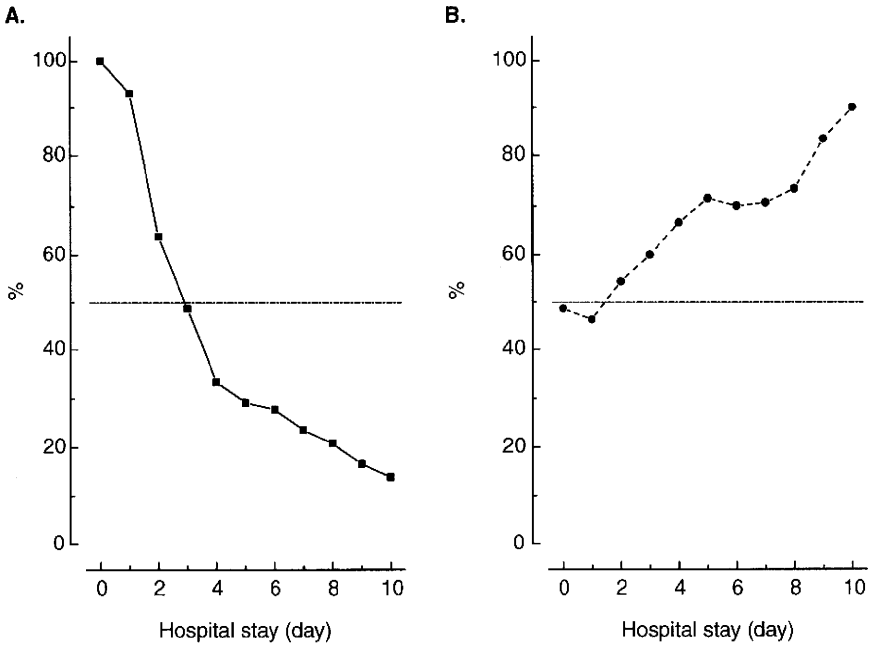


Figure 2. (A) The cumulative percentage of patients with acute peripheral vestibular disorder and spontaneous nystagmus (SN) with respect to the length of hospital stay in the acute stage ($n = 87$). On the third day from the initial visit, SN disappeared in about half of the patients; 20% of the patients still had SN on the eighth day. (B) The prevalence of canal paresis (CP) among these patients with SN ($n = 72$). These findings suggest that when SN is observed on the ninth day, the estimated prevalence rate of CP is approximately 90%. Zero indicates the date of admission.