Clinical Characteristics of Bilateral Meniere’s Disease in a Single Asian Ethnic Group

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Objectives/Hypothesis: To identify the clinical characteristics of patients with bilateral Meniere’s disease (MD) in an Asian population.

Study Design: Cross-sectional retrospective study.

Methods: We compared the clinical features of bilateral MD (BMD) and unilateral MD (UMD) in 320 Asian patients with single ethnicity. Demographic variables; age of onset; inner ear function; the coexistence of related disorders such as vestibular migraine, delayed MD, systemic autoimmune diseases, and familial MD; and prognoses were analyzed and compared.

Results: The overall prevalence of BMD was 5.6%. The mean age of disease onset was 40.3 ± 14.8 and 47.0 ± 14.1 years for patients with BMD and UMD, respectively (P = .07). Demographic variables were not significantly different between patients with BMD and UMD (P > .05). Inner ear function, evaluated by hearing thresholds, caloric tests, and cervical vestibular evoked myogenic potentials, was significantly more deteriorated in the first involved ear of patients with BMD than in the second involved ear or the affected side of patients with UMD (P < .05). Among the comorbid conditions, only the prevalence of delayed MD was significantly higher in patients with BMD than in patients with UMD. Systemic autoimmune disease was found in only three patients with UMD. There was no significant prognostic difference between patients with UMD and BMD (P > .05).

Conclusions: A low prevalence of BMD, a higher frequency of delayed MD in BMD patients, and a low frequency of systemic autoimmune diseases in both UMD and BMD patients are significant findings in an Asian population.

Key Words: Meniere’s disease, bilaterality, endolymphatic hydrops, Asian.

Level of Evidence: 4

INTRODUCTION

Meniere’s disease (MD) is an inner ear disorder characterized by spontaneous recurrent episodes of vertigo with fluctuating and progressive sensorineural hearing loss, tinnitus, and aural fullness. MD primarily involves one side, but bilateral involvement occurs in 2% to 78% of cases.1,2 Most bilateral involvement occurs through a metachronous progression, with the onset of second-ear involvement occurring more than 5 to 10 years after the onset of first-ear involvement.1,2 Although it is not common, bilateral involvement is a major concern in that it can severely affect patients’ quality of life due to progressive bilateral vestibular hypofunction and bilateral sensorineural hearing loss.

Furthermore, disease progression to the other side restricts the choices of function-destructive treatment modalities such as intratympanic gentamicin, labyrinthectomy, and vestibular neurectomy as second-line treatments if a patient’s recurrent vertigo symptoms are not relieved by noninvasive treatments such as lifestyle modifications, medication, and intratympanic steroid injections, especially in cases where the cochlear and vestibular functions of the first involved side are severely deteriorated. Genetic and/or autoimmune pathologies may be pathologic mechanisms of bilateral MD (BMD); however, nothing has been definitively proven so far.3,4 Furthermore, there are still controversies regarding the differences in the clinical characteristics and prognoses between patients with BMD and those with unilateral MD (UMD). Several studies have suggested associations between BMD and a higher frequency of migraines, a family history of MD, and systemic autoimmune diseases, whereas several studies have reported no significant differences in these conditions between patients with BMD and UMD.3,5–7 Additionally, changes in the frequency or duration of vertigo attacks after treatment are reported inconsistently.4,8 However, so far, the number of studies on BMD are still limited in providing sufficient information about its clinical characteristics. In addition, most studies concerning BMD have been based on the data from Caucasian populations, and reports from other ethnicities are lacking. Studies of BMD in a wider variety of countries and different

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ethnic populations are important because MD shows ethnic diversities in epidemiologic and genetic features.\textsuperscript{8–11}

In this study, we investigated the prevalence and clinical features of patients with BMD in a large, homogeneous ethnic Asian population. The results of this study can provide basic epidemiological data and a basis for an improved understanding of different characteristics of BMD in Asian populations.

**MATERIALS AND METHODS**

**Selection of Patients and Parameters for Analysis**

For this study, we enrolled 351 consecutive patients at a single institution (Severance Hospital, Yonsei University College of Medicine) who met the diagnostic criteria of the Barany Society (2015) for definite MD.\textsuperscript{12} Among them, 320 patients who were followed up until December 2017 with a disease duration of more than 5 years were finally enrolled (average disease duration: 7.9 ± 4.5 years) (Table I). The disease duration was required because the time interval between first-ear involvement to the other-ear involvement in metachronous BMD is reported to be more than 5 years.\textsuperscript{1} All of the patients had single Asian ethnicity, and were nationals of the Republic of Korea. Complete neurotological examinations, such as spontaneous nystagmus, gaze-evoked nystagmus, head-shaking nystagmus, positional and positioning tests, cerebellar function tests, cranial nerve exams, oculomotor tests, and otoscopic exam of the tympanic membrane were performed in all patients. Brain magnetic resonance imaging was taken if patients were suspected to have a central lesion or cerebellopontine angle tumor during neurotological examinations or hearing test (pure-tone audiometry and speech audiometry test), and patients with those lesions were excluded from being diagnosed with MD. The mean hearing threshold from pure-tone audiometry (PTA) was calculated by averaging the air conduction thresholds at 500, 1,000, 2,000, 4,000 Hz. Vestibular function was evaluated by bithermal caloric tests and cervical vestibular myogenic potential (cVEMP) assessments according to the same protocol in a previous report.\textsuperscript{13} Unilateral weakness (canal paresis) calculated using Jongkee’s formula in the bithermal caloric test with a value of 225% was regarded as pathological according to normative data from our laboratory.\textsuperscript{14} The abnormal results of the cVEMP test were determined if there was no response to 500 Hz, 95 dB nHL tone burst stimulation. cVEMP threshold was checked when patients who did not have middle ear pathologies in otoscopic examination and impedance audiometry showed one of the following findings and/or symptoms: 1) air-bone gap at low frequency (250 and 500 Hz or only at 250 Hz) on PTA, 2) autophonia, and 3) vertigo induced by sound or pressure stimulation. If cVEMP threshold was less than 70 dB nHL, temporal bone computed tomography (CT) was performed to detect the third window of the inner ear. In the end, there was no patient with an inner ear third window in this study population. The results of hearing thresholds, caloric tests, and cVEMPs from the most recent follow-up were used for analysis. The qualitative variables considered were accompanying vestibular migraine, familial MD, the coexistence of systemic autoimmune disorders, and delayed MD. Migraine was diagnosed according to the diagnostic criteria proposed by the Barany Society and the International Headache Society.\textsuperscript{15} Patients who had at least one family member diagnosed with definite or probable MD within their first- or second-degree relatives were considered to have familial MD. Delayed MD, previously described as delayed hydrops, was diagnosed if sensorineural hearing loss preceded the onset of vertigo episodes by several months or years, as suggested by the Barany Society.\textsuperscript{12} Disease prognosis was assessed according to the Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in MD (American Academy of Otolaryngology–Head and Neck Surgery, 1995).\textsuperscript{16} First-line treatments were medications (betahistine and diuretics) and lifestyle modifications including a low-salt diet and avoiding caffeine and smoking. If the first-line treatments were not successful in controlling a patient’s vertigo symptoms, second-line surgical treatments, such as endolymphatic sac surgery, chemical labyrinthectomy, and vestibular neurectomy, were performed. In bilateral cases, intratympanic steroid injections and endolymphatic sac surgeries were chosen for the second-line treatment for the second-involved ear. Patients with simultaneous bilateral involvement with an interval shorter than 1 month between the first- and second-ear involvement were considered to have synchronous BMD, and other bilateral involvements were categorized as metachronous BMD.\textsuperscript{7}

**Statistical Analysis**

PASW Statistics 18 (IBM, Armonk, NY) was used for statistical analysis. The results are expressed as the mean ± standard deviation. A value of $P < .05$ was considered to be significant. Mann-Whitney rank sum tests and Fisher exact tests or $\chi^2$ tests were used to determine significant differences between continuous variables and categorical variables, respectively. The results from three groups were compared with a Kruskal-Wallis one-way analysis of variance with Dunn’s post-test. Spearman’s correlation was used to measure the strength of the relationships between two sets of data.

**Ethical Consideration**

The institutional review boards of the authors’ institutions approved this study.
RESULTS

Demographics

A total of 18 (5.6%) out of 320 enrolled patients showed BMD. Among the BMD patients, 14 (82.4%) had metachronous involvement and four (17.6%) had synchronous involvement (Table I). The average duration from the first-ear onset to the contralateral progression of the disease for patients with metachronous BMD was 5.6 ± 5.0 years (Table II). Metachronous bilateral involvement occurred within 5 years from the first-side involvement in nine patients. In the other five patients, metachronous bilateral involvement occurred at 7, 10, 11, 13, and 16 years from the first-ear involvement. Although the onset age of the disease had a tendency to be younger in patients with BMD (40.3 ± 14.8 years) than in those with UMD, it was not significantly different between the two groups (47.0 ± 14.2 years) (P = .071) (Table II). The disease duration from the onset in the first involved side of patients with BMD (12.1 ± 7.5 years) was significantly longer than the duration in patients with UMD (7.7 ± 4.1 years) (P = .021) (Table II); however, the disease duration from the onset in the second involved side of patients with BMD (7.7 ± 4.9 years) was not significantly different from the disease duration in patients with UMD (P = .100) (Table II). Both groups showed a higher preponderance of females (66.3%, UMD; 55.6%, BMD) (Table II). The male preponderance between the two groups (P = .443) (Table II).

Cochlear and Vestibular Function

The mean PTA of the lesion side was 43.4 ± 25.6 dB HL for patients with UMD (Table II). In patients with BMD, the mean hearing thresholds of the first involved ear (76.2 ± 25.6 dB HL) was significantly higher than the second involved ear (44.9 ± 15.0 dB HL) (P = .031) (Table II). When the hearing thresholds of BMD patients were compared with those of UMD patients, the average hearing thresholds of the first involved ear in BMD patients were significantly higher than the average hearing threshold of the lesion side in the UMD (43.4 ± 25.6 dB HL, P < .001), whereas the average hearing threshold of the second involved ear in patients with BMD was not significantly different from the hearing threshold of the lesion side in patients with UMD (P = 1.000) (Table II). The unilateral caloric weakness was significantly higher in the BMD group (49.2% ± 33.8%) than in the UMD group (28.3% ± 24.8%) (P = .008) (Table II). The proportion of ears with no response in cVEMP recordings was significantly higher in patients with BMD (UMD, 34.4%; BMD, 66.7%) (P = .002) (Table II). More specifically, no response in cVEMP recordings was identified in the first involved side, second involved side, and both sides in eight, four, and six cases, respectively, in patients with BMD. The difference in the proportion of no response in cVEMP recordings between the initially involved side and the second involved side was not significantly different (P > .05). In summary, cochlear and vestibular functions were more deteriorated in the first involved side of patients with BMD than in patients with UMD.

Comorbidities

The prevalence of comorbid vestibular migraines was not different between the two groups (UMD, 24.2%; BMD, 16.7%) (P = .580) (Table II). The proportion of patients with delayed MD was significantly larger in the BMD group (22.2%) than in the UMD group (5.0%) (P = .013) (Table II). In all the delayed BMD patients, fluctuating vertigo and ear symptoms initiated in the side with antedate sensorineural hearing loss, and typical MD symptoms occurred later in the other side. Among the 30 patients with history of familial MD, 28 (93.3%) had UMD and two (11.1%) had BMD; this difference between groups was not significantly different (P = .876) (Table II). All three patients with proven systemic autoimmune diseases, diagnosed as ankylosing spondylitis, rheumatoid arthritis, and Behcet's disease, had UMD (Table II). Migraines and familial MD were not correlated with amount of hearing or vestibular deficits in either UMD and BMD patients (P > .05).

Prognosis

Based on the 1995 American Academy of Otolaryngology–Head and Neck Surgery guidelines for the evaluation of MD therapy, we divided the six

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*Hearing threshold = average of 500, 1000, 2000, and 4000 Hz. Hearing thresholds of both ears were included in the calculations for patients with unilateral MD.

1P value in the comparison between first involved ear and second involved ear in bilateral MD.

2P value in the comparison between the lesion side ear with unilateral MD and second involved ear with bilateral MD.

3Both ears were considered for patients with bilateral MD.

=cVEMP = cervical vestibular myogenic potential; MD = Meniere’s disease; SD = standard deviation.

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**TABLE II.**

Comparison Between Patients With Unilateral Versus Bilateral MD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unilateral MD, n = 302</th>
<th>Bilateral MD, n = 18</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset, yr, mean ± SD</strong></td>
<td>47.0 ± 14.2</td>
<td>40.3 ± 14.8</td>
<td>.071</td>
</tr>
<tr>
<td><strong>Disease duration, yr, mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First involved ear</td>
<td>7.7 ± 4.1</td>
<td>12.1 ± 7.5</td>
<td>.021</td>
</tr>
<tr>
<td>Second involved ear</td>
<td>7.7 ± 4.9</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td><strong>Time interval of bilateral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>progression, yr, mean ± SD</td>
<td>5.6 ± 5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>101 (33.7)</td>
<td>8 (44.4)</td>
<td>.443</td>
</tr>
<tr>
<td>Female</td>
<td>199 (66.3)</td>
<td>10 (55.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Hearing threshold, dB HL, mean ± SD</strong></td>
<td>43.5 ± 25.6</td>
<td>75.4 ± 32.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First involved ear</td>
<td>43.4 ± 25.6</td>
<td>76.2 ± 25.6</td>
<td>.031*</td>
</tr>
<tr>
<td>Second involved ear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canal paresis, %, mean ± SD</td>
<td>28.3 ± 24.8</td>
<td>49.2 ± 33.8</td>
<td>.008</td>
</tr>
<tr>
<td>Lack of cVEMP response, n (%)</td>
<td>104 (34.1)</td>
<td>24 (66.7)</td>
<td>.002</td>
</tr>
<tr>
<td>Concordant migraine, n (%)</td>
<td>73 (24.2)</td>
<td>3 (16.7)</td>
<td>.580</td>
</tr>
<tr>
<td>Delayed hydrops, n (%)</td>
<td>15 (5.0)</td>
<td>4 (22.2)</td>
<td>.013</td>
</tr>
<tr>
<td>Familial MD, n (%)</td>
<td>28 (9.3)</td>
<td>2 (11.1)</td>
<td>.876</td>
</tr>
<tr>
<td>Concordant autoimmune disease, n (%)</td>
<td>3 (1.0)</td>
<td>0 (0.0)</td>
<td>.404</td>
</tr>
</tbody>
</table>

*P value in the comparison between first involved ear and second involved ear in bilateral MD.

1P value in the comparison between the lesion side ear with unilateral MD and second involved ear with bilateral MD.

Both ears were considered for patients with bilateral MD.

cVEMP = cervical vestibular myogenic potential; MD = Meniere’s disease. SD = standard deviation.

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prognostic classes into a favorable group (class A and B) and an unfavorable group (C, D, E, and F). As a result, most patients in both groups were confined to class A and B (UMD, < 184/302 [61.0%]; BMD, 11/18 [61.1%]), and there was no significant difference in the prognoses between patients with UMD and those with BMD (P = .816) (Table III). During the course of treatment, 75 (24.8%) of the UMD patients and five (27.8%) of the BMD patients underwent second-line treatments due to the failure of the first-line treatment. The rate of failure of the first-line treatment was not significantly different between the two groups (P = .783).

**DISCUSSION**

This is the first study to identify the clinical characteristics of BMD, including prevalence, comorbid conditions, inner ear function, and prognoses, in a large, single-ethnicity Asian population. Several clinical features of BMD in a South Korean population were relatively different from those reported in studies of Caucasian populations. These differences can be summarized as follows: a low prevalence of BMD, a higher frequency of delayed MD in patients with BMD, and a low frequency of systemic autoimmune diseases in both UMD and BMD patients.

Even when considering the different diagnostic criteria and the variable follow-up periods in previous reports as reasons for the variable prevalence of BMD, the 5.4% prevalence of BMD seems to be lower than in other reports (Table IV). If we consider the studies with strict diagnostic criteria for BMD, bilaterality in the Caucasian population has been reported in 2% to 47% of MD patients. Although the lowest prevalence was 2%, most studies reported 20% to 50% prevalence of bilateral involvement in the Caucasian population. In most studies, the interval for contralateral involvement from the onset of first-side involvement is more than 5 years (Table IV); however, some studies show that the involvement of the contralateral ear occurs later in the course of the disease, and it appears that bilateral involvement increases with increased disease duration. Even when considering the studies in which bilateral involvement occurred within 5 years from first-side involvement, the prevalence of BMD was 10% to 35%, which is higher than the prevalence of our study. Compared to the number of studies in the Caucasian population, epidemiological studies of BMD are very rare in Asian populations. Even if we focus on an Asian population, the prevalence (5.6%) of BMD in the current study was less than half of the bilateral involvement over time (7.9%–29%) (Table IV) reported in Japanese nationwide surveys. The different prevalence rates of BMD among countries and ethnicities may reflect different pathological mechanisms in the development of bilaterality such as genetic backgrounds, lifestyles, and predisposing diseases including autoimmune diseases.

Hearing thresholds and vestibular weakness were poorer in the first involved side of BMD than in UMD in this study. The longer disease duration of the first-involved side in patients with BMD is likely to contribute to increased deterioration of inner ear function. It has already been established that inner ear function deteriorates over time in patients with MD and stabilizes at an approximate hearing threshold of 50 to 60 dB at 5 to 10 years from disease onset. Because the difference in the mean disease duration between patients with UMD and BMD was approximately 5 years, the inner ear function of the first involved side of bilateral cases seems to be expended, as there were significant differences in the remaining inner ear function between the first involved side of bilateral patients and unilateral cases as well as between the first and second involved side of bilateral patients. Previous studies from Caucasian and Japanese populations also reported that the hearing thresholds of patients with BMD mostly were in stage 3.

The comorbid conditions of patients with BMD in this study were relatively different from those of other Caucasian population studies (Table IV). Notably, the frequency of delayed MD was significantly higher in patients with BMD (5.6% vs. 22.2% in UMD and BMD, respectively) (Table II). Although there has been no epidemiological study showing a higher frequency of delayed MD in patients with BMD so far, several clinical findings support the relationship between BMD and delayed MD. One report indicated the involvement of autoimmune pathology in the development of endolymphatic hydrops on the contralateral side of patients with delayed hydrops. Furthermore, endolymphatic hydrops in the contralateral side of the ear with delayed MD were identified by 3T MRI. Although the pathological mechanisms of BMD and delayed MD are still unclear, both disease entities may share the common pathological mechanisms of inner ear autoimmunity because autoimmune inner ear disorders involve both ears either synchronously or metachronously. Meanwhile, a discrepancy between autoimmunity and bilaterality was found in this study; systemic autoimmune diseases were not found in BMD patients. Furthermore, the frequency of systemic autoimmune disorders in patients with MD (0.94%) appeared to be much lower than that of Caucasian populations (~11%), which is significantly higher than the general population. However, autoimmune pathology can be...
concerns of MD patients is one of the most frequent concerns of MD patients is

TABLE IV.
Comparison of Clinical Features of Bilateral Meniere's Disease in Caucasian, Japanese, and South Korean Populations

<table>
<thead>
<tr>
<th>Variables</th>
<th>Caucasian</th>
<th>Japanese</th>
<th>Korean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>2%–47%</td>
<td>7.9%–29%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Mean age of onset, yr</td>
<td>33-55</td>
<td>—</td>
<td>40.3 ± 14.8</td>
</tr>
<tr>
<td>Time interval of bilateral progression, yr</td>
<td>Mostly more than 5 to 10 years</td>
<td>Less than 10 years in 78.2% of bilateral cases</td>
<td>5.6 ± 5.0</td>
</tr>
<tr>
<td>Gender, %</td>
<td>Male</td>
<td>Female preponderance (55-69)</td>
<td>Female preponderance</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing threshold, dB HL</td>
<td>Mostly stage 3, 45–58</td>
<td>&gt;60 in 33.4% of bilateral cases</td>
<td>75.4 ± 32.5</td>
</tr>
<tr>
<td>First involved ear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second involved ear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concordant migraine, %</td>
<td>10–43</td>
<td>—</td>
<td>16.7</td>
</tr>
<tr>
<td>Delayed hydrops, %</td>
<td>—</td>
<td>—</td>
<td>22.2</td>
</tr>
<tr>
<td>Familial Meniere's disease, %</td>
<td>13–31</td>
<td>—</td>
<td>11.1</td>
</tr>
<tr>
<td>Concordant autoimmune disease, %</td>
<td>~10</td>
<td>—</td>
<td>0.404</td>
</tr>
</tbody>
</table>

*Stage of Meniere's disease defined by the Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease (American Academy of Otolaryngology-Head and Neck Surgery, 1995).16

1Hearing threshold at initial diagnosis. Values using ± represent the mean ± standard deviation.

Caucasian population is up to 50%, a physician can inform the patients about the much lower frequency of bilateral progression in Asian. Meanwhile, patients with delayed MD or early disease onset (≤40 years) should be informed about the higher possibility of the bilateral progression, although an early age of onset was not statistically different between patients with BMD and UMD, probably due to the small number of bilateral cases. These patients should be followed carefully to assess progress and choose appropriate treatment modalities. In addition, we can inform the patients in whom the disease has progressed to the contralateral ear that the progression and responses to treatment are not very different from those with UMD based upon the present results.

The current study has several limitations. First, this is a retrospective cross-sectional study. The low frequency of BMD could increase if the study is conducted in a single large cohort with a longer follow-up period. Second, due to the small number of patients with BMD, we could not perform further cluster analysis similar to the European cohort with BMD, which could provide more information about the associations among clinical characteristics in patients with BMD.7 For example, the association between familial MD or vestibular migraines and other clinical characteristics in BMD could be analyzed and compared with those of UMD if the patients with BMD could be categorized into groups after cluster analysis. Future multicenter studies of larger populations of BMD will enable us to provide more valuable information about BMD in Asian populations.

CONCLUSION

The prevalence of BMD in the South Korean population seems to be lower than that reported in Caucasian
populations. Most clinical features of patients with BMD, including demographics, comorbid conditions, and prognoses, were not significantly different from those of patients with UMD, except for a higher frequency of delayed MD in patients with BMD. The results of this study can be useful in counseling and choosing treatment strategies for patients with MD in Asian populations.

BIBLIOGRAPHY