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Association Between Migraine and Benign Paroxysmal Positional Vertigo Among Adults in South Korea

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IMPORTANCE Patients with migraine often experience various types of vertigo, and several studies have suggested an epidemiologic and physiologic association of migraine and vertigo with vestibule. However, few researchers have investigated the association between migraine and benign paroxysmal positional vertigo (BPPV).

OBJECTIVE To determine the incidence of BPPV in individuals with migraine in a large national population-based sample.

DESIGN, SETTING, AND PARTICIPANTS This cohort study obtained data from the Korean Health Insurance Review and Assessment Service covering the period January 1, 2002, through December 31, 2013. These data included personal information, health insurance claim codes, diagnostic codes, death records, socioeconomic data, and medical examination data for each individual in the database. A 1:4 matching method was used to select individuals for the migraine group (n = 40 682) and the control group (n = 162 728). Individuals who had a history of BPPV before the index date, for whom a match could not be identified, and who received a migraine diagnosis before age 20 years were excluded from the analysis. Data analysis was conducted from September 1, 2015, to December 31, 2017.

MAIN OUTCOMES AND MEASURES The crude and adjusted (by age, sex, income, region of residence, and medical history [hypertension, diabetes, or dyslipidemia]) hazard ratios for migraine and BPPV were analyzed using the Cox proportional hazards regression model.

RESULTS Of the 40 682 individuals in the migraine group, 10 381 (25.5%) were male and 30 301 (74.5%) were female. Of the 162 728 controls, 41 524 (25.5%) were male and 121 204 (74.5%) were female. The incidence of BPPV was statistically significantly higher in the migraine group than in the control group (2431 [6.0%] vs 3677 [2.3%]). Migraine increased the risk of BPPV (adjusted hazard ratio, 2.54; 95% CI, 2.41-2.68). In a subgroup analysis, the incidence of BPPV in all age groups and in both men and women was statistically significantly higher in the migraine group than in the control group. The incidence of BPPV was the highest in men younger than 40 years (adjusted hazard ratio, 4.49; 95% CI, 3.05-6.62), and the HR decreased in both men and women as age increased.

CONCLUSIONS AND RELEVANCE Migraine appeared to be statistically significantly associated with higher incidence of BPPV; future studies are needed to determine the association between BPPV and specific factors related to migraine.

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Supplemental content

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Migraine is characterized by various forms of moderate to severe headache that lasts from hours to days. Approximately 12% to 15% of the world's population experiences migraine, which varies by country, race/ethnicity, and age.[1,2] The National Health Interview Survey reported that the migraine prevalence in the United States from 2005 to 2012 was 14.2%, with the highest rate among Native American individuals (17.7%) and the lowest among Asian individuals (9.2%).[3] Migraine is more common in females than in males.[2,3] The rate in Asian countries varies among studies; however, few studies exist on the prevalence of migraine in South Korea.[4,5] Telephone interviews and mail surveys conducted in South Korea in 1995 found the prevalence to be 22.2%, which was higher than the rate previously reported.[4] In contrast, a questionnaire interview in 2012 in the same country revealed a 6.1% rate (9.2% in women and 2.9% in men), with the highest prevalence found in women 39 to 49 years of age and men 19 to 29 years of age.[5]

Several studies have hypothesized the pathophysiologic mechanisms of migraine, such as genetic and vascular factors and cortical spreading depression, but the underlying mechanism is still controversial.[6-8] The primary symptoms of migraine are various types of headaches, and these headaches are accompanied by neurologic manifestations termed *auras*. Auras most commonly present as visual, sensory, and speech/language symptoms but can also present as brainstem-associated disorders such as dysarthria, vertigo, tinnitus, hyperacusis, diplopia, ataxia, and decreased level of consciousness.[9]

Benign paroxysmal positional vertigo (BPPV) is the most common cause of vertigo in adults, with a lifetime prevalence of 2.4% reported in 1 study.[10] It occurs when otoconia, normally located in the utricle, are displaced into 1 or more of the 3 semicircular canals. A BPPV diagnosis is made through the identification of characteristic nystagmus as well as history taking and physical examination using methods such as the Dix-Hallpike test and head roll test.[11,12]

Migraine and BPPV are among the most frequently encountered diseases in otoneurologic clinics. However, because migraine and BPPV do not share a common pathophysiologic association, there has been a lack of research on the association between these 2 diseases compared with other inner-ear diseases, such as Meniere disease, vestibular migraine, and vestibular neuritis.[13,14] Migraine has been associated with an increased risk of BPPV in a nationwide cohort sample analysis,[15] but only a few large-scale cohort studies have been undertaken. Thus, we conducted this present cohort study to investigate the incidence of BPPV in adults with migraine, using a large, national, population-based sample.

Key Points

Question Is migraine associated with increases in the risk of benign paroxysmal positional vertigo?

Findings This cohort study in South Korea involving 40 682 individuals with a migraine diagnosis and 162 728 controls found that the incidence of benign paroxysmal positional vertigo was statistically significantly higher in individuals with migraine than in individuals without migraine.

Meaning Migraine appears to be a risk factor for benign paroxysmal positional vertigo; future studies are needed to determine vertigo's association with specific factors related to migraine.

Methods

Study Population and Data Collection

The ethics committee of Hallym University approved the use of these data. The requirement for written informed consent was waived by the institutional review board of Hallym University. Data analysis was conducted from September 1, 2015, to December 31, 2017.

This cohort study obtained data from the Korean Health Insurance Review and Assessment (HIRA) Service database. The Korean National Health Insurance Service selects samples directly from the national population database to prevent nonsampling errors. Approximately 2% (1 million) of the Korean population (50 million) were selected to create the national sample, using randomized stratified sampling methods with proportional allocation to represent the entire population. These data can be classified according to 1476 levels (age [18 categories], sex [2 categories], and income [41 categories]). After data selection, the appropriateness of the samples was verified with a previous study.[16] Details of the methods used to perform these procedures are provided by the National Health Insurance Sharing Service.[17] The database includes personal information, health insurance claim codes (procedure and prescription), diagnostic codes (using the *International Classification of Disease, Tenth Revision* [*ICD-10*]), death records from the Korean National Statistical Office (using the Korean Standard Classification of Diseases), socioeconomic data (residence and income), and medical examination data for each individual in the system. We used data from the HIRA database for the study period January 1, 2002, to December 31, 2013.

Because all South Korean citizens are identified by a 13-digit resident registration number from birth to death, exact population statistics can be determined using this database. Enrollment in the National Health Insurance Service is mandatory for all citizens, and all hospitals and clinics use these resident registration numbers to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one health care facility to another. Moreover, all medical treatments can be tracked without exception by the HIRA. In South Korea, notice of death to an administrative entity is legally required before a funeral can be held. Causes and dates of death are recorded by medical doctors on death certificates.

Participant Selection

Of the 1 125 691 cases with 114 369 638 medical claim codes, we included those individuals with a migraine diagnosis (*ICD-10* code G43) during the 2002-2013 study period. Among them, we selected those who sought treatment for migraine 2 or more times (n = 45 587), and these individuals were followed up for 12 years. Among the individuals with a BPPV diagnosis (*ICD-10*

code H811) during the 2002-2013 study period, we included only those who sought treatment for BPPV 2 or more times (n = 20 796).

We performed 1:4 matching between the individuals with a migraine diagnosis (migraine group) and individuals without a migraine diagnosis (control group). The control group (n = 1 080 104) was selected from the parent population. The matches were processed for age group, sex, income group, region of residence, and medical history of systemic disease (hypertension, diabetes, or dyslipidemia). To prevent selection bias in the matching process, we sorted members of the control group using a random-number order and then made a selection from top to bottom. The matched controls were assumed to be a part of the study at the same time (from 2002 through 2013, or index date) as the matched members of the migraine cohort. Therefore, individuals in the control group who died before the index date were excluded. In both the migraine and control groups, individuals who had a history of BPPV before the index date were excluded (n = 1365 in the migraine group). Also excluded from the migraine group were those for whom we could not identify a match (n = 180) and those who received a migraine diagnosis before age 20 years (n = 3360).

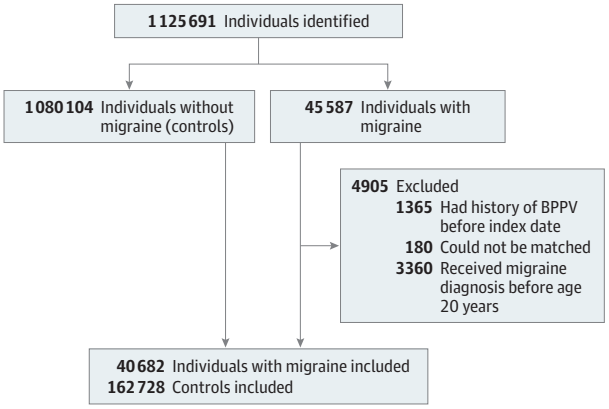
The 1:4 matching method resulted in the inclusion of 40 682 individuals in the migraine group and 162 728 controls (**Figure**). In addition, individuals were selected through the same method, and a 1:4 match with controls was obtained by including individuals with a migraine diagnosis who visited a clinic with a migraine 3 or more times and 5 or more times (eFigures 1 and 2 in the Supplement). However, the migraine and control groups were not matched for ischemic heart disease, cerebral stroke, or depression history because strict matching increased the number of exclusions because of the lack of controls.

Variables

Age groups were classified using 5-year intervals: 20-24, 25-29, 30-34 through 85 years or older; a total of 14 age groups were designated. Income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 11 classes (class 1-11 [lowest income to highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Medical history was evaluated using *ICD-10* codes. For diagnostic accuracy, individuals were considered to have hypertension (*ICD-10* codes I10 and I15), diabetes (*ICD-10* codes E10-E14), or dyslipidemia (*ICD-10* code E78) if they were treated for the condition 2 or more times. Individuals were considered to have ischemic heart disease (*ICD-10* codes I24 and I25) and cerebral stroke (*ICD-10* codes I60-I66) if they were treated for the condition 1 or more times. Depression was defined by a psychiatrist using the *ICD-10* codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder). We selected the individuals who were treated for depression 2 or more times during the study period.

Figure. Cohort Selection Process



Of the total 1 125 691 individuals identified from the Korean National Health Insurance Service–National Sample Cohort, 40 682 individuals with a migraine diagnosis were matched with 162 728 controls by age, sex, income, region of residence, and medical history.

Statistical Analysis

To analyze the hazard ratio (HR) of migraine for BPPV, we created a Cox proportional hazards regression model. In this analysis, a crude (simple) model and adjusted model (by age, sex, income, region of residence, and medical history [systemic disease such as hypertension, diabetes, or dyslipidemia and comorbid disease such as ischemic heart disease, cerebral stroke, or depression]) were used, and 95% CIs were calculated.

For the subgroup analyses, we divided individuals by age (young [<40 years], middle aged [≥40 years and <60 years], older [≥60 years]) and sex. The results were statistically analyzed using SPSS, version 22.0 (IBM).

Results

Of the 40 682 individuals in the migraine group, 10 381 (25.5%) were male and 30 301 (74.5%) were female. Of the 162 728 controls, 41 524 (25.5%) were male and 121 204 (74.5%) were female. The incidence rate of BPPV was statistically significantly higher at 6.0% (n = 2431) in the migraine group compared with the 2.3% (n = 3677) rate in the control group.

The distributions of age, sex, income, region of residence, and medical history (hypertension, diabetes, or dyslipidemia) were comparable between the migraine and control groups (**Table 1**). In addition, the incidence rates of comorbid diseases such as ischemic heart disease (2785 [6.8%] vs 9230 [5.7%]), stroke (5664 [13.9%] vs 14 989 [9.2%]), and depression (7572 [18.6%] vs 14 729 [9.1%]) were also statistically significantly higher in the migraine group than in the control group.

The adjusted HR of the migraine group was 2.54 (95% CI, 2.41-2.68) (**Table 2**). The adjusted HR of the migraine group who visited the clinic with a migraine 3 or more times was 2.59 (95% CI, 2.43-2.76) (eTable 1 in the Supplement), and it increased for those who visited the clinic with a migraine 5 or more times (adjusted HR, 2.73; 95% CI, 2.50-2.98) (eTable 2 in the Supplement). In the subgroup analyses, the incidence

Table 1. General Characteristics of Individuals in the Migraine and Control Groups

Variable	No. (%)	
	Migraine (n = 40 682)	Control Group (n = 162 728)
Age group, y		
20-24	1971 (4.8)	7884 (4.8)
25-29	2616 (6.4)	10 464 (6.4)
30-34	3606 (8.9)	14 424 (8.9)
35-39	4234 (10.4)	16 936 (10.4)
40-44	4767 (11.7)	19 068 (11.7)
45-49	5079 (12.5)	20 316 (12.5)
50-54	4411 (10.8)	17 644 (10.8)
55-59	3413 (8.4)	13 652 (8.4)
60-64	3116 (7.7)	12 464 (7.7)
65-69	2932 (7.2)	11 728 (7.2)
70-74	2271 (5.6)	9084 (5.6)
75-79	1362 (3.3)	5448 (3.3)
80-84	639 (1.6)	2556 (1.6)
≥85	265 (0.7)	1060 (0.7)
Sex		
Male	10 381 (25.5)	41 524 (25.5)
Female	30 301 (74.5)	121 204 (74.5)
Income class		
1 (lowest)	822 (2.0)	3288 (2.0)
2	3087 (7.6)	12 348 (7.6)
3	2935 (7.2)	11 740 (7.2)
4	3095 (7.6)	12 380 (7.6)
5	3275 (8.1)	13 100 (8.1)
6	3558 (8.7)	14 232 (8.7)
7	3836 (9.4)	15 344 (9.4)
8	4317 (10.6)	17 268 (10.6)
9	4757 (11.7)	19 028 (11.7)
10	5332 (13.1)	21 328 (13.1)
11 (highest)	5668 (13.9)	22 672 (13.9)
Region of residence		
Urban	17 538 (43.1)	70 152 (43.1)
Rural	23 144 (56.9)	92 576 (56.9)
Hypertension history		
Yes	15 845 (38.9)	63 380 (38.9)
No	24 837 (61.1)	99 348 (61.1)
Diabetes history		
Yes	7103 (17.5)	28 412 (17.5)
No	33 579 (82.5)	134 316 (82.5)
Dyslipidemia history		
Yes	12 469 (30.6)	49 876 (30.6)
No	28 213 (69.4)	112 852 (69.4)
Ischemic heart disease history		
Yes	2785 (6.8)	9230 (5.7)
No	37 897 (93.2)	153 498 (94.3)
Cerebral stroke history		
Yes	5664 (13.9)	14 989 (9.2)
No	35 018 (86.1)	147 739 (90.8)
Depression history		
Yes	7572 (18.6)	14 729 (9.1)
No	33 110 (81.4)	147 999 (90.9)
BPPV		
Yes	2431 (6.0)	3677 (2.3)
No	38 251 (94.0)	159 051 (97.7)

Abbreviation: BPPV, benign paroxysmal positional vertigo.

Table 2. Risk of Benign Paroxysmal Positional Vertigo in Individuals With Migraine

Group	Hazard Ratio			
	Crude	95% CI	Adjusted[a]	95% CI
Migraine	2.72 (2.58-2.85)	2.58-2.85	2.54 (2.41-2.68)	2.41-2.68
Control	1.00	NA	1.00	NA

Abbreviation: NA, not applicable.

[a] Adjusted model for age, sex, income, region of residence, and medical history (hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, or depression).

Table 3. Incidence of Benign Paroxysmal Positional Vertigo in Individuals With Migraine, by Age and Sex

Variable	Hazard Ratio			
	Crude	95% CI	Adjusted[a]	95% CI
Age <40 y, men (n = 15 420)				
Migraine	4.86	3.33-7.10	4.49	3.05-6.62
Control	1.00	NA	1.00	NA
Age <40 y, women (n = 46 715)				
Migraine	3.60	3.15-4.12	3.42	2.98-3.93
Control	1.00	NA	1.00	NA
Age ≥40 y and <60 y, men (n = 21 895)				
Migraine	3.71	3.03-4.53	3.51	2.86-4.31
Control	1.00	NA	1.00	NA
Age ≥40 y and <60 y, women (n = 66 455)				
Migraine	2.60	2.39-2.82	2.40	2.21-2.61
Control	1.00	NA	1.00	NA
Age ≥60 y, men (n = 14 950)				
Migraine	3.26	2.72-3.91	3.06	2.54-3.68
Control	1.00	NA	1.00	NA
Age ≥60 y, women (n = 38 335)				
Migraine	2.19	1.99-2.41	2.03	1.84-2.23
Control	1.00	NA	1.00	NA

Abbreviation: NA, not applicable.

[a] Adjusted model for age, sex, income, region of residence, and medical history (hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, or depression).

of BPPV in all age groups and in both men and women was statistically significantly higher in the migraine group than in the control group (**Table 3**). The adjusted HR was highest in men younger than 40 years (HR, 4.49; 95% CI, 3.05-6.62), and the HR decreased in both men and women as age increased.

Discussion

The risk for BPPV was statistically significantly higher in the migraine group compared with the control group in this study. In addition, as the number of visits to the clinic with migraine increased, the risk for BPPV also increased. In the subgroup analysis adjusted by age, the incidence of BPPV in the migraine group was statistically significantly higher than that in

the control group at all ages. The incidence of BPPV was the highest in the young age group (<40 years). In the same age group, the incidence in men was higher than that in women. In a similar national cohort study in Taiwan by Chu et al,[15] the risk of BPPV in the migraine group was higher than that in the control group (HR, 2.03; 95% CI, 1.41-2.97). In addition, the risk of BPPV among those younger than 40 years (HR, 2.63; 95% CI, 1.28-5.84) was higher compared with those older than 40 years (HR, 1.84; 95% CI, 1.19-2.88).

The incidence of BPPV according to sex was statistically significantly higher in the migraine group in both men and women in this study. However, in the study by Chu et al,[15] no substantial difference in BPPV incidence was found in the male cohort (HR, 1.66; 95% CI, 0.77-3.72), and the incidence of BPPV was substantially higher in the migraine group (HR, 2.17; 95% CI, 1.42-3.39) than in the control group of the female cohort.

The primary differences between the present study in South Korea and the work by Chu et al[15] in Taiwan are that we analyzed a longer follow-up period and included a larger number of individuals. In addition, we selected patients who received treatments with the same medical claim codes more than 2 times the number of patients in the migraine and BPPV cohorts in the Chu et al[15] study.

The association between BPPV and migraine has been studied not only in the context of a national cohort, such as by Chu et al,[15] but also in retrospective analyses at single institutions. Teixido et al[18] reported that, in their study, 60 (35.5%) of the 169 patients who met the diagnostic criteria for migraine had BPPV, whereas 152 (45.8%) of the 332 participants in the control group had BPPV. In addition, the incidence of BPPV in the active migraine group (n = 30) was substantially higher than that in the inactive migraine group (n = 8). These results were not in accordance with the incidence of BPPV in our study population because the follow-up period was only 2 years and the sample size was smaller in the Teixido et al[18] study. Moreover, Teixido et al[18] conducted their study in 2 balance clinics; therefore, the comorbidity of BPPV and migraine was higher than that observed in the present study. Yetiser and Gokmen[19] examined more detailed characteristics of BPPV (affected side, type of canal, and cure rate) that were not covered by the nature of our data. However, only 1 substantial difference in the sex ratio was found between the control and BPPV groups, and the other factors, including cure rate, were not different between the groups.[19] Because the study by Yetiser and Gokmen[19] was conducted on patients enrolled in 1 of 2 centers, as with the study by Teixido et al,[18] its results are somewhat inconsistent with our findings. Nevertheless, these studies provide further information about the differences in the clinical course of BPPV.

The pathophysiologic association between migraine and BPPV is not well understood. Ishiyama et al[20] postulates that repeated vasospasm can affect the microvasculature of the inner ear. Repeated vasospasm may stress and damage the vestibular cells, leading to the displacement of otoconia from the macula. In addition, suppression of the inner-ear microvasculature as a result of vasospasm may lead to cochlear symptoms, such as hearing disturbance and vestibular symptoms.[21] The vascular effect of migraine varies from small-vessel disease to large-vessel disease.

Recurrent vasospasm is associated with the oxidative stress of endothelial cells, which is a possible pathogenetic mechanism common to both migraine and BPPV.[22,23] The specific pathway for oxidative stress in migraine has not yet been established, but several studies have reported a reduction in superoxide dismutase activity in patients with migraine.[24-26] In a study of oxidative stress associated with BPPV, levels of proinflammatory mediators, such as interleukin 1β (IL-1β), IL-6, and TNF, were elevated in the serum of patients experiencing a BPPV attack and decreased after repositioning maneuvers such as the Epley maneuver.[23] In addition, total antioxidant capacity and paraoxonase levels, which are antioxidant parameters, were reduced during a BPPV attack.[23] Therefore, oxidative stress and inflammatory processes in the inner ear may be associated with the formation and migration of the otolith. This pathologic linkage may be enhanced with migraine; however, further research is needed.

Strengths and Limitations

A strength of this study is that we analyzed the epidemiologic association between migraine and BPPV using a data set we constructed by matching individuals with a migraine diagnosis and controls by age, sex, income, region of residence, and medical history. In a large-scale, nationwide cohort study such as this, controlling the estimated confounding variables increases the reliability of the results. In addition, a controlled 1:4 match between a migraine group and a control group makes the results of this study more reliable, enhancing the strength of this study. We analyzed the medical claim codes of the individuals included in the HIRA database, allowing us to obtain the exact date of migraine diagnosis. Because the HIRA data are kept for all citizens in South Korea, the individuals included in our analysis were not missed during the follow-up period. Moreover, because the time of diagnosis was clear, the confounding effect of the history of BPPV before the onset of migraine was minimized.

This study has a few limitations. We could not obtain descriptive information from individuals, beyond that contained in the HIRA database. Such information, including the type of lesioned semicircular canal, smoking and drinking history, and treatment method, may be helpful in the diagnosis and treatment of BPPV. Specific information on types of migraine and types of aura experienced by individuals with migraine was also unavailable. Thus, future studies will need to determine whether BPPV is associated with specific factors related to migraine.

Conclusions

Migraine was found to be statistically significantly associated with an increased incidence of BPPV. The incidence of BPPV was statistically significantly higher in both male and female adults with a migraine diagnosis.

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Concept and design: Hong, Park.
Study concept and design: Choi.
Acquisition, analysis, or interpretation of data: Kim, Hong, Choi.
Drafting of the manuscript: Hong, Park.
Critical revision of the manuscript for important intellectual content: Kim, Choi.
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