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Increased risk of Bell palsy in patient with migraine

A longitudinal follow-up study

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Abstract

Migraine is thought to be associated with Bell palsy. This study aimed to investigate the risk of Bell palsy in migraine patients.

The Korean National Health Insurance Service-National Sample Cohort was collected from 2002 to 2013. A total of 45,164 migraine patients were matched for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia and compared with 180,656 controls. The migraine group included participants diagnosed with migraine [International Classification of Disease (ICD)-10: G43] who underwent treatment more than once. Participants with Bell palsy were included on the basis of the ICD-10 (G510) and treatment with steroids. A history of hypertension, diabetes, and dyslipidemia was determined using ICD-10 codes. Crude (simple) and adjusted hazard ratios (HRs) of Bell palsy in migraine patients were analyzed using the Cox proportional hazards model. Subgroup analyses were conducted based on age and sex.

Bell palsy occurred in 0.6% (262/44,902) of the migraine group and 0.5% (903/179,753) of the control group. The adjusted HR of Bell palsy was 1.16 in the migraine group compared with the control group [95% confidence interval (95% CI) = 1.01–1.33, $P = .34$]. Among age-related subgroups, participants ≥30 and <60 years old in the migraine subgroup demonstrated a 1.28-times higher risk of Bell palsy than the control group (95% CI = 1.05–1.57, $P = .014$).

Migraine increased the risk of Bell palsy in the total population. Among age subgroups, migraine patients ≥30 and <60 years old had an increased risk of Bell palsy.

Abbreviations: CIs = confidence intervals, HIRA = Health Insurance Review & Assessment, HRs = hazard ratios, NHIS-NSC = Korean National Health Insurance Service-National Sample Cohort.

Keywords: Bell palsy, facial palsy, Korean, migraine, risk factors

1. Introduction

Facial palsy has multiple etiologies that stem from viral (varicella zoster virus), congenital, and traumatic causes.[1] Among these, idiopathic acute peripheral facial palsy, which is referred to as Bell palsy, accounts for 60% to 75% of cases of facial palsy.[2] Approximately 11 to 40 people per 100,000 experience Bell palsy worldwide each year.[3,4] The incidence of Bell palsy peaks in middle age and has no gender preference.[3] Although Bell palsy is thought to be triggered by viruses, the pathophysiology is complex, and several other causes have been reported. For example, vascular ischemia, immunological disorders, inflammation, and autonomic dysfunction have been suggested as risk factors for Bell palsy.[3] Interestingly, 1 study has shown an association between facial palsy and migraine.[5]

A migraine is a primary headache characterized by recurrent headache attacks triggered by various factors.[6] As much as 10% of the global population is thought to experience migraine headaches.[7] Disorders of the central nervous system and immune system, as well as inflammation, genetics, and vascular ischemia have all been proposed as possible contributors to migraine.[7] Although previous studies considered that migraine headaches were triggered by the dilation of cerebral vessels, recent evidence supports that migraine attacks can also occur in association with cardiovascular disturbances in the absence of vasodilation.[8] Many studies have reported a risk of ischemic stroke in migraine patients.[9] These complex etiologies and

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relationships to vascular ischemia may provide a link between migraine and Bell palsy.

A recent population cohort study suggested that the incidence of Bell palsy was increased in migraine patients.[5] That study estimated that migraine patients had a 1.9-fold increased risk of Bell palsy over a 5-year follow-up period [95% confidence interval (95% CI) = 1.68–2.17, $P < .001$].[5] However, the study included patients who were diagnosed with migraine or Bell palsy only once, and the annual incidence of Bell palsy was higher than that reported in previous studies (83.2 vs 20–30 per 100,000 person-years).[2] Because of the possibility of misdiagnoses or subclinical consultation cases in a large population database such as the National Health Insurance Research Database, using multiple inclusion criteria and ensuring that treatment has been provided are criteria that help ensure the fidelity of the analysis.

This study hypothesized that migraines increase the risk of Bell palsy. To confirm this hypothesis, the hazard ratios (HRs) for Bell palsy were investigated in migraine patients and compared with a control population. The representative population included a wide range of age groups, and the control population was matched for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Multiple inclusion criteria were used to ensure that the diagnoses of Bell palsy and migraine were properly classified.

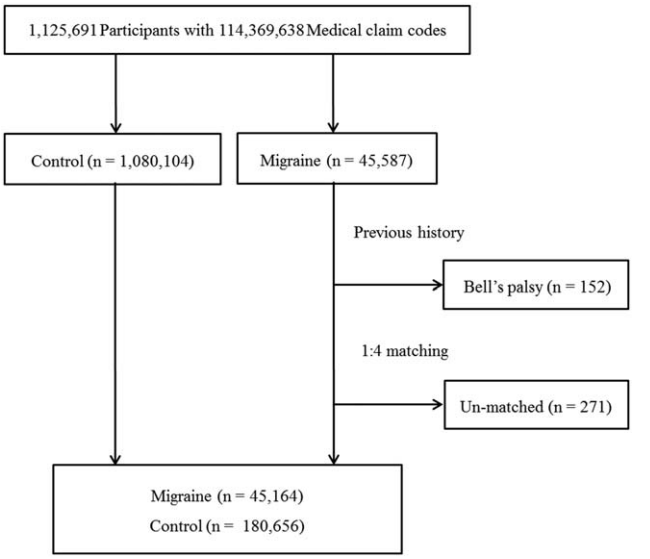

Figure 1. A schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 participants, 45,164 migraine patients were matched with 180,656 controls for age group, sex, income group, region of residence, and past medical history.

2. Materials and methods

2.1. Study population and data collection

The Ethics Committee of Hallym University (2014-I148) approved the use of the data. Written informed consent was exempted by the Institutional Review Board.

This national cohort study relies on data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The detailed description of this data was described in our previous studies.[10]

2.2. Participant selection

Of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were diagnosed with migraine based on the ICD-10 code (G43). Among them, we selected the participants who were treated more than once (n = 45,587). Therefore, the participants were followed up to 12 years.

Bell palsy was diagnosed based on the ICD-10 code (G510). We only included participants who were treated more than once and were prescribed steroids. From 2002 through 2013, 5244 participants with Bell palsy were selected.

The migraine patients were matched 1:4 with participants in the control group who were not diagnosed with migraine from 2002 through 2013. The control group was selected from the general population (n = 1,080,104). The matches were processed by age group, sex, income group, region of residence, and past medical history (hypertension, diabetes, and dyslipidemia). To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random number order and then were selected from top to bottom. It was assumed that the matched control participants were being evaluated at the same time as each matched migraine participant (index date). Therefore, participants in the control group who died before the index date were excluded. In both the migraine and control groups, the participants who had a history of Bell palsy before the index date were excluded. In the migraine group, 152 participants were excluded. Migraine patients for whom we could not identify sufficient matching participants were excluded (n = 271). Finally, 1:4 matching resulted in the inclusion of 45,164 migraine patients and 180,656 controls (Fig. 1).

2.3. Variables

The age groups were classified using 5-year intervals: 0 to 4, 5 to 9, 10 to 14, and 85+ years. A total of 18 age groups were designated. The 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 (lowest income)-11 (highest income)]. Region of residence was divided into 16 areas according to the 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.

The past medical history of the participants was evaluated using ICD-10 codes. For accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were checked if the participants were treated more than once.

2.4. Statistical analyses

The Cox-proportional hazards model was used to analyze the HR of Bell palsy in the migraine group. Crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia) models were employed in this analysis.

For the subgroup analysis, we divided the male and female participants by age (<30 years, ≥30 and <60 years, and ≥60 years).

Two-tailed analyses were conducted, and *P* values less than .05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

3. Results

Bell palsy occurred in 0.6% (262/44,902) of the migraine group and 0.5% (903/179,753) of the control group ($P=.033$) (Table 1). Age, sex, income level, region of residence, and past medical history of hypertension, diabetes, and dyslipidemia were exactly matched between both groups.

The HR for Bell palsy was high in the migraine group (crude HR = 1.16, 95% CI = 1.01–1.33, $P=.034$) (Table 2). The risk of Bell palsy was 1.16 times higher than that in the control group in the adjusted model (95% CI = 1.01–1.33, $P=.34$).

The HR of Bell palsy was also high in the subgroups of participants ≥30 and <60 years old compared with that in the control group (HR = 1.28, 95% CI = 1.05–1.57, $P=.014$) (Table 3). In this subgroup, the risk of Bell palsy was elevated in the migraine group even after adjusting for confounders (HR = 1.28, 95% CI = 1.05–1.57, $P=.015$). The subgroups of participants in the migraine group who were <30 and ≥60 years old did not have an increased risk of Bell palsy. In the subgroup analyses based on sex, subgroups of men and women did not have a high risk of Bell palsy.

4. Discussion

In the present study, migraine was found to increase the risk of Bell palsy. This increased risk in migraine patients was evident in the ≥30 and <60-year-old population. Few previous studies have reported a relationship between migraine headaches and Bell palsy. The details of the pathophysiology of Bell palsy have not been completely unraveled. Vascular ischemia, immunologic disorders, infectious diseases, and psychological disorders have all been suggested to be associated with Bell palsy.[1] Thus, migraine headaches could also contribute to various aspects of the pathophysiologic mechanism(s) leading to Bell palsy.

The direct neural effects from the trigeminal nerve to the facial nerve could contribute to the risk of facial palsy in migraine patients. A case was reported of a 32-year-old woman with migraine who suffered from recurrent facial paralysis.[11] That study proposed that a reciprocal connection between the trigeminal nerve and the facial nerve could explain the concurrent trigeminal neuralgia and facial palsy. Specifically, the sensory pain afferents of the nervus intermedius, which branches from the maxillary nerve, innervate the facial nerve.[12] However, the concurrent peripheral neural dysfunction of both the trigeminal and facial nerves is rare. In addition to concurrent trigeminal and facial nerve dysfunction, the facial nerve could be gradually weakened leading to paralysis in migraine patients. Repetitive nociceptive neural stimuli in these patients may increase the susceptibility of the facial nerve to injury.

Common pathophysiologic mechanisms exist that could underlie both migraine and Bell palsy. For instance, cardiovascular ischemia is a risk factor for both conditions.[13]

Although the pathophysiologic mechanism of migraines is not completely understood, alteration of the trigeminovascular function has been suggested to trigger migraines.[14,15] Aura migraines are thought to result from a cortical spreading depression induced by cerebral ischemia and inhibition of neural activity.[15,16] Prior studies have demonstrated a 2-fold increase in the risk of stroke and cardiovascular diseases in migraine patients.[17] Oxidative stress could also influence both migraine and Bell palsy. Oxidative stress has been shown to occur during migraine attacks and accumulate following chronic or recurrent migraine attacks.[18] A recent study suggested that a migraine is a neuroprotective response to brain oxidative stress.[19] Oxidative stress that occurs in the brain following upregulation of antioxidants, neural proliferation, and mitochondrial defense responses in migraine patients may be a defensive, neuroprotective mechanism. This increase in oxidative stress in

Table 1

General characteristics of participants.

Characteristics	Total participants		
	Migraine (n, %)	Control group (n, %)	*P*
Age, y			1.000
0–4	11 (0.0)	44 (0.0)	
5–9	68 (0.2)	272 (0.2)	
10–14	352 (0.8)	1408 (0.8)	
15–19	1185 (2.6)	4740 (2.6)	
20–24	1550 (3.4)	6200 (3.4)	
25–29	1862 (4.1)	7448 (4.1)	
30–34	2562 (5.7)	1024 (5.7)	
35–39	3044 (6.7)	12,176 (6.7)	
40–44	4223 (9.4)	16,892 (9.4)	
45–49	4473 (9.9)	17,892 (9.9)	
50–54	5444 (12.1)	21,776 (12.1)	
55–59	4808 (10.6)	19,232 (10.6)	
60–64	3625 (8.0)	14,500 (8.0)	
65–69	3093 (6.8)	12,372 (6.8)	
70–74	3446 (7.6)	13,784 (7.6)	
75–79	2776 (6.1)	11,104 (6.1)	
80–84	1604 (3.6)	6416 (3.6)	
85+	1038 (2.3)	4152 (2.3)	
Sex			1.000
Male	11,897 (26.3)	47,588 (26.3)	
Female	33,267 (73.7)	133,068 (73.7)	
Income			1.000
1 (lowest)	1440 (3.2)	5760 (3.2)	
2	3664 (8.1)	14,656 (8.1)	
3	3307 (7.3)	13,228 (7.3)	
4	3251 (7.2)	13,004 (7.2)	
5	3319 (7.3)	13,276 (7.3)	
6	3545 (7.8)	14,180 (7.8)	
7	4042 (8.9)	16,168 (8.9)	
8	4391 (9.7)	17,564 (9.7)	
9	5097 (11.3)	20,388 (11.3)	
10	6119 (13.5)	24,476 (13.5)	
11 (highest)	6989 (15.5)	27,956 (15.5)	
Region of residence			1.000
Urban	19,042 (42.2)	76,168 (42.2)	
Rural	26,122 (57.8)	104,488 (57.8)	
Hypertension			1.000
Yes	16,471 (36.5)	65,884 (36.5)	
No	28,693 (63.5)	114,772 (63.5)	
Diabetes			1.000
Yes	7355 (16.3)	29,420 (16.3)	
No	37,809 (83.7)	151,236 (83.7)	
Dyslipidemia			1.000
Yes	12,978 (28.7)	51,912 (28.7)	
No	32,186 (71.3)	128,744 (28.7)	
Bell palsy			0.033*
Yes	262 (0.6)	903 (0.5)	
No	44,902 (99.4)	179,753 (99.5)	

* Chi-square test. Significance at $P<.05$.

Table 2

Crude and adjusted hazard ratios (95% confidence interval) of migraine for Bell palsy.

Characteristics	Bell palsy			
	Crude	P	Adjusted†	P
Migraine	1.16 (1.01–1.33)	.034*	1.16 (1.01–1.33)	.034*
Control	1.00		1.00	

* Cox-proportional hazard regression model, significance at $P < .05$.

† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

migraine patients could affect the risk of Bell palsy. A recent study reported that the serum levels of antioxidants were elevated in Bell palsy patients compared with those in the controls.[20]

Adverse emotional or psychological responses to migraine headaches could also increase the risk of Bell palsy. Several common psychological disorders, including depression, anxiety, bipolar disorder, and obsessive-compulsive and attention-deficit/hyperactivity disorders, are increased in migraine patients.[21] Among these psychiatric disorders, depression and anxiety have the strongest association with migraine.[21] Compared with controls, migraine patients have a higher prevalence of depression.[22] These psychological problems also have synergistic effects. For example, depression may mediate anxiety in migraine patients.[23] These emotional disorders may also be a risk factor for Bell palsy. This is supported by the findings from a retrospective cohort study in which in patients with anxiety disorders had a 1.53-fold increased risk of Bell palsy (95% CI= 1.21–1.94, $P < .001$).[24]

This study relied on data obtained from a large national population, which was verified in previous study.[25] Both migraine and Bell palsy were strictly selected. This study included patients with a diagnosis of migraine [ICD-10 code (G43)] on at least 2 different occasions. Because migrainous attacks could be repeated, the evaluation of the prevalence of migraine, rather than the incidence of migraine, was more adequate for this study. In a previous study, the prevalence of migraine in Korea was reported as being approximately 6.1%.[26] This value is slightly higher than that in the present study, which was 4.0% (45,587/1,125,691). This low prevalence of migraine may be due to the strict inclusion criteria used in this study. Only symptomatic migraine patients who needed medical consultation were included in this study. For the diagnosis of Bell palsy, multiple inclusion criteria were used with the ICD-10 code and treatment of steroid. The incidence of Bell palsy in this study was approximately 29.58 per 100,000 individuals (3996/1,125,691). Previous studies reported comparable incidences of SSNHL, ranging from approximately 20 to 30 per 100,000 individuals.[2] The subjects in the control group were randomly selected and matched to the migraine patients by age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Among these matched variables, income and region of residence should minimize the effects of medical care accessibility. Because Bell palsy and migraine were classified in accordance to the ICD-10 codes and medical care, the matching and adjustment of these socioeconomic variables were crucial. However, several limitations still exist in the present study. Although this study used a large representative population and matched and adjusted possible confounders, other confounders such as cardiovascular comorbidities and emotional disorders remain. Although past medical histories of hypertension, dyslipidemia, and diabetes were adjusted, lifestyle factors, such as smoking and alcohol consumption, could not be considered in this study. These lifestyle factors were not available in NHIS data. In addition, the degree of Bell palsy was not considered. The duration and severity of the migraine headaches were not consistent among the study populations, which could affect the relationship between migraine and Bell palsy. The missed diagnoses could not be excluded. Only migraine patients who were diagnosed by a clinician were included in this study. Likewise, Bell palsy patients who were diagnosed by a clinician and underwent steroid treatment were included. Consequently, Bell palsy patients who had a spontaneous recovery or could not undergo steroid treatment were excluded. However, these strict inclusion criteria for migraine and Bell palsy ultimately minimized the overestimation of the risk of Bell palsy in migraine patients.

Table 3

Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for Bell palsy according to age and sex.

Characteristics	Bell palsy			
	Crude	P	Adjusted†	P
Age <30 y (n=25,140)				
Migraine	1.52 (0.68–3.34)	.310	1.52 (0.68–3.34)	.310
Control	1.00			1.00
Age ≥30 y and <60 y (n=122,770)				
Migraine	1.28 (1.05–1.57)	.014*	1.28 (1.05–1.57)	.015*
Control	1.00		1.00	
Age ≥60 y (n=77,910)				
Migraine	1.05 (0.86–1.27)	.660	1.04 (0.86–1.27)	.662
Control	1.00		1.00	
Men (n=59,485)				
Migraine	1.28 (0.98–1.67)	.075	1.27 (0.98–1.66)	.075
Control	1.00		1.00	
Women (n=166,335)				
Migraine	1.12 (0.96–1.32)	.156	1.12 (0.96–1.32)	.157
Control	1.00		1.00	

* Cox-proportional hazard regression model, significance at $P < .05$.

† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia.

Migraine increases the risk of Bell palsy in the overall population. This elevated risk of Bell palsy persisted after participants were matched and adjustments were made for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia. Within the age-related subgroups, migraine patients in the high prevalence group, ≥30 and <60 years, showed an increased risk of Bell palsy.

Author contributions

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