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Increased risk of ischemic heart disease in young patients with migraine: A population-based, propensity score-matched, longitudinal follow-up study

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ABSTRACT

Background: The association between migraine and the risk of ischemic heart disease (IHD) remains controversial. The purpose of the present population-based, propensity score-matched follow-up study was to investigate whether young migraineurs are at a higher risk of developing IHD.

Methods: A total of 11,541 subjects aged between 18 and 45 years with at least two ambulatory visits with the principal diagnosis of migraine in 2001 were enrolled in the migraine group. We used a logistic regression model that included age, sex, pre-existing comorbidities, and socioeconomic status as covariates to compute the propensity score. The non-migraine group consisted of 11,541 propensity score-matched, randomly sampled subjects without migraine. The 3-year IHD-free survival rate and the cumulative incidence of IHD were estimated using the Kaplan–Meier method. Stratified Cox proportional hazard regression with patients matched by propensity score was used to estimate the effect of migraine on the risk of developing subsequent IHD.

Results: The mean age in both groups was 32.3 years. During follow-up, 121 subjects in the migraine group and 55 in the non-migraine group developed IHD. The incidence rate of IHD was 4.56 (95% confidence interval [CI], 3.78 to 5.44) per 1000 person-years in the migraine group and 2.00 (95% CI, 1.51 to 2.61) per 1000 person-years in the non-migraine group. Compared to the non-migraine group, the HR of IHD for the migraine group was 2.50 (95% CI, 1.78 to 3.52, $P < 0.0001$).

Conclusions: This study showed an increased risk of developing IHD in young patients with newly diagnosed migraine.

1. Introduction

Migraine, a common incapacitating neurovascular headache, can occur at any age, but the incidence peaks in early- to mid-adolescence [1]. Migraine has been associated with an increased risk of vascular disorder [2,3]. Epidemiological studies have shown an increased risk of ischemic stroke in migraineurs [4–6], and the risk of ischemic stroke appears to be greater at a younger age [7]. However, the relationship between migraine and ischemic heart disease (IHD) remains controversial. One cohort study on male physicians aged 40 or older found that migraine was associated with an increased risk of myocardial infarction [8], and a cohort study on women aged over 45 found that migraines with aura had a higher risk of IHD [4]. However, other studies failed to demonstrate any association between migraine and IHD [9–11]. In addition, most of these studies were conducted in a selected population and the participants were middle-aged or older. While migraine is primarily a headache disorder that usually develops in the young population, few studies have focused on young migraineurs and the corresponding IHD risk. Elucidating the IHD risk in young migraineurs would be informative for clinical risk assessment. The purpose of this population-based, propensity score-matched longitudinal follow-up study was therefore to investigate whether young migraineurs are at a higher risk of IHD.

2. Methods and materials

2.1. Data source

The data used in this study were obtained from the complete National Health Insurance (NHI) claim database in Taiwan for the period 2000 to 2003. The NHI program has been implemented in Taiwan since 1995, and the coverage rate was 96% of the whole population in 2000 and 97% at the end of 2003, i.e. more than 21.9 million persons. It should

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[1] Takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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be noted that the rationale for using the NHI database after 2000 is that, from Jan 1st, 2000, according to the rules of the Bureau of NHI, the NHI claim data have been encoded using the standardized International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM).

2.2. Ethics statement

To keep individual information confidential to satisfy regulations on personal privacy in Taiwan, all personal identification numbers in the data were encrypted by converting them into scrambled numbers before data processing. This study was exempt from full review by the National Taiwan University Hospital Research Ethics Committee and the need for informed consent was waived because the data used in this study consisted of de-identified secondary data released for research purposes and were analyzed anonymously, which complies with the regulations of the Department of Health, Executive Yuan, Republic of China.

2.3. Study subjects and design

We used a propensity score-matched cohort design to study the effect of migraine on the risk of developing subsequent IHD in a young adult population. The study population consisted of a migraine group and a non-migraine group, both selected from Taiwanese residents in the complete NHI claim database in 2001, in which more than 21.6 million persons were registered. To control for potential confounding effects of an imbalance in vascular risk factors and clinical characteristics, we used propensity score matching to create comparable cohorts of patients with and without migraine [12,13].

The migraine group consisted of subjects aged between 18 and 45 years who had received a principal diagnosis of migraine (ICD-9-CM code 346) in ambulatory medical care visits between January 1, 2001 and December 31, 2001. To maximize case ascertainment, only patients who had at least 2 ambulatory visits with the principal diagnosis of migraine in this period were initially considered for inclusion in the migraine group (n = 18,615). The index visit was defined as the first ambulatory visit during which a principal diagnosis of migraine was made. The exclusion criteria for recruitment of subjects into the migraine group were: (1) a previous diagnosis of migraine (ICD-9-CM code 346) during 2000 (n = 6655) to increase the likelihood of identifying only new migraine cases in 2001 and (2) a previous diagnosis of IHD (ICD-9-CM codes 410–414) before the index visit (n = 645) which resulted in 7003 subjects being excluded because of one or more of these criteria. A total of 11,612 subjects were therefore included in the migraine group at this stage. Information on pre-existing comorbidities, including diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), dyslipidemia (ICD-9-CM code 272), renal disease (ICD-9-CM codes 580–587), and stroke (ICD-9-CM codes 430–438), was acquired by tracking the ambulatory medical care and inpatient records in the NHI database in the year before the index visit. The case ascertainment for these medical comorbidities was defined from ≧1 hospital discharge or ≧2 ambulatory visits with a relevant principal or secondary diagnosis code. Since previous studies have suggested that the risk of IHD may be affected by socioeconomic status, such as geographical region, level of urbanization, and income level [14,15], these factors were also included as variables in assessing the risk of IHD. Information about the geographical location of residence of each subject was obtained from the population household registry and was classified as Northern, Central, Eastern, or Southern Taiwan. As recommended by the Taiwan National Health Research Institute [16], urbanization levels in Taiwan were classified into 7 strata, with level 1 referring to "most urbanized" and level 7 to "least urbanized" communities. However, since the numbers of subjects in levels 5, 6, and 7 were relatively small, these 3 levels were merged into a single group labeled level 5. For information on income level, we used the insured payroll-related amount as a proxy for income, with levels of NT$0, NT$1–NT$15,840, NT$15,841–NT$25,000, and ≥NT$25,001 (NT$ indicates new Taiwan dollar). We selected NT$15,840 as the first cutoff point of income level because this is the government-stipulated minimum wage for full-time employees in Taiwan. Since household registry information was not available for 71 of the 11,612 subjects in the migraine group, these 71 subjects were excluded from the analysis, leaving 11,541 subjects in the final migraine group.

The non-migraine group was taken from the remaining subjects without a diagnosis of migraine in the same 2001 NHI claim database. The first ambulatory medical care visit during 2001 was assigned as the index visit. The exclusion criteria for recruiting subjects into the non-migraine group were: (1) a previous diagnosis of migraine (ICD-9-CM code 346) before the index visit and (2) a previous diagnosis of IHD (ICD-9-CM codes 410–414) before the index visit. Information about pre-existing co-morbidities and socioeconomic status was obtained as described above. Because the number of subjects in the NHI database is very large, we used a two-stage propensity-score matching method [17,18]. For each subject in the migraine group, we first randomly sampled 20 age- and sex-matched non-migraine subjects who met the above criteria, giving a total of 230,820 non-migraine subjects. In the second stage, a logistic regression model including age, sex, pre-existing co-morbidities, and socioeconomic status as covariates was used to predict the probability (i.e. propensity score) of migraine. An 8-to-1 greedy matching algorithm [12] was then used to identify a unique matched control from the non-migraine subjects for each migraine patient based on the propensity score, resulting in a total of 11,541 subjects in the propensity score-matched non-migraine group.

2.4. Outcome

All the ambulatory medical care records and inpatient records for each subject in the propensity score-matched migraine and non-migraine groups from their index visit until the end of 2003 were retrieved and the mortality data for subjects who died during follow-up were obtained from the national mortality registry. The date of the first occurrence of a principal diagnosis of IHD (ICD-9-CM codes 410–414) in the follow-up period was defined as the primary endpoint. The case ascertainment for IHD required ≧1 hospital discharge or ≧2 ambulatory medical care visits with the principal diagnosis of IHD. All subjects were followed from the index visit to the first occurrence of IHD, death, or end of follow-up (whichever occurred first).

2.5. Statistical analysis

The Chi-square test and Student's *t* test were used to examine differences in demographic variables, comorbid medical disorders, and propensity scores between the migraine and non-migraine groups. The method of standardized differences was used to assess the balance of covariates between the two groups before and after propensity score matching; this method was preferred to hypothesis testing methods because the standardized difference does not depend on sample size [19]. An absolute standardized difference of 0 for a covariate indicates no between-group imbalance for that covariate, and values < 0.1 indicate an inconsequential imbalance [20]. The incidence rate of IHD was calculated as the number of incident IHD cases divided by IHD-free person-years. The IHD-free survival probabilities for the two groups were estimated using the Kaplan–Meier method. The cumulative incidence was then calculated as one minus the IHD-free survival probability, and the significance of differences in cumulative incidence rates between the two groups was tested using the log-rank test. Stratified Cox proportional hazard regression with patients matched by propensity score was used to estimate the effect of migraine on the occurrence of IHD. An alpha level of 0.05 was considered statistically significant for all analyses. The analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

3. Results

Table 1 shows the demographic and clinical characteristics of the migraine and non-migraine groups before propensity score matching. The migraine group had a higher prevalence of certain pre-existing medical comorbidities, including hypertension (P < 0.0001), dyslipidemia (P < 0.0001), renal disease (P < 0.0001), and stroke (P < 0.0001), than the non-migraine group. There were also significant differences in the distribution of monthly income, urbanization level, and geographic region between the two groups. After propensity score matching, the matched cohorts were well-balanced in terms of all observed covariates

Table 1
Demographic characteristics and comorbid medical disorders of the migraine and non-migraine groups before propensity score matching. Data are expressed as "N (%)" or "mean ± SD".

Variable	Migraine group (N = 11,541)	Non-migraine group (N = 230,820)	P value
Sex (women)	8156 (70.7)	163,120 (70.7)	0.0000
Age (years)	32.3 ± 7.7	32.2 ± 7.7	0.0472
Diabetes (yes)	115 (1.00)	2075 (0.86)	0.2802
Hypertension (yes)	349 (3.02)	3639 (1.58)	<0.0001
Dyslipidemia (yes)	206 (1.78)	2196 (0.95)	<0.0001
Renal disease (yes)	101 (0.44)	1227 (0.53)	<0.0001
Stroke (yes)	106 (0.46)	525 (0.23)	<0.0001
Monthly income			<0.0001
NT$0	2410 (20.9)	50,924 (22.1)	
NT$1–NT$15,840	1371 (11.9)	25,356 (11.0)	
NT$15,841–NT$25,000	4617 (40.0)	89,099 (38.6)	
≧NT$25,001	3143 (27.2)	65,441 (28.3)	
Urbanization level			<0.0001
1 (most urbanized)	2090 (18.1)	42,579 (18.4)	
2	1308 (11.3)	28,888 (12.5)	
3	3195 (27.7)	68,819 (29.9)	
4	1967 (17.0)	32,514 (14.1)	
5 (least urbanized)	2981 (25.9)	58,020 (25.1)	
Geographic region			<0.0001
Northern	5148 (44.6)	108,208 (46.9)	
Central	2352 (20.4)	44,972 (19.5)	
Southern	3788 (32.8)	72,216 (31.3)	
Eastern	253 (2.2)	5424 (2.3)	
Propensity score	0.0496 ± 0.015	0.0475 ± 0.010	<0.0001

US $1 = NT $34 in 2001.