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Increased risk of chronic fatigue syndrome in patients with migraine: A retrospective cohort study

Chi-Ieong Lau [a,b,c], Che-Chen Lin [d,e], Wei-Hung Chen [a,f], Han-Cheng Wang [a,f,g], Chia-Hung Kao [h,i,*]

[a] Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[b] Division of Clinical Neurology, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[c] College of Medicine, Fu-Jen Catholic University, Taipei, Taiwan
[d] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[e] College of Medicine, China Medical University, Taichung, Taiwan
[f] College of Medicine, Taipei Medical University, Taipei, Taiwan
[g] College of Medicine, National Taiwan University, Taipei, Taiwan
[h] Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan
[i] Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

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ABSTRACT

Objective: The common concurrence of migraine and chronic fatigue syndrome (CFS) has been reported but whether migraine poses a higher risk of CFS remains unknown. In this retrospective case–control study, we examined the association between the 2 disorders by using a nationwide, population-based database in Taiwan.
Methods: The data were retrieved and analyzed from the National Health Insurance Research Database (NHIRD) of Taiwan; 6902 newly diagnosed migraine cases from 2006–2010 were identified in a subset of the NHIRD, and 27,608 migraine-free individuals were randomly selected as the comparison cohort. The multivariate Cox proportional hazards regression model was used to investigate the risk of CFS in migraineurs after adjustment for demographic characteristics and comorbidities.
Results: After adjustment for the covariates, the risk of CFS was 1.5-fold higher in the migraine cohort than in the comparison cohort (52.72 vs. 28.85 per 10,000 person-years). Intriguingly, the risk was most prominent in the oldest group (≥65 years), with a 2.11-fold increased risk (95% confidence interval 1.31–3.41) of CFS. In addition, the adjusted cumulative incidence of CFS in the follow-up years was higher in the migraine group (log-rank test, $P < .0001$), and CFS incidence appeared to increase with the frequency of migraine diagnoses.
Conclusion: The current study demonstrated an increased risk of CFS in migraineurs. Proposed mechanisms in previous studies such as mitochondrial dysfunction and central sensitization may underlie the shared pathophysiology of these seemingly distinct but potentially overlapping disorders.

Introduction

Migraine is a common disorder with relapsing episodes of moderate to severe headache, nausea, vomiting, and sensory hypersensitivities that last for hours to days [1]. Chronic fatigue syndrome (CFS), however, is a less common and less recognized illness characterized by profound, unexplained fatigue for more than 6 months that significantly interferes with daily activities [2].

By definition, an addition of 4 or more symptoms from a list of 8, including postexertion malaise, unrefreshing sleep, impaired memory, muscle pain, joint pain, sore throat, tender cervical nodes and headaches, must also be met to fulfill the criteria of CFS [2]. Among these ancillary symptoms, headache is commonly reported [3]. Nevertheless, the types of headache in CFS are poorly designated. Thus far, only one study explored the types of headache in CFS and revealed a higher prevalence of migraine in CFS patients than in controls [4]. Conversely, fatigue is also common among migraineurs, with one study reporting an increased prevalence of CFS in chronic migraineurs [5]. The common concurrence of the 2 disorders leads to the speculation that their pathophysiology may overlap [4].

Moreover, in addition to headaches contributing to the ancillary criteria of CFS, migraine and various disorders, such as irritable bowel syndrome, fibromyalgia, and temporomandibular joint disorder, are common comorbidities of CFS [6]. Consequently, these disorders may be variable manifestations of the same biological processes [6]. Investigating whether migraineurs are at a higher risk of developing subsequent CFS may therefore provide additional evidence and shed light on the potential overlapped pathophysiology of this spectrum of disorders. The current study conducted a nationwide, population-based

* Corresponding author at: Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404, Taiwan.
E-mail address: d10040@mail.cmuh.org.tw (C.-H. Kao).

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cohort study by using data from the National Health Insurance Research Databases (NHIRD) of Taiwan to address the question.

Methods

Data source

The Taiwan government reorganized 13 government-managed insurance programs into the nationwide, single-payer Taiwan National Health Insurance (NHI) in 1995. The NHI cover rate has reached over 99% of the 23 million residents of Taiwan since 1998. The Taiwan government entrusted the National Health Research Institutes (NHRI) to manage all reimbursement claims data from the NHI and to establish the National Health Insurance Research Databases (NHIRD). All personal identification information is encrypted to safeguard patient privacy before being released for research. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

The study population was constructed from a subset of the NHIRD called the Longitudinal Health Insurance Database (LHID). The LHID was built from one million randomly sampled insured individuals from 1996 to 2000. According to an NHRI report [7], there is no difference in age or sex distribution between the populations of the LHID and NHIRD. The LHID consists of annual historical claims data of one million people. The claims data includes beneficiary registries, outpatient and inpatient records, prescriptions, and records of other medical services. The NHRI created an anonymous identification number to link the files of each insurant because the identification information is encrypted.

In the NHIRD, disease records are based on the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM). To survey the disease history of a patient, we collected outpatient and inpatient data from the disease records.

Study population

This study employed a population-based, retrospective cohort design. The migraine cohort consisted of migraine patients newly diagnosed (ICD-9-CM code: 346) from 2006 to 2010 and aged older than 20 years. The index date of the migraine cohort was fixed as the initial migraine diagnosis date. The comparison subjects were individuals without migraine diagnoses selected from the LHID and randomly frequency matched by age (per 5 years) and sex with 1:4 ratios. Those in the comparison cohort were randomly assigned the same index date as the matched cases. Both cohorts excluded individuals with CFS diagnosed before the index date. Study follow-up continued until December 31, 2011 or until a subject withdrew from the health insurance program or experienced CFS occurrence.

Outcome and comorbidity assessment

An instructive study outcome was the occurrence of CFS (ICD-9-CM code: 780.71). The study also collected comorbidity histories as a confounding factor. A comorbidity was defined as a participant having a comorbidity diagnosis before the index date. The comorbidities included hypertension (ICD-9-CM codes: 401–405), diabetes mellitus (DM; ICD-9-CM code: 250), hyperlipidemia (ICD-9-CM code: 272), anxiety (ICD-9-CM codes: 300.0, 300.2, 300.3, 308.3, and 309.81), and depression (ICD-9-CM codes: 296.2–296.3, 300.4, and 311).

Statistical analysis

A chi-squared test was performed to demonstrate the number and proportions of the sex and comorbidity distributions between the migraine and comparison cohorts and to test their differences. A t test was conducted to show the mean and standard deviation (SD) of the age distributions of the 2 cohorts and to test their differences. The cumulative incidence of CFS was calculated by dividing the total number of CFS occurrences by the total sum of follow-up for each cohort by 10,000 per person-years. The cumulative incidence curves were measured using the Kaplan–Meier method. A log-rank test was performed to assess the difference in incidence curves between the participants with and without migraine. To determine the risk of migraineurs developing CFS, single-variable and multivariable Cox proportional hazards regression models were used to estimate crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The sensitivity test of the Cox proportional hazards regression model was used to analyze the effect of migraine under the various demographic and comorbidity conditions. In this study, data management and analysis were performed using SAS Version 9.3 software (SAS Institute, Cary, NC, USA). The level of significance for 2-sided testing was $P < .05$.

Results

The study population comprised a cohort of 6902 migraine patients and a comparison cohort of 27,608 subjects with similar mean ages (45.5 years) and the same sex ratio (male: 26.7%) (Table 1). Except for DM proportion, the comorbidity proportions in the migraine cohort were much higher than those in the comparison cohort.

CFS incidence was 52.72 per 10,000 person-years in the migraine cohort and 28.85 per 10,000 person-years in the comparison cohort (Table 2). The CFS cumulative-incidence curve for the migraine cohort was also greater than the curve for the comparison cohort (Fig. 1; $P < .0001$). After adjustment for age, sex, hypertension, DM, hyperlipidemia, anxiety, and depression, patients with migraine had a 1.50-fold increased risk of CFS compared with subjects without migraine (HR = 1.50, 95% CI = 1.20–1.88).

Table 3 shows the association between the frequency of migraine and CFS risk. There was no difference of CFS risk between the comparison cohort and patients with a lower frequency of medical visits due to migraine (HR = 0.92, 95% CI = 0.68–1.23). A higher frequency of medical visits due to migraine (average frequency 3–5 and ≥6) was significantly associated with an increased risk of CFS. The results also revealed that CFS risk was increased with an increase in frequency of medical visits due to migraine (for trend, $P < .0001$).

Table 4 shows the results of the sensitivity analysis, which estimated the effect of migraine according to the statuses of various demographic factors and comorbidities. Relative to the subject without migraine, the patient with migraine was significantly associated with an increased risk of CFS according to the statuses of various demographic factors and comorbidities, except for the status of young age (<45 years), patients without hypertension, patients with DM, and patients with depression. However, the results showed that the trend of CFS incidence for patients

Table 1
Demographic status and comorbidity compared between comparison and migraine cohort.

Variable	Comparison cohort N = 27,608 (%)	Migraine cohort N = 6902 (%)	p-Value
Age, years (SD)[a]	45.5 (15.1)	45.5 (15.0)	0.9147
Sex			>0.99
Female	20232 (73.3)	5058 (73.3)	
Male	7376 (26.7)	1844 (26.7)	
Comorbidities			
Hypertension	5481 (19.9)	1765 (25.6)	<0.0001
DM	2248 (8.1)	545 (7.9)	0.5022
Hyperlipidemia	4114 (14.9)	1382 (20.0)	<0.0001
Anxiety	2643 (9.6)	1752 (25.4)	<0.0001
Depression	1256 (4.5)	844 (12.2)	<0.0001
CAD	3019 (10.9)	1141 (16.5)	<0.0001

Abbreviation: CAD: coronary artery disease.
[a] t test.