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Age-specific and gender-dependent impact of primary headache disorders on dementia risk
Population-based longitudinal study

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Abstract

Dementia is a global burden of public health. Headache disorders are the third most common cause of disability worldwide and common problems in the elderly population. Few studies focused on the relationship between primary headache disorders (PHDs) and cognitive status, and the results remain controversial. The aim of this countrywide, population-based, retrospective study was to investigate potential association between PHDs and dementia risk.

We enrolled 1346 cases with PHDs to match the 5384 individuals by age, gender and co-morbidities. The definition of PHDs, dementia, and risk factors of dementia was identified according to The International Classification of Diseases, Ninth Revision, Clinical Modification. Cox regression was administered for estimating hazard ratios (HR) for dementia.

During more than 5 years of follow-up, PHDs individuals had 1.52 times ($P<.05$) greater risk to develop all dementia compared with individuals without PHDs. Elderly (aged $\geq$65 years) patients with PHDs displayed significantly higher risk to develop all dementia ($P<.01$) and non-Alzheimer non-vascular dementia (NAVD) $P<.01$). Female PHDs individuals were at higher risk of suffering from all dementia ($P<.05$) and NAVD ($P<.05$). The influence of PHDs on all dementia was highest in the first 2 years of observation.

The results indicated PHDs are linked to a temporarily increased risk for dementia, mainly NAVD, with age-specific and gender-dependent characteristics.

Abbreviations: AD = Alzheimer's disease, AF = atrial fibrillation, TUD = tobacco use disorder, CAI = carotid artery insufficiency, CKD = chronic kidney disease, CVA = cerebral vascular accident, HR = hazard ratio, IHD = ischemic heart disease, NAVD = non-Alzheimer non-vascular dementia, PD = Parkinson's disease, PHD = Primary headache disorder, VD = vascular dementia.

Keywords: Alzheimer, dementia, headache, migraine, risk factor, vascular

1. Introduction

Dementia is a clinical syndrome of progressive deterioration in memory, executive function, language, and behavior, eventually leading to impaired activities of daily living. There are many different types of dementia. Alzheimer's disease (AD) and vascular dementia (VD) are the first and second leading causes of dementia, respectively.[1,2] In 2010, there are an estimated 35.6 million people worldwide suffer from dementia. The number of

dementia patient will be almost 2-fold every 20 years, achieving 65.7 million in 2030.[3] It is a major and growing challenge of global public health and social care.[4] Among risk factors for dementia, age is associated with incidence of dementia, which is considered as risk factors for a number of medical comorbidities and conditions,[5–8] such as hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease (IHD), atrial fibrillation (AF),[9] tobacco use disorder (TUD), alcoholism,[10] obesity,[11] Parkinson's disease (PD),[12] cerebral vascular accident (CVA),[13] depression,[14] chronic kidney disease (CKD)[15] and carotid artery insufficiency (CAI).[16] It is of interest and importance to identify potential risk factors for dementia and to establish an appropriate preventive strategy contributing to public health.

Headache disorders, which affect nearly half of the adult population, are the third most common cause of disability worldwide.[17,18] PHDs, which characterized by recurrent headache without clear underlying pathogenic mechanism, consist of tension-type headache, migraine, cluster headache, and other primary headaches.[19,20] Although it is true that the prevalence of PHDs decreases markedly after age 50, PHDs are still common problems in the elderly population.[21–23]

In the present study, we hypothesized that incidence of PHDs is correlated to dementia with great likelihood. We conducted a retrospective countrywide, population-based cohort study of individuals with PHDs to elucidate whether PHDs are potential risk factor for dementia.

2. Material and methods

2.1. Database

Our research employed the data in Longitudinal Health Insurance Database (LHID 2005) released by the Taiwan National Health Research Institute (NHRI) and covered the period of 1997 to 2010. The National Health Insurance (NHI) program, began in 1995, is a government compulsory insurance that provided comprehensive health care to all Taiwan citizens. The LHID 2005, included data of ambulatory and outpatient/ inpatient care services of 1 million people insured, was retrieved randomly from over 25 million individuals registered in the NHI program. The age and gender distribution of individuals in the LHID 2005 was similar to the primary database according to the government statement. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) is the diagnostic coding system for disease adopted by the NHI. Taiwanese government gave a scrambled and anonymous number before releasing data for research to safeguard the privacy of people insured. The NHI randomly reviews the healthcare declaration to verify medical claims for diagnoses and treatments. A disease diagnosis without valid supporting clinical findings may be considered a medical fraud by the NHI with a penalty of 100-fold of the payment declared by the treating physician or hospital. Previous reports have shown the reliability of the diagnosis coding in the LHID.[31,32] The Institutional Review Board of Tri-Service General Hospital approved the study (TSGHIRB No.: 1-104-05-112). Because data in the LHID 2005 is de-identified, the signed informed consent of participants was waived.

2.2. Study population

From 967,854 individual outpatient care data in the LHID 2005 between 2000 and 2005, we excluded the cases with a prior diagnosis of dementia and PHDs or with missing identification of gender or cases under the age of 18 years. After that, we identified patients (N=1,346) newly diagnosed with PHDs as the study group according to tension-type headache (ICD-9-CM 307.81), migraine (ICD-9-CM 346), and other headache syndromes (ICD-9-CM 339) from 2000 to 2005.

Next, based on age, sex and comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, IHDs, AF, TUD, alcoholism, obesity, PD, CVA, major depression, CKD, and CAI, 5384 cases were randomly selected with a ratio of 4:1, to match the study group. Furthermore, we set the date of PHDs diagnosis as the index date, and then every case was followed until the day of dementia was diagnosed. For cases did not develop dementia, the study endpoint was the end of the study period (31 December 2010) or insurance termination date.

2.3. Definitions of dementia subtypes by ICD classification

First, we classified dementia subtypes into Alzheimer disease (AD, ICD-9-CM codes 331.0), (VD, ICD-9-CM code 290.4), and non-Alzheimer non-vascular dementia (NAVD, ICD-9-CM code 294.1). Second, medical comorbidities recognized as potential risk factors for dementia consisting of hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), IHDs (ICD-9-CM codes 410–414), AF (ICD-9-CM code 427.3), TUD (ICD-9-CM code 305.1), alcoholism (ICD-9-CM codes 291, 303.9, 334.4, 980.0), obesity (ICD-9-CM codes 278, 649.1, 783.1), Parkinson disease (ICD-9-CM code 332.0), CVA (ICD-9-CM codes 430–432, 433–437), major depression (ICD-9-CM code 296), CKD (ICD-9-CM code 585), CAI (ICD-9-CM code 433.10) were identified before the index date according to the above ICD codes.

2.4. Statistical analyses

We administered Pearson chi-square test to evaluate the differences of categorical variables including age groups, sex, hypertension, diabetes mellitus, hyperlipidemia, IHDs, AF, TUD, alcoholism, obesity, PD, CVA, major depression, CKD, and CAI between the study and control group. Next, we employed Cox proportional hazard regressions to investigate the adjusted hazard ratio (HR) for the impact of PHDs on dementia risk after adjustment for the above variables. Furthermore, we performed Kaplan–Meier analysis to calculate the cumulative incidence of dementia for each group. Statistical analyses were carried out with the Statistical Package for the Social Science version 22.0 (SPSS Inc., Chicago, IL).

3. Results

The study consisted of 1346 PHDs patients and 5384 age- and sex-matched non-PHDs individuals. The clinical characteristics displayed in Table 1 showed that the distribution of age, sex, and risk factors in patients with PHDs were similar to those without PHDs. Results of the multivariate Cox regression analysis revealed that PHDs patients had higher risks of developing all-cause dementia compared to the control group (HR=1.52, 95% CI: 1.04 –2.15, $P<.05$) over a 5-year observation period (Table 2). Furthermore, patients with PHDs had 1.56 times (95% CI: 1.11–3.04, $P<.05$) greater risk to develop NAVD, rather than AD and VD, compared with the non-PHDs group.

Next, in order to explore if PHDs is an age-dependent risk factor for all-cause dementia and dementia subtypes, we divided the study cases into 3 groups based on age (<45, 45–64, and ≥65

Table 1

Baseline demographic status and comorbidity compared between comparison and PHD group.

Variable	PHD cohort N=1,346 (%)	Comparison cohort N=5,384 (%)	P value
Age, years (SD)*	47.38 (14.56)	46.74 (15.77)	.183
<45	820 (60.92)	3,280 (60.92)	
45-64	404 (30.01)	1,616 (30.01)	
≥65	122 (9.07)	488 (9.07)	
Sex			.999
Female	959 (71.25)	3,836 (71.25)	
Male	387 (28.75)	1,548 (28.75)	
Comorbidity			
Hypertension	72 (5.35)	305 (5.66)	.342
DM	25 (1.86)	101 (1.88)	.732
Hyperlipidemia	22 (1.63)	99 (1.84)	.142
IHD	14 (1.04)	53 (0.98)	.476
AF	1 (0.07)	7 (0.13)	.503
TUD	0 (0)	2 (0.04)	.640
Alcoholism	1 (0.07)	4 (0.07)	.737
Obesity	0 (0)	0 (0)	—
PD	4 (0.30)	9 (0.17)	.052
CVA	11 (0.82)	60 (1.11)	.213
Depression	3 (0.22)	15 (0.28)	.501
CKD	12 (0.89)	40 (0.91)	.497
CAI	0 (0)	0 (0)	—

AF = atrial fibrillation, CAI = carotid artery insufficiency, CKD = chronic kidney disease, CVA = cerebral vascular accident, DM = diabetes mellitus, IHD = ischemic heart disease, PD = Parkinson's disease, PHD = primary headache disorders, TUD = tobacco use disorder.
* t test

years). Multivariate Cox regression analysis displayed only elderly (≥65 years of age) PHDs patients had significantly higher risk for development of all dementia (adjusted HR = 2.23, 95% CI: 1.34–3.45, P <.01) and NAVD (adjusted HR = 2.26, 95% CI: 1.37–3.34, P <.01) than the control group. We also analyzed whether PHDs is a gender-dependent risk factor for development of dementia. The result of gender-specific analysis disclosed that female PHDs had greater risk to develop all dementia (adjusted HR = 1.49, 95% CI: 1.01–2.12, P <.05) and NAVD (adjusted HR = 1.54, 95% CI: 1.00–2.41, P <.05) than the matched controls.

Moreover, we investigated the incidence of all-cause dementia and dementia subtypes in accordance with different time intervals. The results showed that the impact of PHDs on all-cause dementia and NAVD was significant in the first (HR = 1.81, 95% CI: 1.01–3.45, P <.05) and second year (HR = 2.71, 95% CI: 1.09–6.12, P <.05) of observation period, respectively (Table 3). Finally, Kaplan–Meier analysis revealed that significantly greater cumulative incidence of all-cause dementia (Fig. 1) and NAVD in the PHDs group than in the control group.

4. Discussion

The countrywide, retrospective and longitudinal cohort study showed that the individuals with PHDs were at higher risk for

Table 2

Incidence of dementia and dementia subtype and multivariate Cox proportional hazards regression analysis measured hazard ratio for study cohort.

Variable	PHD cohort			Comparison cohort			Adjusted HR (95% CI)
	Event	PYs	Rate	Event	PYs	Rate	
All dementia	40	6,337	63.12	104	25,304	41.10	1.52 (1.04–2.15)*
AD	3	6,337	4.73	10	25,304	3.95	1.15 (0.25–4.23)
VD	1	6,337	1.58	3	25,304	1.19	1.30 (0.20–11.78)
NAVD	36	6,337	56.81	91	25,304	35.96	1.56 (1.11–3.04)*
<45 yrs							
All dementia	2	2,976	6.72	19	12,558	15.13	0.04 (0.10–1.90)
AD	0	2,976	0	0	12,558	0	–
VD	0	2,976	0	0	12,558	0	–
NAVD	2	2,976	6.72	19	12,558	15.13	0.04 (0.10–1.90)
45–64 yrs							
All dementia	12	2,665	45.02	30	9,422	31.84	1.41 (0.71–2.45)
AD	0	2,665	0	3	9,422	3.18	0
VD	0	2,665	0	1	9,422	1.06	0
NAVD	12	2,665	45.02	26	9,422	27.59	1.63 (0.85–3.13)
≥65 yrs							
All dementia	26	697	373.27	55	3,323	165.50	2.23 (1.34–3.45)**
AD	3	697	43.07	7	3,323	21.06	2.01 (0.47–6.94)
VD	1	697	14.36	2	3,323	6.02	2.27 (0.34–9.76)
NAVD	22	697	315.85	46	3,323	138.42	2.26 (1.37–3.34)**
Male							
All dementia	13	1,799	72.26	32	7,123	44.93	1.61 (0.97–2.98)
AD	1	1,799	5.56	2	7,123	2.81	1.87 (0.22–10.01)
VD	0	1,799	0	1	7,123	1.40	0
NAVD	12	1,799	66.71	29	7,123	40.72	1.64 (0.76–3.44)
Female							
All dementia	27	4,539	59.49	72	18,182	39.60	1.49 (1.01–2.12)*
AD	2	4,539	4.41	8	18,182	4.40	1.00 (0.20–3.98)
VD	1	4,539	2.20	2	18,182	1.10	1.99 (0.26–10.04)
NAVD	24	4,539	52.88	62	18,182	34.10	1.54 (1.00–2.41)*

Model adjusted for age, sex, hypertension, DM, IHD, hyperlipidemia, AF, TUD, alcoholism, obesity, PD, CVA, depression, CKD, and CAI

AD = Alzheimer's disease, AF = atrial fibrillation, CAI = carotid artery insufficiency, CKD = chronic kidney disease, CVA = cerebral vascular accident, DM = diabetes mellitus, IHD = ischemic heart disease, NAVD = non-Alzheimer non-vascular dementia, PD = Parkinson's disease, PHD = primary headache disorders, PYs = person-years, Rate = incidence rate, per 10,000 person-years, TUD = tobacco use disorder, VD = vascular dementia.
* P <.05;
** P <.01.

Table 3

Incidence of dementia and dementia subtype and multivariate Cox proportional hazards regression analysis measured hazard ratio for study cohort by various time intervals.

Variable	PHD cohort			Comparison cohort			Adjusted HR (95% CI)
	Event	PYs	Rate	Event	PYs	Rate	
Follow <1 yr							
All dementia	13	11	11,393.51	22	34	6537.89	1.78 (1.04–3.71)*
AD	1	11	876.42	1	34	297.18	3.30 (0.34–15.50)
VD	0	11	0	1	34	297.18	0
NAVD	12	11	10,517.09	20	34	5943.54	1.81 (1.01–3.45)*
Follow ≥1, <2 yrs							
All dementia	8	32	2495.32	15	109	1370.74	2.19 (1.01–5.13)*
AD	0	32	0	2	109	182.77	0
VD	0	32	0	1	109	91.38	0
NAVD	8	32	2495.32	12	109	1096.59	2.71 (1.09–6.12)*
Follow ≥2 yrs							
All dementia	19	6294	30.19	67	25,161	26.63	1.11 (0.88–1.76)
AD	2	6294	3.18	7	25,161	2.78	1.05 (0.27–4.80)
VD	1	6294	1.59	1	25,161	0.40	3.52 (0.34–27.77)
NAVD	16	6294	25.42	59	25,161	23.45	1.06 (0.58–1.77)

Model adjusted for age, sex, hypertension, DM, hyperlipidemia, IHD, AF, TUD, alcoholism, obesity, PD, CVA, depression, CKD, and CAI.

AD = Alzheimer's disease, AF = atrial fibrillation, CAI = carotid artery insufficiency, CKD = chronic kidney disease, CVA = cerebral vascular accident, DM = diabetes mellitus, IHD = ischemic heart disease, NAVD = non-Alzheimer non-vascular dementia, PD = Parkinson's disease, PHD = primary headache disorders, PYs = person-years, Rate = incidence rate, per 10,000 person-years, TUD = tobacco use disorder, VD = vascular dementia.

* $P < .05$

development of dementia, mainly NAVD after adjustment of age, gender, and medical comorbidities. Meanwhile, women and the elderly group (aged more than 65 years) with PHDs were found more likely to developing dementia, especially NAVD than the matched controls. The current data revealed a temporal association of PHDs with dementia and PHDs are risk factors for dementia.

A recent study has demonstrated that non-migrainous headaches and migraine had an association with a higher risk of VD.[24] It has been also demonstrated that non-migrainous
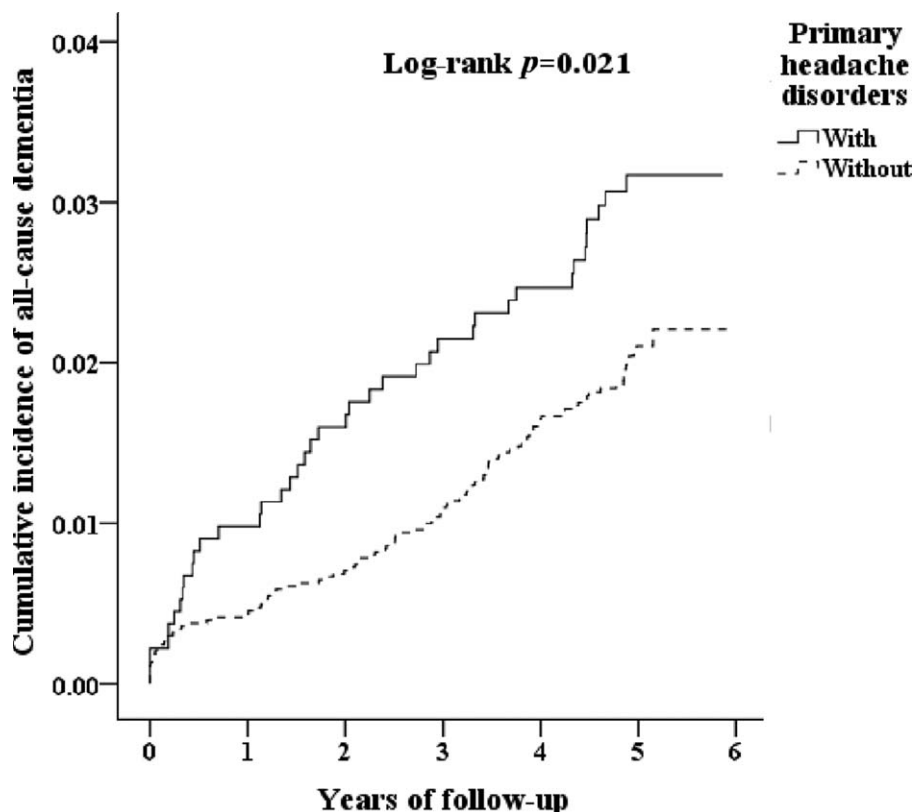

Figure 1. The cumulative incidence of all-cause dementia for the individual with and without primary headache disorders.

headache was associated with the development of VD and mixed dementia.[25] Our study outcome is compatible with the 2 longitudinal, population-based, registry studies mentioned above. However, these studies did not exclude certain possible confounding medical factors. In this countrywide population-based cohort study, we statistically controlled possible medical confounding factors, providing more specific results about the impact of PHDs on dementia. Compared with non-PHDs groups, PHDs patients with had a null risk of VD in the present study. This finding differed from the prior study[24] that indicated any headache was associated with a greater risk of VD. Differences in study populations, clinical settings and methodologies might contribute to the discrepancies. In our study, we found that PHDs individuals are more prone to develop NAVD other than AD or VD. Recent epidemiological neuroimaging and neuropathological data indicate considerable overlap between AD and VD, suggesting synergistic influences of both pathologies on cognitive impairment. Classical neuropathologic changes of AD (amyloid plaques and neurofibrillary tangles) can be present in VD.[26] In addition, high likelihood of developing dementia in NAVD patients may be attributable to involvement of non-Aβ pathways. Future studies to elucidate the impact of PHDs on NAVD are warranted.

In our study, the risk of dementia was higher in the elderly PHDs group (age ≥65-year-old), instead of the younger PHDs group (age <45 and 45–64), in line with previous studies[27] reporting the incidence rate of dementia raises with age in the global population. Meanwhile, female PHDs were found more likely to developing dementia, which supported those of former studies showing dementia prevalence was higher among women than men.[28] From the analysis of multivariate Cox proportional hazards regression, we found that the influence of PHDs on dementia was only significant in the first 2-year observation period. The prior studies[21,22] investigating prevalence of headache in an elderly population provided the data that the prevalence of headache decreased steadily with age, which might be one of the reasons of the temporal impact of PHDs on dementia.

Several possible mechanisms might underlie the higher dementia risk among patients with PHDs. First, PHDs are famous as recurrent or persistent painful disorder of head without any transparent underlying mechanism,[19,20,29] suggesting that brain morphometric changes related to pain-processing included the somatosensory cortex, prefrontal cortices, anterior cingulate, insular, thalamus, amygdalae, hippocampus, cerebellum, basal ganglia as well as areas within the temporal and parietal cortices. It is worth noting that[30] identified that memory networks included the medial and lateral temporal, prefrontal, and anterior/retrosplenial/posterior cingulate cortices as well as temporoparietal junctions, cerebellum, insular, thalamus, and amygdalae. Overlapping structural brain changes in pain and memory networks may contribute to the greater risk for dementia in patients with PHDs. Second, previous studies showed that subcortical white matter (WM) hyperintensity in migraine headache, which has been linked to cognitive decline.[31,32] A higher prevalence of WM abnormalities has been detected in non-migrainous headache as well.[33,34] Furthermore, WM hyperintensity has been proposed to be associated with a greater dementia risk.[35] Consequently, subtle brain WM changes might be another possible explanation for the increased dementia risk in PHDs patients.

Finally, the earlier study showed that the PHDs prevalence was higher for among women than men.[36] In addition, female PHDs individuals might have more psychiatric comorbidities, included depression, than male PHDs individuals.[37,38,39] demonstrated that individuals with a medical history of depression had a nearly 2-fold increased risk of developing dementia, compared to those without a depression history. Therefore, depression among patients with PHDs might be a risk factor for later dementia. Further studies are necessary to verify these presumptions.

5. Study limitations

Certain limitations should be taken into account when interpreting the results. First, the diagnosis of PHDs, dementia, and risk factors of dementia were according to the ICD-9-CM codes recorded in the LHID 2005, the diagnostic accuracy of which influenced the results. Furthermore, potential biases of diagnoses and misclassification might occur because the diagnoses were obtained retrospectively without advanced verifications by headache and dementia specialists. Second, information of medicine use, educational level, daily physical activity, and nutrition status[8] are difficult to ascertain from the LHID 2005; nevertheless, these factors may have an impact on dementia risk. In regard to the issue, we excluded cases with previous diagnosis of dementia from our study. However, the huge database may still comprise some unrecognized cases with minimal cognitive impairment and dementia had not coded by a clinician. Finally, our results only displayed an association rather than straightforward relationship between PHDs and dementia. Further researches will be required to provide an insight into the mechanism underlying the association disclosed in the present study. All limitations mentioned above should be taken into account in the future prospective studies.

6. Conclusion

Our study showed that individuals with PHDs are at relatively greater risk for suffering from dementia and PHDs had a potentially age-specific, gender-dependent impact on dementia risk. For clinical practice, the results have important implications that clinician should pay close attention to elderly and female individuals with PHDs and monitor them with neuropsychological tests. Early identification of dementia in individuals with PHDs and effective interventions are warranted to promote the quality of care for these patients.

Author contributions

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