Gallstone Disease and the Risk of Stroke: A Nationwide Population-based Study

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Background: Gallstone disease (GD) and stroke share a number of risk factors including diabetes and hyperlipidemia. This nationwide population-based study was designed to estimate the risk of stroke after a diagnosis of GD. *Methods:* Data were obtained from the Taiwan National Health Insurance Research Database. A total of 135,512 patients with a diagnosis of GD and 271,024 age- and gender-matched non-GD control patients were included to assess the risk of stroke using Cox proportional hazard regression. *Results:* During the study period (2000-2003), 12,234 (153.67/10,000 person-years) strokes occurred among the GD patients, and 20,680 (114.83/10,000 person-years) among the controls. The diagnosis of GD carried a higher risk of developing ischemic and hemorrhagic stroke, with a hazard ratio (HR) of 1.28 and 1.33 (95% confidence interval [CI], 1.25-1.31 and 1.25-1.41, both $P < .0001$), respectively. Stroke risk was increased in both genders but at a higher rate in younger age. The GD group had significantly higher prevalence rate of comorbidities that are known stroke risk factors, including hypertension, diabetes, and coronary artery disease. Stroke risk was higher in the GD group with or without any of these comorbidities. *Conclusions:* In this population-based longitudinal follow-up study, GD carried a significantly higher stroke risk, particularly for younger age with or without stroke risk factors. Stroke preventive measures maybe needed for patients with GD, especially those of younger age and with stroke risk factor(s). **Key Words:** Stroke—gallstone disease—cholelithiasis—epidemiology—risk factors.

Gallstone disease (GD; cholelithiasis) is a common disorder worldwide with varying prevalence in different populations. In the United States, the prevalence of GD has been reported to be approximately 7.9% in men and 16.6% in women,[1] and in Europe 1%-5% in men and 2%-6% in women of young age (20-30 years).[2] The

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prevalence increases with age and has been reported to be 9%-25% in men and 22%-30% in women of older age (50-60 years).[2] In Asians, its range is from 4.21%-15%,[3] and in Taiwan one epidemiologic survey reported rates of 17% in men and 18.7% in women.[4] GD is a multifactorial disease with risk factors including gender, age, genetic factors, race, obesity, rapid weight loss, diet, alcohol use, diabetes, hyperlipidemia, drug use, and pregnancy.[5-7]

Stroke is a debilitating and life-threatening disorder and is the second leading cause of death worldwide.[8] There are nonmodifiable, well-documented modifiable, and less well-documented modifiable risk factors for stroke.[9] The generally nonmodifiable risk factors include age,[10,11] gender,[12] low birth weight,[13] race,[14] and genetic background.[15] The well-documented modifiable risk factors include hypertension,[16] diabetes,[17] hyperlipidemia,[18] atrial fibrillation,[19] other cardiac conditions,[20] asymptomatic carotid stenosis,[21] sickle cell disease,[22] cigarette smoking,[23] postmenopausal hormone therapy,[24] oral contraceptives,[25] diet,[26] physical inactivity,[27] and obesity.[28] The less well-documented modifiable risk factors include migraine,[29] metabolic syndrome,[30] alcohol consumption,[31] drug abuse,[32] sleep-disordered breathing,[33] hyperhomocysteinemia,[34] elevated lipoprotein(a),[35] hypercoagulability,[36] inflammation, and infection.[37]

GD and stroke have certain risk factors in common, including gender, age, genetic background, race, obesity, diet, alcohol consumption, diabetes, and hyperlipidemia. However, to the best of our knowledge, no study to date has sought to evaluate the relationship between GD and stroke. This nationwide population-based study was designed to investigate whether there is an increased risk of stroke after a diagnosis of GD in Taiwan.

Materials and Methods

Database

This study used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institute to collect data for this study. The NHIRD contains all the claims data in the National Health Insurance program, which covers 98% of the population of Taiwan. The NHIRD includes deidentified secondary data released by the National Health Research Institute for research purposes, and thus this study was exempt from full review by the institutional review board.[38,39]

The disease history was collected from inpatient files and the disease definition was based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Sample

This was a population-based retrospective cohort study. The GD cohort comprised individuals with GD (ICD-9-CM 574) newly diagnosed in 2000-2003. The index date of the GD cohort was the date of the initial GD diagnosis. The comparison cohort, composed of individuals without a GD diagnosis in the NHIRD, was a 2-fold frequency matched by age (per 5 years) and sex. The index date of the comparison cohort was randomly assigned in accordance with the index year of the GD cohort. We excluded individuals with stroke diagnosed before the index date or aged less than 20 years. The study follow-up was terminated when the individual withdrew from the insurance program, event occurrence, or until December 31, 2010.

The event of interest in the study was the development of stroke (ICD-9-CM 430-438). The study also investigated the

Table 1. *Demographic characteristics and comorbidities of patients with gallstone disease (GD) and subjects in the comparison group*

Variables	Comparison group, N = 271,024	Patients with GD, N = 135,512	*P* value
Age, y, n (%)			>.99
<45	61,310 (22.6)	30,655 (22.6)	
45-64	101,020 (37.3)	50,510 (37.3)	
≥65	108,694 (40.1)	54,347 (40.1)	
Sex, n (%)			>.99
Female	137,440 (50.7)	68,720 (50.7)	
Male	133,584 (49.3)	66,792 (49.3)	
Medical history, n (%)			
Without any comorbidity	236,328 (87.2)	99,697 (73.6)	<.0001
Hypertension	22,069 (8.1)	19,601 (14.5)	<.0001
Diabetes mellitus	12,901 (4.8)	14,467 (10.7)	<.0001
Coronary artery disease	12,129 (4.5)	13,548 (10.0)	<.0001
Atrial fibrillation	2,343 (.9)	2,736 (2.0)	<.0001
Hyperlipidemia	4,550 (1.7)	6,744 (5.0)	<.0001