Hyperthyroidism and Risk of Ischemic Stroke in Young Adults
A 5-Year Follow-Up Study

Jau-Jiuan Sheu, MD, MPH; Jiunn-Horng Kang, MD, MSc; Hsiu-Chen Lin, MD; Herng-Ching Lin, PhD

Background and Purpose—Case reports or case series have reported the association between hyperthyroidism and cerebrovascular disease. However, hyperthyroidism has never been considered as a potential risk factor for stroke in young people. The aim of the present study is to estimate the risk for ischemic stroke among hyperthyroidism patients aged 18 to 44 years during a 5-year period after the diagnosis of hyperthyroidism as compared to a cohort of patients without hyperthyroidism during the same period.

Methods—A total of 3176 patients with hyperthyroidism were included as the study cohort and 25 408 patients without hyperthyroidism were included as comparison cohort. Each patient was individually tracked for 5 years from their index ambulatory visit to identify those in whom ischemic stroke developed. Cox proportional hazard regressions were performed to compute the 5-year stroke-free survival rate between these 2 cohorts.

Results—Of the total sample of 28 584 patients, 198 patients (0.7%) had ischemic strokes during the 5-year follow-up period (31 [1.0% of the hyperthyroidism patients] from the study cohort and 167 [0.6% of comparison patients] from the comparison cohort). After adjusting for the patient's age, gender, income, level of urbanization, hypertension, diabetes, atrial fibrillation, hyperlipidemia, coronary heart disease, and whether they were using antiarrhythmics, the hazard of having ischemic stroke during the 5-year follow-up period was 1.44-times greater (95% CI, 1.02–2.12; P=0.038) for patients with hyperthyroidism than for patients in the comparison cohort.

Conclusions—We conclude that hyperthyroidism is associated with an increased risk for ischemic stroke among young adults. (*Stroke*. 2010;41:961-966.)

Key Words: hyperthyroidism ■ ischemic stroke

Hyperthyroidism is a common endocrine disorder, affecting 0.5% to 2% of the population, and young adults comprise a significant proportion of those with this disorder.[1,2] Although hyperthyroidism may involve short-term and long-term cardiovascular consequences,[3] data concerning the association between hyperthyroidism and cardiovascular outcomes are inconsistent.[4] Hyperthyroidism is well-known to be associated with an increased risk of atrial fibrillation among people aged 60 years or older,[5] and there is a high risk for cardioembolic stroke in hyperthyroidism patients with atrial fibrillation.[6] However, there is a marked absence of data relating to the risk of stroke in young adults with hyperthyroidism.

Hyperthyroidism may also be associated with various types or etiologies of cerebrovascular disease, including Moyamoya disease, antiphospholipid syndrome, giant cell arteritis, Takayasu arteritis, and cerebral venous thrombosis. However, only case reports or case series were found in the literature, and the causal relationship between hyperthyroidism and these syndromes cannot be established.[6] Regarding stroke subtypes, according to the Trial of Org 10172 in Acute Stroke Treatment criteria,[8] previous studies have found that strokes of other determined etiologies explained ≈25% of ischemic strokes in young people, including dissection, antiphospholipid syndrome, Moyamoya disease, systemic lupus erythematosus, migraine-related stroke, and coagulopathy.[9,10] In addition, strokes of undetermined etiology accounted for one-third to one-quarter of ischemic strokes among young people[11,12] and, to the best of our knowledge, hyperthyroidism has never been considered as a potential risk factor for stroke. The aim of the present study is to estimate the risk for ischemic stroke among hyperthyroidism patients aged 18 to 44 years during a 5-year period after the diagnosis of hyperthyroidism as compared to a cohort of patients without hyperthyroidism during the same period.

Materials and Methods

Database

This study used a database (Longitudinal Health Insurance Database [LHID]) provided to scientists in Taiwan by the Taiwan National Health Research Institute in 2007 for research purposes. This data set includes original claims data for 1 000 000 beneficiaries between the years 1996 and 2006 from Taiwan's National Health Insurance (NHI) program, a single-payer payment system that finances affordable health care for all Taiwanese citizens. As of 2007, 22.60 million (>98%) of Taiwan's population of 22.96 million were enrolled in this program. The LHID, which the Taiwan National Research Institute created by systematically selecting a representative database from the year 2005 registry of NHI beneficiaries, consists of 1 000 000 randomly selected subjects. The Taiwan National Health Research Institute reported that there were no statistically significant differences in age, gender, or health care costs between the sample group in the LHID and all beneficiaries under the NHI program. Therefore, the LHID offers a unique opportunity to identify the risk of stroke occurring among young patients with hyperthyroidism.

Validity of diagnoses is usually a concern with claims data sets. Thus, the NHI Bureau of Taiwan performs routine sampling of patient charts to cross-check claims from every hospital, followed by punitive measures for fraudulent coding. Any hospital with outlier charges or outlier practice patterns, or that is suspected of malpractice, faces the risk of an audit and may be subject to heavy penalties from the NHI Bureau when discrepancies, overcharging, or malpractice are discovered. Deterrence is further reinforced by the reimbursement system of NHI, which ties a hospital reimbursement rate to its patient severity profile. It is generally believed that the checks and balances of NHI promote accurate coding.[13] Because the LHID consists of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Institutional Review Board.

Study Sample

The study design was a prospective, case-cohort study. We selected all patients younger than 45 years old who visited ambulatory care centers with a principal diagnosis of hyperthyroidism (ICD-9-CM code 242, thyrotoxicosis with or without goiter) during the 4-year period from January 1, 1998 to December 31, 2001 as the study cohort (n=5935). We excluded patients who had hyperthyroidism diagnosed before 1998 to increase the likelihood of identifying only new hyperthyroidism cases (n=217). In this study, we assigned their first visits for the treatment of hyperthyroidism as the index ambulatory care visit. We also excluded those patients younger than 18 years old to limit our study sample to the adult population (n=402). Furthermore, to avoid mistaken diagnoses, we only selected patients who had at least 2 consensus-diagnosed episodes of hyperthyroidism during the study period and who had been prescribed antithyroid drugs (n=3261). We found there were no young adults with hyperthyroidism receiving radioiodine therapy during this period.

To exclude other causes of ischemic stroke in young people, we also excluded patients who had congenital heart or circulatory disease (ICD-9-CM 745 to 747), acute rheumatic fever or chronic rheumatic heart disease (ICD-9-CM codes 390 to 398), other forms of heart disease (ICD-9-CM codes 420 to 429), arterial dissection (ICD-9-CM code 443.2), cerebral arteritis (ICD-9-CM code 437.4), migraine (ICD-9-CM code 346), systemic lupus erythematosus (ICD-9-CM code 710.0), primary hypercoagulable state (ICD-9-CM code 289.81), or disorders of mitochondrial metabolism (ICD-9-CM code 277.87) (n=75) diagnosed. We also excluded patients who had any type of stroke (ICD-9-CM codes 430 to 438) before their index ambulatory care visit (n=10). As a result, 3176 hyperthyroidism patients were included as the study cohort.

The comparison cohort of this study was selected from the remaining patients in the LHID. We randomly extracted 25 408 subjects from the registry of beneficiaries (8 for every patient in the study cohort) matched with the study cohort patients in terms of age (18–24, 25–34, and 35–44), gender, and the year of index ambulatory care visit. We selected their first ambulatory visits occurring in the index year as the index ambulatory care visit. We excluded patients with hyperthyroidism or stroke diagnosed between 1996 and 2006. In addition, the exclusion criteria for selecting the comparison cohort were the same as those for the patient cohort. Each patient (n=28 584) in this study was individually tracked for 5 years from the index ambulatory visit to identify those who had at least 2 consensus-diagnosed episodes of ischemic stroke (ICD-9-CM codes 433 to 436).

In this study, we also took potential confounders into consideration in the regression modeling. These confounders included sociodemographic characteristics (age, gender, and income [0, NT$1–NT$15 840; NT1$15 841–NT$25 000; ≥NT$25 001]), level of urbanization, and the geographical location (Northern, Central, Eastern, and Southern Taiwan) of the community in which the patient resided, as well as comorbid medical disorders identified by the diagnosis codes that either occurred in the inpatient setting or appeared in ≥2 ambulatory care claims coded 6 months before and after the index ambulatory care visits, including hypertension, diabetes, hyperlipidemia, atrial fibrillation, and coronary heart disease, which all may exacerbate the risk of stroke. Furthermore, we have adjusted for whether a patient used antiarrhythmics during the follow-up period in the regression modeling. In this study, we selected NT$15 840 as the first income level cut-off point because this is the government-stipulated minimum wage for full-time employees in Taiwan. In addition, urbanization levels in Taiwan are divided into 7 strata in Taiwan National Health Research Institute publications, with level 1 referring to the "most urbanized" and level 7 referring to the "least urbanized" communities. However, given that there were only small numbers of hyperthyroidism cases in levels 5, 6, and 7, these 3 levels were combined into a single group, which is hereafter referred to as level 5.

Statistical Analysis

In this study, we used the SAS statistical package (version 8.2; SAS System for Windows) to perform all analyses in this study. Pearson χ^2 tests were performed to compare differences in sociodemographic characteristics, select comorbid medical disorders, and determine the risk for stroke for the study and comparison cohorts. We used the Kaplan-Meier method to estimate 5-year stroke-free survival rates and the log-rank test was also performed to examine differences in the risk for stroke between the 2 cohorts. Finally, Cox proportional hazard regressions were performed to compute the 5-year survival rate between these 2 cohorts after adjustment for the variables mentioned. In addition, our data met the proportionality assumption (meaning that survival curves for 2 strata, hyperthyroidism patients and patients in the comparison cohort, have hazard functions that are proportional over time). A 2-tailed level of 0.05 was considered significant in the models.

Results

Of the 28 584 sampled patients, the mean ages were 32.1 (SD, 7.4 years) and 32.3 (SD, 7.5 years) for patients with and without hyperthyroidism, respectively (P=0.093). The distributions of sociodemographic characteristics and comorbid medical disorders for these 2 cohorts are presented in Table 1. After matching for age and gender, patients with hyperthyroidism were more likely to have comorbidities such as hypertension (P=0.007) and diabetes (P<0.001) at the time of the index ambulatory care visits than patients in the comparison cohort. No significant differences in the level of urbanization and the geographic location of the communities in which the patients resided were observed between these 2 cohorts.

Table 2 shows the distributions of ischemic stroke during the 5-year follow-up period for these 2 cohorts. Because the National Health Insurance Research Database allows us to

Table 1.   Demographic Characteristics and Comorbid Medical Disorders for Patients in Taiwan With Hyperthyroidism and Patients in the Comparison Cohort, 1998–2001 (n=28 584)

Variable	Patients With Hyperthyroidism n=3176		Comparison Patients n=25 408		
	Total N	Column %	Total N	Column %	P
Gender					1.000
Male	557	17.5	4456	17.5	
Female	2619	82.5	20 952	82.5	
Age, yr					1.000
<25	599	18.9	4792	18.9	
25–34	1323	41.7	10 584	41.7	
35–44	1254	39.4	10 032	39.4	
Hypertension					0.007
Yes	16	0.5	61	0.2	
No	3160	99.5	25 347	99.8	
Diabetes					<0.001
Yes	24	0.8	79	0.3	
No	3152	99.2	25 329	99.7	
Coronary heart disease					0.896
Yes	3	0.1	26	0.1	
No	3173	99.9	25 382	99.9	
Hyperlipidemia					0.198
Yes	7	0.2	33	0.1	
No	3169	99.8	25 375	99.9	
Atrial fibrillation					0.624
Yes	6	0.2	11	0.0	
No	3170	99.8	25 397	100.0	
Taking antiarrhythmics					<0.001
Yes	26	0.8	66	0.3	
No	3150	99.2	25 342	99.7	
Monthly income					0.008
0	1793	56.5	14 738	58.0	
NT$1–NT$15 840	339	10.7	3002	11.8	
NT$15 841–NT$25 000	692	21.8	5193	20.4	
≥NT$25 001	352	11.1	2475	9.8	
Geographic region					0.737
Northern	2222	70.0	17 601	69.3	
Central	415	13.1	3476	13.7	
Southern	496	15.6	4013	15.8	
Eastern	43	1.4	318	1.3	
Urbanization level					0.924
1	645	20.3	5122	20.2	
2	552	17.4	4477	17.6	
3	312	9.8	2603	10.2	
4	221	7.0	1796	7.1	
5	1446	45.5	11 410	44.9	

Table 2.   Crude and Adjusted Hazard Ratios for Stroke Among the Sample Patients During the 5-Year Follow-Up Period Starting From the Index Ambulatory Care Visit (n=28 584)

Presence of Ischemic Stroke	Total Sample		Comparison		Hyperthyroidism	
	N	%	N	%	N	%
5-year follow-up period						
Yes	198	0.7	167	0.7	31	1.0
No	28,386	99.3	25,241	99.3	3,145	99.0
Crude HR (95% CI)	…		1.00		1.49† (1.01–2.19)	
Adjusted* hazard ratio (95% CI)	…		1.00		1.44† (1.02–2.12)	

*Adjustments are made for patient's age, gender, hypertension, diabetes, atrial fibrillation, coronary heart disease, hyperlipidemia, use of antiarrhythmics, monthly income, urbanization level, and geographical region.

†$P<0.05$.

trace all use of medical services for all enrollees, all sampled patients could be followed-up throughout the study period. Of the total sample of 28 584 patients, 198 patients (0.7%) had ischemic strokes during the 5-year follow-up period: 31 from the study cohort (1.0% of the hyperthyroidism patients) and 167 comparison patients (0.6% of patients from the comparison cohort).

The log-rank test reveals that patients with hyperthyroidism had significantly lower 5-year stroke-free survival rates than patients in the comparison cohort ($P=0.028$). In addition, we found that the mean and median times between ambulatory care visits and the onset of ischemic stroke were 983 (SD, 528 days) and 1004 days, respectively, for patients with hyperthyroidism. The Figure illustrates the results of Kaplan-Meier survival analysis.

Table 2 also presents the crude and adjusted hazard ratios for ischemic stroke by cohort. Patients with hyperthyroidism were more likely to have ischemic strokes during the follow-up period than patients in the comparison cohort (hazard ratio, 1.49; 95% CI, 1.01–2.19; $P=0.021$). After adjusting for the patient's age, gender, income, level of urbanization, hypertension, atrial fibrillation, diabetes, hyperlipidemia, coronary heart disease, and use of antiarrhythmics, the hazard of having ischemic stroke during the 5-year follow-up period was 1.44-times greater (95% CI, 1.02–2.12; $P=0.038$) for patients with hyperthyroidism than for patients in the comparison cohort.

Discussion

The previous hospital-based studies of young people with ischemic stroke showed that no cause has been found in up to one-third of young patients despite extensive investigation of etiologies.[11,12] Inadequately recognized genetic factors and poorly understood risk factors may contribute to this large proportion of undetermined etiology in young people with stroke.[10] Although previous studies showed hyperthyroidism increased stroke mortality in elderly patients,[7,14] the risk of stroke did not increase in patients aged 25 to 74 with hyperthyroidism diagnosed by free thyroxine index measurement.[15] To the best of our knowledge, this study is among the
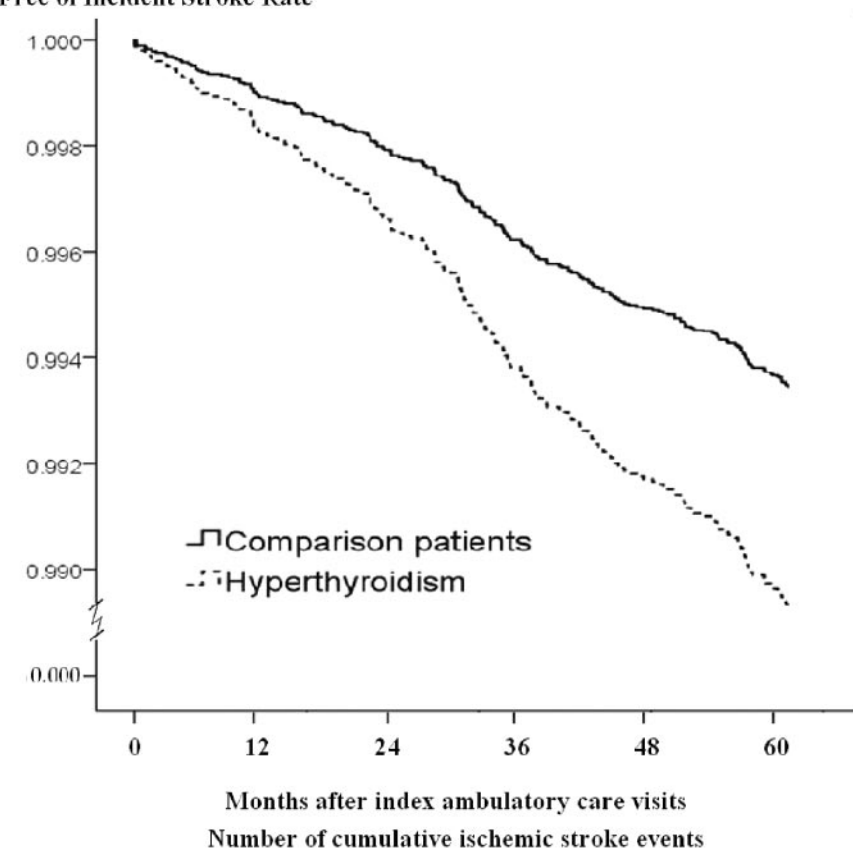
Free of Incident Stroke Rate

Figure. Ischemic stroke-free survival rates for patients with hyperthyroidism and comparison patients in Taiwan from 1998 to 2001.

Months after index ambulatory care visits

Number of cumulative ischemic stroke events

Hyperthyroidism	7	13	18	26	31
Comparison	27	56	97	131	167

first population-based epidemiological study to investigate the risk of ischemic stroke focusing on young adults with hyperthyroidism in the 5 years after the hyperthyroidism diagnosis, adjusting for demographic characteristics and comorbid medical disorders, and our findings indicate that hyperthyroidism may be a risk factor of young ischemic stroke.

We also found that the median time between the first ambulatory care visit and the onset of ischemic stroke was 1004 days for patients with hyperthyroidism, and thus half of the strokes occurred >1004 days after a diagnosis of hyperthyroidism. Our study indicates hyperthyroidism and antithyroid therapy may be associated with short-term and long-term cerebrovascular consequences. These results are in accordance with previous studies suggesting that hyperthyroidism and radioiodine therapy are associated with increased long-term vascular risk.[3,7] Considering that 12 to 18 months is the optimum duration of antithyroid drug therapy,[16] efforts to prevent stroke should last even after restoration of euthyroidism.

Except for cardioembolic stroke related to atrial fibrillation, the actual mechanisms contributing to the association between hyperthyroidism and stroke are not fully understood. Hyperthyroidism is associated with prominent cardiovascular effects such as systolic hypertension, which may contribute to vascular morbidity and mortality.[17] Increased stiffness and intima-media thickness, 2 indices of atherosclerosis, are found in the carotid artery in patients with hyperthyroidism, which are attributable to harmful effects of increased cardiac output and widened pulse pressure.[18,19] There are several factors contributing to the hypercoagulable state observed in hyperthyroidism, including increase in blood volume, increase in the levels of acute phase reactants, and increase in thrombin and fibrinogen activity.[20] Decreased levels of plasminogen and tissue plasminogen activator and increased levels of $\alpha 2$ antiplasmin and thrombin-activatable fibrinolysis inhibitor lead to decreased fibrinolysis in patients with hyperthyroidism.[20,21] An increase of plasma von Willebrand factor level in patients with hyperthyroidism indicates endothelial dysfunction and is associated with enhanced platelet plug formation.[22,23] As a result, there are hypercoagulability, hypofibrinolysis, and endothelial dysfunctions in hyperthyroidism, and all may contribute to the increased risk of thromboembolism.

One strength of this study is the use of a population-based data set, which enables us to trace all cases of hyperthyroidism and stroke during the study period. Moreover, the large sample size affords considerable statistical power for detecting real differences between the 2 cohorts. Nevertheless, this study has a few limitations that should be addressed.

First, hyperthyroidism and stroke diagnoses, which rely on administrative claims data reported by physicians or hospitals, may be less accurate than diagnoses made according to standardized criteria. However, to avoid mistaken diagnoses,

we only selected patients who had at least 2 diagnosed episodes of hyperthyroidism during the study period and who have been prescribed antithyroid drugs. In addition, virtually all hospitals in Taiwan capable of admitting stroke patients are equipped with CT or MRI scanners, which increase the validity of stroke diagnoses considerably.

Second, individual information such as smoking, alcohol consumption, dietary factor, body mass index, oral contraceptive use, and family history of stroke, all of which may contribute to stroke, was not available through the administrative data set. In addition, simply including hypertension, atrial fibrillation, and other stroke risk factors in the model may not adequately adjust for the confounding because duration of these risk factors may also contribute to the development of stroke. Smoking promotes the induction of hyperthyroidism in Graves disease and the development of toxic goiter.[24] Smoking is also an important risk factor in ischemic stroke. Thus, the association between hyperthyroidism and ischemic stroke may be partially explained by the residual confounding effect of smoking. However, in Taiwan, there is a much higher prevalence of smoking in males than females evident whether in a community study or in a hospital-based study of young people with ischemic stroke.[9,25] Patients with hyperthyroidism were mainly female; therefore, the confounding effect of smoking may be small in this study. Because obesity may be associated with a reduced risk for hyperthyroidism,[24] there even may be some underestimation of the odds ratio of the development of stroke among patients with hyperthyroidism. The increased risk of stroke among persons with a positive family history of stroke is related to the expression of genetic heritability of stroke risk factors, a shared environment such as lower physical activity and socioeconomic status, or both.[26] However, our selection criteria excluded arterial dissection, inherited coagulopathy, and disorders of clotting factors, which have a familial component in up to 20% of cases,[27] and may lessen the confounding effect of family history of stroke. In addition, we took urbanization level and monthly income as socioeconomic indicators in the model to minimize the environmental effect. Further study is needed to clarify these issues and confirm our findings.

Third, there may be a surveillance bias in that patients with hyperthyroidism diagnosed are likely to have more frequent check-ups and, thus, to have their stroke detected by a physician. However, because there has been a lack of clinical evidence linking hyperthyroidism to stroke in young people, in clinical practice, young adults with hyperthyroidism are usually followed-up by their endocrinologists. Hyperthyroidism patients visit a neurologist or emergency specialist only when they have neurological symptoms and then receive brain CT/MRI studies to diagnose stroke. Finally, as a further potential limitation, the study population is mainly composed of Taiwanese of Chinese descent receiving antithyroid drugs, and the results may not be capable of generalization to other populations or patients receiving radioiodine therapy.

Conclusions

Our study shows an association between hyperthyroidism and the risk of subsequent ischemic stroke in young adults. Because a more thorough evaluation may help elucidate the etiology of stroke in young adults,[8,10] our results indicate a need for thyroid function testing and detection of hyperthyroidism in surveys to identify the etiology of ischemic stroke in young people.

Disclosures

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, Taiwan, and managed by the National Health Research Institutes. The interpretations and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or the National Health Research Institutes.

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