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Sudden Sensorineural Hearing Loss Increases the Risk of Stroke

A 5-Year Follow-Up Study

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Background and Purpose—No previous study has investigated the incidence or risk of cerebrovascular diseases developing after the sudden sensorineural hearing loss (SSNHL). This study sets out to estimate the risk of stroke development among SSNHL patients during a 5e-year follow-up period after hospitalization for acute episodes of SSNHL.

Methods—Our study design features a study cohort and a comparison cohort. The study cohort consists of all patients hospitalized with a principal diagnosis of sudden hearing loss (n=1,423), whereas the control cohort comprised all patients hospitalized for an appendectomy in 1998 (n=5692) as a surrogate for the general population. Each patient was tracked from hospitalization in 1998 until the end of 2003. Cox proportional hazard regressions were performed as a means of computing the 5-year stroke-free survival rates after adjustment for possible confounding factors.

Results—Of the total sample, 621 patients (8.7%) had strokes during the 5-year follow-up period: 180 (12.7% of the SSNHL patients) from the study cohort and 441 (7.8% of patients undergoing an appendectomy) from the control cohort. After adjusting for other factors, the hazard of stroke during the 5-year follow-up period was 1.64-times (95% CI, 1.31 to 2.07; $P<0.001$) greater for SSNHL patients than for appendectomy patients.

Conclusions—Our findings suggest that SSNHL can be an early warning sign of impending stroke. We suggest that SSNHL patients should undergo a comprehensive hematologic and neurological examination to help clinicians identify those potentially at risk for stroke developing in the near future. **(*Stroke*. 2008;39:000-000.)**

Key Words: hearing loss ■ stroke ■ sudden sensorineural hearing loss

Sudden sensorineural hearing loss (SSNHL) occurs abruptly, developing rapidly within 72 hours, and is a frightening experience for patients. The estimated incidence rates for SSNHL in Taiwan are ≈8.85 for males and ≈7.79 for females per 100 000 people, based on a nationwide population-based study.[1] Although it has a high spontaneous recovery rate (40% to 65%),[2] possible causes and pathogenesis of SSNHL remain unknown. For this reason, SSNHL remains one of the most controversial and challenging issues in otology.

Previous studies have proposed underlying causes for SSNHL, including vascular occlusion, viral or bacterial infection, ruptured inner ear membrane, autoimmune diseases, and acoustic tumors.[3–5] Of these possible causes, vascular involvement in the pathogenesis of SSNHL has drawn a good deal of attention during the past few decades. Recently, some researchers have suggested that SSNHL could be an early sign of stroke, particularly anterior inferior cerebellar artery infarction.[6–12] One study by Lee et al[11] reported that 4 out of 12 patients had SSNHL from 1 day to 2 months preceding the onset of anterior inferior cerebellar artery stroke. Another study[12] by these authors found that 5 out of 16 patients experienced acute auditory syndromes from 1 to 10 days preceding the onset of anterior inferior cerebellar artery stroke. However, to the best of our knowledge, no study has investigated the incidence or risk of cerebrovascular diseases developing after the onset of SSNHL. Clearly, the lack of studies on the association between SSNHL and the subsequent risk for stroke prevents otolaryngologists and related health professionals from further distinguishing the simultaneous contributions of vascular, biochemical, metabolic, and immune factors to the pathogenesis of this disorder.

This study, therefore, set out to estimate the risk for stroke among SSNHL patients during a 5-year follow-up period after hospitalization for acute episodes of SSNHL. We used Taiwan's National Health Insurance Research Database (NHIRD). Taiwan initiated its National Health Insurance program in March 1995 to finance health care for all its citizens. This nationwide population-based dataset allows us

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to trace all medical service utilization history for all citizens, and it provides a unique opportunity to examine the association of SSNHL and the subsequent risk for stroke while adjusting for clinical and demographic factors.

Materials and Methods

Database

This study used data from the NHIRD provided by the Bureau of National Health Insurance of the Department of Health in Taiwan covering the years 1998 to 2003. The dataset includes all claims data from Taiwan's National Health Insurance program, a single-payer payment system that finances health care for all Taiwanese citizens and offers unrestricted access to any health care provider of the patient's choice. There are currently >21 million enrollees in the National Health Insurance program, ≈96% of the island's population. Hundreds of articles have used the NHIRD as the basis for their studies. Although there are no documented sensitivity and specificity studies about its coding accuracy, it is generally believed that the National Health Insurance's checks and balances foster accurate coding. Thus, the NHIRD offers a unique opportunity to identify the risk of stroke occurring among SSNHL patients. Because the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Internal Review Board.

Study Sample

Our study design features a study cohort and a comparison cohort. The study cohort comprised all patients who were hospitalized with a principal diagnosis of sudden hearing loss (ICD-9-CM code 388.2). We excluded readmissions, because SSNHL often involves >1 admission episode. Ultimately, our study sample included 1423 SSNHL patients.

Our control cohort consisted of all patients hospitalized for an appendectomy during 1998, with an ICD-OP code of 47.0 as the primary operative procedure. Patients undergoing an appendectomy were excluded if they had also had SSNHL diagnosed. The reason we selected appendectomy patients as the comparison group was that patients undergoing appendectomies were relatively indistinguishable from the general population. Previous studies have also reported that there are no statistically significant differences between this comparison population and the general population in Taiwan with regard to either gender ($P>0.05$) or age ($P>0.05$).[13,14] Furthermore, the procedures involved in an appendectomy have no known long-term impact on increased risk of stroke and SSNHL. Again, patients with a diagnosis of stroke before appendectomy were also excluded.

A total of 1423 patients had SSNHL and 16 413 patients underwent appendectomies in 1998. Because there was a significant difference in the mean age between SSNHL and appendectomy patients, we further refined our control cohort criteria by randomly selecting 5692 appendectomy patients (4 for every SSNHL patient) matched with the study group in terms of age (<45, 45 to 64, 65 to 74, and ≥75 years). Each patient was tracked from index hospitalization in 1998 until the end of 2003 to distinguish all patients in whom any type of stroke developed (ICD-9-CM codes 430 to 438). In addition, to calculate the stroke-free survival time after hospitalization for a 5-year period, the data were also linked to death certificate data in Taiwan, with cases censored if individuals died from nonstroke causes during that time (647 patients had already died from nonstroke causes: 129 from the study cohort and 518 from the comparison cohort).

The regression modeling also adjusted for socio-demographic characteristics, using gender, level of urbanization, and the geographical location of the community in which the patient resided (Northern, Central, Eastern, and Southern Taiwan), and income-related insurance payment amount as a proxy for income (0, NT$1 to NT$15 840, NT$15 841 to NT$25 000, ≥NT$25 001; NT$ indicates new Taiwan dollar) as variables. The reason we selected NT$15 840 as the first income level cutoff point was because this is the government-stipulated minimum wage for full-time employees in Taiwan.

Table 1. Demographic Characteristics and Comorbid Medical Disorders for SSNHL Patients and Appendectomy Patients in Taiwan 1998 (n=7115)

	SSNHL Patients		Appendectomy Patients		
Variable	Total N	%	Total N	%	*P*
Gender					0.330
Male	776	54.5	3022	53.1	
Female	647	45.5	2670	46.9	
Age, yr					1.000
<45	554	38.9	2216	38.9	
45–64	566	39.8	2264	39.8	
65–74	235	16.5	940	16.5	
>74	68	4.8	272	4.8	
Hypertension					<0.001
Yes	120	8.4	327	5.7	
No	1303	91.6	5365	94.3	
Diabetes					<0.001
Yes	144	10.1	246	4.3	
No	1279	89.9	5446	95.7	
Hyperlipidemia					0.007
Yes	11	0.8	16	0.3	
No	1412	99.2	5676	99.7	
Renal disease					0.784
Yes	15	1.1	55	1.0	
No	1408	98.9	5637	99.0	
Monthly income					<0.001
0	299	21.0	1726	30.3	
NT$1–NT$15 840	251	17.6	849	14.9	
NT$15 841–NT$25 000	514	36.1	2233	39.2	
≥NT$25 001	359	25.2	884	15.6	
Urbanization level					<0.001
1	456	32.0	1552	27.3	
2	400	28.1	1604	28.2	
3	266	18.7	990	17.4	
4	172	12.1	824	14.5	
5	129	9.1	722	12.7	
Geographic region					<0.001
Northern	689	48.4	2603	45.7	
Central	417	29.3	1280	22.5	
Southern	288	20.2	1633	28.7	
Eastern	29	2.0	176	3.1	

Previous studies have established that the occurrence of stroke is associated with both geographical regions and levels of urbanization;[15,16] therefore, these are also taken into account as variables in the regression modeling. In accordance with Taiwan National Health Research Institute publications,[17] urbanization levels in Taiwan are divided into 7 strata, with level 1 referring to the "most urbanized" and level 7 referring to the "least urbanized" communities. However, given that there were only very small numbers of SSNHL cases in levels 5, 6, and 7, these 3 levels were combined into a single group,

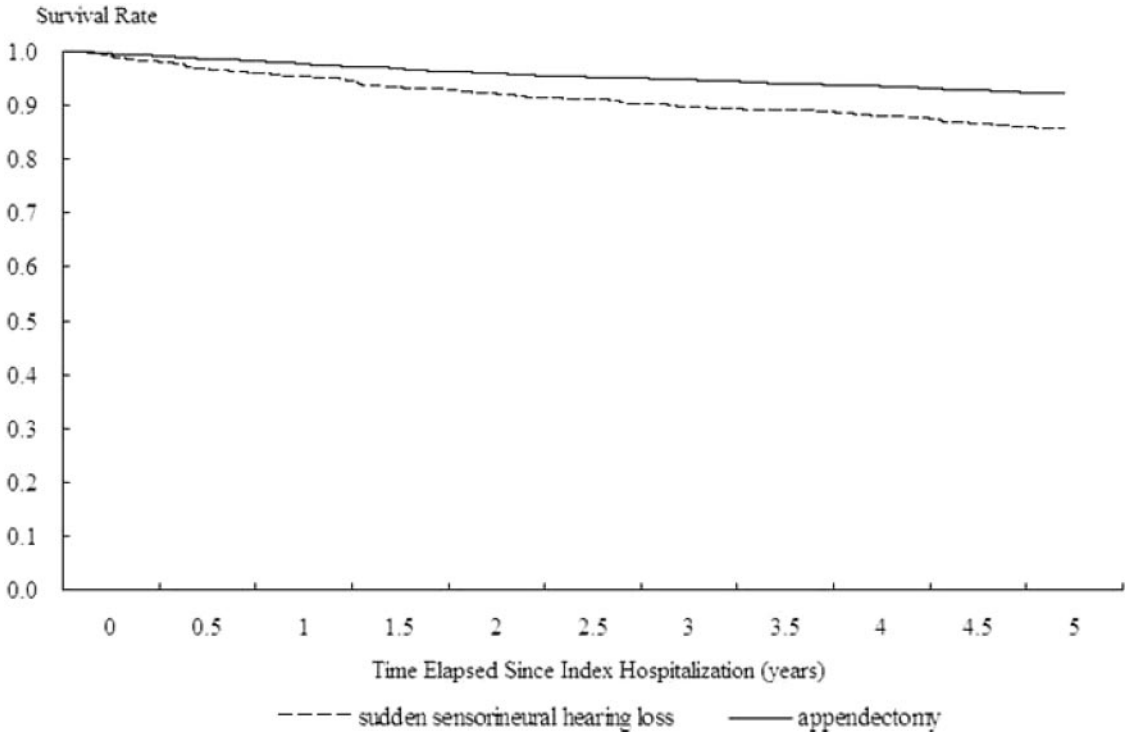

Figure. Stroke-free survival rates for sudden sensorineural hearing loss and appendectomy patients in Taiwan, 1998 to 2003.

thereafter referred to as level 5. Details on select comorbid medical disorders at the time of the index discharge, including hypertension, diabetes, hyperlipidemia, and renal disease, were also extracted from the claims data, because these conditions may exacerbate the risk of stroke.

Statistical Analysis

The SAS statistical package (SAS System for Windows, version 8.2) was used to perform the analyses in this study. Pearson χ^2 tests were performed to examine the differences between the 2 cohorts in terms of socio-demographic characteristics, select comorbid medical disorders, and the risk for stroke. The 5-year stroke-free survival rate was then estimated using the Kaplan-Meier method, using the log-rank test to examine the differences in the risk for stroke between the 2 cohorts. Cox proportional hazard regressions were also performed as a means of computing the adjusted 5-year survival rate, after adjustment for the variables mentioned. Finally, we present hazard ratios along with the 95% CI using a significance level of 0.05 for this study.

Results

Table 1 presents the distributions of demographic characteristics and select comorbid medical disorders for these 2 cohorts. After matching for age, Table 1 shows that SSNHL patients were more likely to have comorbidities such as hypertension ($P<0.001$), diabetes ($P<0.001$), and hyperlipidemia ($P=0.007$) at the time of the index hospitalization as compared to the appendectomy patients. The SSNHL patients tended to have monthly incomes more than NT$25 001 ($P<0.001$), and to reside in the most urbanized areas ($P<0.001$) and in the northern part of Taiwan ($P<0.001$).

Of the total sample of 7115 patients, 621 patients (8.7%) had strokes during the 5-year follow-up period: 180 (12.7% of the SSNHL patients) from the study cohort and 441 (7.8% of patients undergoing an appendectomy) from the control cohort. In addition, the average time between index hospitalization and the onset of stroke was 804 (±624) days for the SSNHL patients. The log-rank test indicated that SSNHL patients had significantly lower 5-year stroke-free survival rates than appendectomy patients ($P<0.001$). The results of Kaplan-Meier survival analysis are presented in the Figure.

Details of the adjusted hazard ratios for stroke, by cohort, based on Cox proportional hazard regression, are provided in Table 2. After adjusting for the patients' gender, income, level of urbanization, and comorbid medical disorders, the hazard of stroke during the 5-year follow-up period was 1.64-times (95% CI, 1.31 to 2.07; $P<0.001$) greater for SSNHL patients than for appendectomy patients. As expected, patients with hypertension (hazard ratio, 6.30; 95% CI, 4.91 to 8.09; $P<0.001$), diabetes (hazard ratio, 2.75; 95% CI, 2.05 to 3.68; $P<0.001$), and hyperlipidemia (hazard ratio, 5.83; 95% CI, 2.09 to 16.24; $P<0.001$) had a greater likelihood of stroke, after adjusting for other factors. Surprisingly, patient income and level of urbanization were not significantly related to stroke.

In addition, we have calculated the adjusted hazard for stroke during the 1-, 2-, 3-, and 4-year follow-up periods; we found the hazard of stroke was 1.94-times ($P<0.001$), 1.62-times ($P<0.001$), 1.63-times ($P<0.001$), and 1.61-times ($P<0.001$) greater, respectively, for SSNHL patients than for appendectomy patients.

Discussion

To the best of our knowledge, this study is the first attempt to investigate the risk of stroke among SSNHL patients in the 5 years after hospitalization for an acute SSNHL episode, after adjusting for patient demographic characteristics and comorbid medical disorders. Our study shows for the first time to

Table 2. Adjusted Hazard Ratio for Stroke During the 5-Year Follow-Up Period for SSNHL and Appendectomy Patients in Taiwan*

	Stroke Occurrence		
Variables	Hazard Ratio†	95% CI	*P*
Cohort			
SSNHL	1.64	1.31–2.07	<0.001
Appendectomy (reference group)	1.00		
Gender			
Male	1.26	1.02–1.56	0.030
Female (reference group)	1.00		
Age, yr			
<45 (reference group)	1.00		
45–64	5.82	3.89–8.71	<0.001
65–74	14.29	9.50–21.52	<0.001
>74	19.45	12.00–31.52	<0.001
Hypertension			
Yes	6.30	4.91–8.09	<0.001
No (reference group)	1.00		
Diabetes			
Yes	2.75	2.05–3.68	<0.001
No (reference group)	1.00		
Hyperlipidemia			
Yes	5.83	2.09–16.24	<0.001
No (reference group)	1.00		
Renal disease			
Yes	0.90	0.42–1.94	0.786
No (reference group)	1.00		
Monthly income			
0 (reference group)	1.00		
NT$1–NT$15 840	1.30	0.92–1.67	0.153
NT$15 841–NT$25 000	1.16	0.87–1.47	0.371
≥NT$25 001	1.09	0.76–1.56	0.476
Urbanization level			
1 (reference group)	1.00		
2	0.93	0.73–1.20	0.594
3	0.88	0.66–1.17	0.368
4	1.09	0.82–1.48	0.535
5	1.11	0.81–1.53	0.509

*Total sample=7115.

†Hazard ratios were all derived from the same Cox regression model and adjusted for all other variables.

our knowledge that the likelihood of the development of stroke was 1.64-times as great among SSNHL patients during the 5-year follow-up period as compared to counterparts who had undergone an appendectomy. Our findings support the previous report that SSNHL can be an early warning of an impending stroke.

Rather than focusing on patients with unilateral anterior inferior cerebellar artery infarction, like the 2 studies by Lee et al[11,12] that found that ≈30% of those had experienced SSNHL from between 1 day to 2 months before the onset of stroke, our study sample started with SSNHL patients, following-up each patient for 5 years. We found that 12.7% of the SSNHL patients had a stroke and had a greater likelihood of experiencing stroke during the 5-year follow-up period than that of the general population. Our pioneering study can better demonstrate the link between SSNHL and the subsequent development of stroke. In addition, our finding supports a vascular origin in the pathogenesis of SSNHL, at least in some patients.

Interestingly, we also found that among SSNHL patients who had strokes, only 12.2% occurred within 3 months after SSNHL onset, 31.4% occurred in the first year, and approximately half (50.6%) occurred in the first 2 years. In other words, approximately half of the strokes occurred >2 years after SSNHL onset. This suggests that efforts to prevent the development of stroke should last for several years after an episode of sudden deafness. Pathogenesis for the early and late onset of stroke after SSNHL may differ, however, so further studies should be performed to clarify this issue.

The actual mechanisms contributing to the association between SSNHL and the subsequent development of stroke remain unclear. We speculate that SSNHL may share a common etiology with stroke, because recent studies[18–20] consistently report that SNNHL patients have significantly higher plasma fibrinogen and cholesterol levels than the general population. Elevated plasma fibrinogen and cholesterol levels have been demonstrated to contribute to atherosclerosis and thrombosis and, in the case of SSNHL patients, may lead to stroke. More specifically, Lee et al[12] speculated that the association between SSNHL and subsequent stroke onset could be explained by the particular vulnerability of the cochlea to ischemia. The inner ear is especially sensitive to transient ischemia because of its high energy requirement and lack of adequate collateral blood supply. Consequently, SSNHL appears to be an early sign of impending anterior inferior cerebellar artery infarction.

A particular strength of this study is the use of a population-based dataset, which enables us to trace all stroke incidents. Furthermore, the large sample size affords considerable statistical power for detecting the real differences between the 2 cohorts. Nevertheless, this study still suffers from a few limitations that should be addressed. First, SSNHL patients in this study were identified from the NHIRD under the principal diagnosis code for sudden hearing loss; however, to date, we still do not have any clear universal definition for SSNHL. The database did not contain information regarding severity of hearing loss, extent of hearing recovery, tobacco use, body mass index, and the medical history of cardiovascular disease and atrial fibrillation, which would not be identified in the administrative database if not undergoing active management, and all of which might relate to the risk for stroke. Because previous studies have observed a greater frequency of heavy smoking among SSNHL patients,[21] and because it was not possible to adjust for tobacco use in this study, the odds ratio of SSNHL patients experiencing stroke may even be underestimated.

Conclusions

We have found that during a 5-year follow-up period, the risk for stroke was ≈1.6-times greater among SSNHL patients

compared to patients who underwent an appendectomy, and that this association was totally independent of any initial comorbid hypertension, diabetes, hyperlipidemia, renal diseases, and demographic factors. Our finding shows that SSNHL is an early sign of stroke, a fact that has important clinical implications for the care of SSNHL patients. We suggest that SSNHL patients, particularly those with other vascular conditions or elderly patients, should undergo a comprehensive hematologic and neurological examination to help clinicians identify those who are potentially at risk for stroke in the near future. Furthermore, because approximately half of the strokes occurred >2 years after SSNHL onset, routine follow-up examinations should be executed for at least several years after patients are discharged from hospitals for treatment of SSNHL.

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Disclosure

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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