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Increased Risk of Sudden Sensorineural Hearing Loss in Patients With Human Immunodeficiency Virus Aged 18 to 35 Years

A Population-Based Cohort Study

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Importance: No case series or cohort studies to date in the English literature have evaluated sudden sensorineural hearing loss (SSHL) in patients with human immunodeficiency virus (HIV).

Objective: To investigate the risk of developing SSHL in patients with HIV.

Design and Setting: Retrospective cohort population-based study using data from the Taiwan National Health Insurance Research Database.

Participants: In total, 8760 patients with HIV and 43 800 control subjects without HIV were selected from insurance claims between January 1, 2001, and December 31, 2006.

Main Outcome Measure: The incidence of SSHL was assessed and determined at the end of 2009.

Results: Among patients aged 18 to 35 years, the incidence of SSHL was 2.17-fold higher in the HIV group than in the control group (4.32 vs 1.99 per 10 000 person-years, $P = .03$). The risk of developing SSHL increased with HIV infection; an adjusted hazard ratio of 2.169 (95% CI, 1.071-4.391) was calculated using a Cox proportional hazards regression model. Among male patients, the incidence of developing SSHL was 2.23-fold higher (95% CI, 1.06-4.69) in the HIV group than in the control group. The incidence of SSHL did not differ significantly between the HIV group and the control group for patients 36 years or older.

Conclusion and Relevance: Human immunodeficiency virus infection is significantly associated with an increased risk of developing SSHL in patients aged 18 to 35 years, particularly among male patients.

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UP TO 84% OF INDIVIDUALS with human immunodeficiency virus (HIV) have symptoms or signs that may warrant being seen by an otolaryngologist.^{1,2} Furthermore, 29% to 44% of patients with HIV have been shown to have a conductive, sensorineural, or mixed-type hearing impairment.³⁻⁵

The origin of hearing loss associated with AIDS, either sensorineural or central, may occur as a result of a central nervous system neoplasm, as a secondary effect of iatrogenic causes after ototoxic drug administration, as a direct result of the effects of HIV on the central nervous system or on the peripheral auditory nerve, or as a result of other infection (cytomegalovirus, cryptococcal meningitis, herpesvirus, toxoplasmosis, or viral or bacterial infection).⁶ Sensorineural hearing loss may affect 21% to 49% of individuals with HIV or AIDS, typically causing greater losses in high-

frequency perception and indicating a need for studies of auditory pathway injuries caused by HIV.⁷ Sudden sensorineural hearing loss (SSHL), by definition, differs from chronic sensorineural hearing loss. We hypothesized that SSHL may share a similar mechanism with chronic sensorineural hearing loss to a certain degree. Sudden sensorineural hearing loss has been reported as a rare presentation in patients with HIV.⁸ However, no case series or cohort studies to date in the English literature have evaluated SSHL in patients with HIV.

To identify the effect of HIV infection on the risk of developing SSHL, a population-based cohort study was conducted that took advantage of a large data set available from the Taiwan National Health Insurance Research Database. We investigated whether the risk of developing SSHL increased with the progression of HIV infection as determined by the number of follow-up years required for patients with HIV to develop SSHL.

DATA SOURCES

The National Health Insurance Program in Taiwan is a universal health care system that covers 99% of the country's population of 23 million.⁹ Data used in this analysis were obtained from the Taiwan National Health Insurance Research Database, which contains all claims data from January 1, 1996, through December 31, 2010, for the 23 million beneficiaries. No significant differences were noted in age, sex, or health care costs between the sample group and all enrollees. The database contains encrypted patient identification numbers; the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes of the diagnoses and procedures; and details on prescribed drugs, admission dates, and discharge and basic sociodemographic information, including sex and date of birth.

STUDY DESIGN

A retrospective cohort study was conducted among patients with HIV (HIV group) and matched control subjects (control group). The HIV group included patients with an initial diagnosis of HIV infection (*ICD-9-CM* codes 042-044). Patients with HIV were identified through a diagnosis made at admission or by a specialist during a minimum of 3 hospital visits. Individuals without a medical claim for HIV infection who matched patients in the HIV group for sex, age, and index date were randomly selected for the control group. The index date for the patients with HIV was the date between January 1, 1996, and December 31, 2010, when the patient was first registered as having AIDS. The index dates for the control group were matched based on the index dates of the HIV group. Baseline comorbidities that may have manifested before the index date included the following *ICD-9-CM* codes: stroke (430-438), coronary artery disease (410-414, A270, and A279), diabetes mellitus (250), and chronic renal disease (582, 583, 585, 586, and 588). Sudden sensorineural hearing loss (388.2) was identified by the referring teaching hospital and the referring tertiary medical center. The consensus definition of SSHL in Taiwan is a sensorineural hearing loss of 30 dB or more during at least 3 contiguous audiometric frequencies that develops during a period of a few hours to 3 days. Routine peer review was conducted within the Taiwan Health Insurance Bureau to maintain consistency in diagnosis between the referring teaching hospital and the referring tertiary medical center. To investigate the association between the occurrence of SSHL and the disease process of HIV infection, only patients with newly diagnosed HIV between January 1, 2001, and December 31, 2006, were included in the study. The insurance claims data from January 1, 1996, to December 31, 2000, were used to confirm that none of the enrolled patients had contracted HIV before December 31, 2001. Patient follow-up visits were to be performed for a minimum of 5 years (January 1, 2006, to December 31, 2010). To determine the incidence of SSHL (*ICD-9-CM* code 388.2), the patients in the HIV group and the control group were followed up until the end of 2010 or until they were censored because of death. The identification numbers of all individuals in the Taiwan National Health Insurance Research Database were encrypted to protect privacy. The Chi Mei Medical Center (Tainan, Taiwan) institutional review board approved the study.

STATISTICAL ANALYSIS

Descriptive statistical analyses were performed using Pearson χ^2 test to compare the differences in sociodemographic characteristics and comorbidities between the HIV group and the

control group. The incidence rate was calculated as the number of SSHL cases identified during the follow-up period divided by the total person-years for each group by sex, age, and the number of follow-up years. The risk of developing SSHL was compared by estimating the incidence ratio using a Poisson regression. A Cox proportional hazards regression model with propensity score matching was used to estimate the hazard ratio between the HIV group and the control group. Propensity score matching was used to reduce selection bias in our hypothesis,⁹ which can bundle many confounding covariates that may be present in an observational study with this number of variables. Propensity score matching identified the predicted probability of obtaining 1 individual with HIV vs 1 control subject from the logistic regression model conditional on baseline covariates (ie, age, sex, geographic region, and annual income) and baseline comorbidities (ie, chronic renal disease, diabetes mellitus, coronary artery disease, and stroke). A Kaplan-Meier analysis was used to calculate the cumulative incidence rates of SSHL in the 2 cohorts, and the log-rank test was used to analyze the differences between the survival curves. All analyses were performed using available software (SAS, version 9.2; SAS Institute, Inc), and the statistical significance level was 2-sided $P < .05$.

RESULTS

THE INCIDENCE OF SSHL
BASED ON PATIENT CHARACTERISTICS

Based on the claims data from January 1, 2001, to December 31, 2006, a total of 8760 patients with HIV met the eligibility criteria as described in the "Study Design" subsection of the "Methods" section, and an additional 43 800 individuals were randomly selected for inclusion in the control group. Of the patients with HIV, 935 (10.7%) were female, and 7825 (89.3%) were male. The annual incidence of HIV infection in Taiwan averaged 6.41 cases per 100 000 from January 1, 2001, to December 31, 2006. The sociodemographic characteristics of patients in the HIV group and the control group were similar in sex and age distribution (**Table 1**). The differences in annual income and geographic region between the 2 groups were not statistically significant ($P > .99$ and $P = .99$, respectively).

SSHL IS ASSOCIATED WITH HIV INFECTION
IN PATIENTS AGED 18 TO 35 YEARS

The estimated risks for developing SSHL based on sex, age, and the number of follow-up years in the HIV group and the control group were compared. The mean (SD) age was 34.56 (10.71) years. The relationship between age and risk of SSHL among patients in the HIV group was explored by dividing the HIV group into a younger age group (18-35 years) and an older age group (≥ 36 years).

In patients aged 18 to 35 years, a significantly higher risk of developing SSHL was noted in the HIV group, with a crude hazard ratio of 2.175 (95% CI, 1.075-4.401) and an adjusted hazard ratio (adjusted for age, sex, geographic region, and annual income) of 2.169 (95% CI, 1.071-4.391) ($P < .05$). By the end of the follow-up period, the incidence of SSHL was higher in the HIV group than in the control group ($P = .03$, log-rank test) (**Figure**).

Table 1. Demographic Characteristics and Baseline Comorbidities Among the Human Immunodeficiency Virus (HIV) Group and the Control Group in Taiwan

Variable	No. (%)		P Value
	HIV Group (n = 8760)	Control Group (n = 43 800)	
Age group, y			
18-35	5306 (60.6)	26 541 (60.6)	.97
≥36	3454 (39.4)	17 259 (39.4)	
Sex			
Female	935 (10.7)	4628 (10.6)	.77
Male	7825 (89.3)	39 172 (89.4)	
Baseline comorbidity			
Stroke			
Yes	94 (1.1)	479 (1.1)	.87
No	8666 (98.9)	43 321 (98.9)	
Coronary artery disease			
Yes	84 (1.0)	394 (0.9)	.59
No	8676 (99.0)	43 406 (99.1)	
Chronic renal disease			
Yes	57 (0.7)	223 (0.5)	.10
No	8703 (99.3)	43 577 (99.5)	
Diabetes mellitus			
Yes	187 (2.1)	910 (2.1)	.73
No	8573 (97.9)	42 890 (97.9)	
Geographic region			
North	4546 (51.9)	22 713 (51.9)	.99
Central	1593 (18.2)	8025 (18.3)	
South	2479 (28.3)	12 358 (28.2)	
East	142 (1.6)	704 (1.6)	
Annual income, NT\$			
<15 840	4677 (53.4)	23 400 (53.4)	>.99
15 841-25 000	2334 (26.6)	11 658 (26.6)	
>25 001	1749 (20.0)	8742 (20.0)	

Abbreviation: NT, New Taiwan.

The incidence rates of SSHL classified by sex, age, and the number of follow-up years were compared between the HIV group and the control group. A significantly higher incidence of SSHL was noted in the HIV group compared with the control group, with an incidence rate ratio (IRR) of 2.17 (95% CI, 1.07-4.40), particularly for the male participants, who had an IRR of 2.23 (1.06-4.69) (**Table 2**).

SSHL IS NOT ASSOCIATED WITH HIV INFECTION IN PATIENTS 36 YEARS OR OLDER

In patients 36 years or older, the incidence of SSHL did not differ significantly between the HIV group and the control group. The IRR was 0.72 (95% CI, 0.29-1.84) (Table 2).

COMMENT

INCREASED RISK OF DEVELOPING SSHL IN PATIENTS WITH HIV AGED 18 TO 35 YEARS

The major finding in this study is that patients aged 18 to 35 years who were diagnosed as having HIV between January 1, 2001, and December 31, 2006, had a substantially higher incidence of SSHL than the general popu-

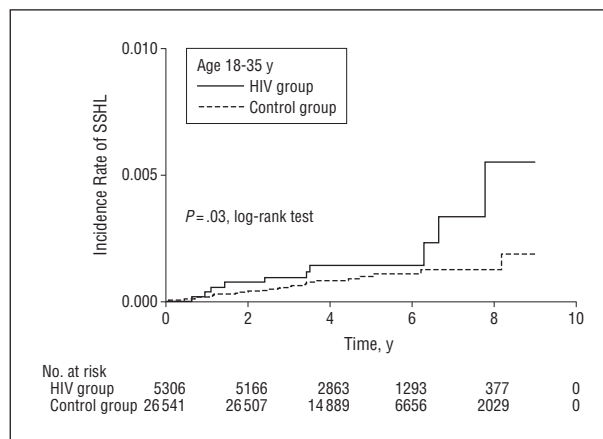


Figure. Incidence of sudden sensorineural hearing loss (SSHL) among the human immunodeficiency virus (HIV) group and the control group in Taiwan (January 1, 2000, through December 31, 2010).

lation without HIV. The IRR of SSHL in this age group was 2.17 ($P = .03$) (Table 2).

The underlying reason why an increased risk of SSHL was observed only in patients younger than 36 years is unclear. There was a trend in which the prevalence of SSHL increased (1.99 vs 4.45 per 10 000 person-years for those aged 18-35 vs ≥36 years) with patient age among the control group, which was selected and matched from the general population (Table 2). The prevalence rate of SSHL among patients aged 18 to 35 years in the HIV group was close to that among patients 36 years or older in the control group (4.32 vs 4.45 per 10 000 person-years). We concur that HIV accelerates the biological aging of patients with HIV. This mechanism of increased risk of SSHL in those aged 18 to 35 years with HIV may correlate with observations by Schouten et al¹⁰ and by Onen et al.¹¹ Schouten et al¹⁰ found that individuals with HIV develop serious non-AIDS diseases 5 years earlier than normal. Onen et al¹¹ compared the prevalence of non-AIDS diseases between older persons with HIV and the general population and suggested that HIV accelerates the biological aging.

Among the patients with HIV who were 36 years or older, 9.3% (320 of 3454) died after the second follow-up year, and 42.4% (1465 of 3454) died after the fourth follow-up year. Among individuals who were 36 years or older in the control group, only 0.9% (159 of 17 259) died after the second follow-up year, and 41.6% (7178 of 17 259) died after the fourth follow-up year. Patients with HIV died a few years earlier than healthy controls. However, of the individuals in the control group who contracted SSHL, 33.3% (13 of 39) sustained SSHL during follow-up years 2 through 4. There were fewer follow-up years for those 36 years or older in the HIV group than in the control group. An insufficient number of follow-up years to reveal the prevalence of SSHL may account for the insignificance of the IRR between the HIV group and the control group for individuals 36 years or older.

Patients with HIV who developed SSHL most often (45.5%) contracted SSHL during follow-up years 0 through 2. This finding implies that SSHL is unassociated with the severity and progression of HIV infection.

Table 2. Risk of Sudden Sensorineural Hearing Loss (SSHL) Among the Human Immunodeficiency Virus (HIV) Group and the Control Group

Characteristic	HIV Group				Control Group				Incidence Rate Ratio (95% CI) ^b	P Value
	Total No.	No. With SSHL	Person-Years	Rate ^a	Total No.	No. With SSHL	Person-Years	Rate ^a		
Age Group 18-35 y										
All	5306	11	25 439	4.32	26 541	26	130 722	1.99	2.17 (1.07-4.40)	.03
Sex										
Male	4720	10	22 896	4.37	23 593	23	117 648	1.95	2.23 (1.06-4.69)	.03
Female	586	1	2543	3.93	2948	3	13 075	2.29	1.71 (0.18-16.48)	.64
Follow-up, y										
0 to 2	5306	5	10 396	4.81	26 541	10	53 048	1.89	2.55 (0.87-7.46)	.09
>2 to 4	5166	3	9240	3.25	26 507	11	47 623	2.31	1.41 (0.39-5.04)	.60
>4	2863	3	5803	5.17	14 889	5	30 052	1.66	3.11 (0.74-13.00)	.12
Age Group ≥36 y										
All	3454	5	15 506	3.22	17 259	39	87 570	4.45	0.72 (0.29-1.84)	.50
Sex										
Male	3105	3	13 805	2.17	15 579	32	78 168	4.09	0.53 (0.16-1.73)	.29
Female	349	2	1701	11.76	1680	7	9402	7.45	1.58 (0.33-7.60)	.57
Follow-up, y										
0 to 2	3454	2	6378	3.14	17 259	15	34 371	4.36	0.72 (0.16-3.14)	.66
>2 to 4	3134	1	5514	1.81	17 100	13	30 690	4.24	0.43 (0.06-3.27)	.41
>4	1669	2	3614	5.53	9922	11	22 509	4.89	1.13 (0.25-5.11)	.87

^aPer 10 000 person-years.

^bThe HIV group compared with the control group.

Because our investigation, to our knowledge, is the first retrospective cohort study to date of the association between SSHL and HIV infection and because of the few case reports^{8,12-14} in the literature, we were unable to find related studies that were in agreement with our results. However, a discrepancy exists in the published literature regarding the chronic severity of sensorineural hearing loss. Khoza and Ross¹⁵ and others¹⁶ found that the degree of severity of hearing loss did not worsen with the progression of HIV or AIDS, whereas Chandrasekhar et al⁴ proposed that sensorineural hearing loss was more severe in patients with more severe HIV infection.

The mechanisms that contribute to the association between HIV infection and the subsequent development of SSHL remain unclear. We speculate that SSHL in patients with HIV may share a common origin with chronic sensorineural hearing loss; recent investigators have consistently reported the prevalence of chronic sensorineural hearing loss among patients with HIV. For example, prominent viral-like particles in the cochlea of patients with AIDS have been demonstrated in pathological studies^{17,18} of the temporal bone. The ear is no less susceptible to AIDS-associated diseases than any other organ and is particularly prone to cytomegalovirus infection.¹⁹ The otologic symptoms, including bilateral sudden or progressive hearing loss, may represent a combination of the effects of HIV infection coupled with opportunistic microorganisms or the possible ototoxic effects of certain therapeutic agents.²⁰ If the former is the case, every effort should be made to improve the immunity of patients with HIV. Human immunodeficiency virus testing in the case of bilateral SSHL is advised if there are other signs or symptoms present to suggest possible HIV infection.

Both HIV infection and AIDS are reportable diseases in Taiwan. The present study examined risks in patients

who contracted HIV between January 1, 2001, and December 31, 2006. The government in Taiwan has provided all citizens having HIV with free access to highly active antiretroviral therapy since April 1997. This approach ensures that all patients with HIV in this study received free access to highly active antiretroviral therapy. These results could serve as a valuable reference for the present patient population as long as Taiwan's government maintains the policy of free highly active antiretroviral therapy supply.

STRENGTHS AND LIMITATIONS OF THE STUDY

This study indicates that there is an elevated risk of developing SSHL in patients with HIV aged 18 to 35 years based on the results from a large sample (8760 individuals with HIV and 43 880 control subjects). This large population-based data set allowed for the demonstration of risk factors for developing SSHL in Taiwan, with a minimal tendency toward selection bias. The large sample size also enhanced the statistical power and precision of risk appraisal.²¹

However, this study is not without limitations. Several suspected risk factors for SSHL were unavailable in the insurance database (eg, personal history of smoking and noise exposure). The inability to assess these factors may result in a degree of bias. The insurance claims data did not include information about the severity of hearing loss or other laboratory test results. Furthermore, a population-based study cannot explore the underlying mechanism that may link HIV to SSHL.

Awareness of the elevated risk of developing SSHL in patients with HIV who are aged 18 to 35 years could prompt the early detection and treatment of SSHL. Sched-

uled auditory examinations for patients with HIV to assess the presence of chronic hearing impairment may enable the early detection of SSHL in the future. In addition, medications that enhance immune activity may benefit patients with HIV who are at risk of developing SSHL.

In conclusion, HIV infection is associated with a significantly increased risk of the development of SSHL in patients aged 18 to 35 years, particularly among men. Scheduled auditory examinations for patients with HIV to assess the presence of chronic hearing impairment are advised to enable the early detection of SSHL.

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Author Contributions: Dr Lin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Y.-S. Lin. *Drafting of the manuscript:* Y.-S. Lin. *Statistical analysis:* Weng and Y.-S. Lin. *Administrative, technical, and material support:* C. Lin, S.-W. Lin, Weng, and Y.-S. Lin. *Study supervision:* C. Lin and S.-W. Lin.

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