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Sudden Hearing Loss with Vertigo Portends Greater Stroke Risk Than Sudden Hearing Loss or Vertigo Alone

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Abstract

Background—Because it is unknown whether sudden hearing loss (SHL) in acute vertigo is a “benign” sign (reflecting ear disease) or a “dangerous” sign (reflecting stroke), we sought to compare long-term stroke risk among patients with (1) “SHL with vertigo,” (2) “SHL alone,” and (3) “vertigo alone” using a large national health-care database.

Methods—Patients with first-incident SHL (International Classification of Diseases, Ninth Edition, Clinical Modification [ICD-9-CM] 388.2) or vertigo (ICD-9-CM 386.x, 780.4) were identified from the National Health Insurance Research Database of Taiwan (2002–2009). We defined SHL with vertigo as a vertigo-related diagnosis ± 30 days from the index SHL event. SHL without a temporally proximate vertigo diagnosis was considered SHL alone. The vertigo-alone group had no SHL diagnosis. All the patients were followed up until stroke, death, withdrawal from the database, or current end of the database (December 31, 2012) for a minimum period of 3 years. The hazards of stroke were compared across groups.

Results—We studied 218,656 patients (678 SHL with vertigo, 1998 with SHL alone, and 215,980 with vertigo alone). Stroke rates at study end were 5.5% (SHL with vertigo), 3.0% (SHL alone), and 3.9% (vertigo alone). Stroke hazards were higher in SHL with vertigo than in SHL alone (hazard ratio [HR], 1.93; 95% confidence interval [CI], 1.28–2.91) and in vertigo alone (HR, 1.63; 95% CI, 1.18–2.25). Defining a narrower window between SHL and vertigo (± 3 days) increased the hazards.

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Conclusions—The combination of SHL plus vertigo in close temporal proximity is associated with increased subsequent stroke risk over SHL alone and vertigo alone. This suggests that SHL in patients with vertigo is not necessarily a benign peripheral vestibular sign.

Keywords

Sudden hearing loss; vertigo; dizziness; vertebrobasilar stroke; diagnosis

Introduction

Identifying stroke among patients presenting with vertigo is one of the most challenging issues in neurology, neurotology, and emergency medicine, and missed stroke in this context is frequent.¹ Most clinicians seek to differentiate stroke from peripheral vestibulopathy using the presence of focal neurological signs. Unfortunately, only 19% of patients with stroke presenting with acute vestibular syndrome have focal findings.² Among these patients, the head impulse test, nystagmus, and test of skew deviation (HINTS) battery of bedside ocular motor tests has been shown to be highly sensitive and specific for stroke.^{2–6}

HINTS is based on key physiological differences between vestibular eye movement responses when central versus peripheral vestibular structures are injured.⁵ Not surprisingly, then, HINTS is most likely to fail when strokes affect the inner ear directly, because labyrinthine infarction is presumably physiologically indistinguishable from vestibular neuritis or labyrinthitis.⁵ As a result, infarctions affecting the anterior inferior cerebellar artery (AICA) territory, which supplies blood to the inner ear in the majority of people, are the most challenging to reliably identify.^{7,8} Among patients with AICA infarction, 60% have a combined audiovestibular loss.⁹

It has been suggested, therefore, that new hearing loss in the context of acute vertigo might be an important stroke predictor.⁴ Classical teaching, however, tells us that the comorbid presence of hearing loss indicates a peripheral-type vertigo.¹⁰ Many practitioners take acute hearing loss as a benign symptom when associated with vertigo and link it with pure inner ear disorders such as Menière disease or labyrinthitis, and, therefore, a lower risk for stroke. The underlying cause of sudden hearing loss (SHL) is also debated. Some specialists believe that SHL results from viral inner ear infection, whereas others favor a vascular origin. A large, population-based study showed that patients with SHL have a higher, long-term risk of stroke when compared with control subjects,¹¹ but the increased risk is roughly half of that in patients with vertigo presentations.¹² Among those with a proven AICA infarction, only 3% are said to initially present with an isolated SHL.⁹ In patients with SHL, 20%-60% complain of vertigo, and sometimes vertigo is their main symptom.¹³ Prior studies comparing SHL with and without vertigo found that hearing loss recovers more poorly if patients have vertigo, implying potentially different etiologies between these 2 groups.¹⁴

Thus, whether SHL is a benign symptom or a dangerous stroke predictor in patients with vertigo remains to be clarified. This specific issue has not been studied directly, largely because of a segregation between research on vertigo (without hearing loss) and research on hearing loss (without vertigo).¹⁵ In the present study, we use a population-based database to

compare stroke risk across patients with SHL alone, those with both SHL and vertigo, and those with vertigo alone. We hypothesized that the combination of SHL and vertigo would predict a higher stroke risk relative to patients with either SHL or vertigo alone.

Methods

Data Source

We used data from the National Health Insurance Research Database (NHIRD) of Taiwan. The NHIRD contains records of approximately 23 million enrollees dating back to March 1995, representing almost 99% of the total population in Taiwan. We reviewed records from the Longitudinal Health Insurance Database (LHID), which includes claims data for 1 million enrollees randomly selected from all beneficiaries of the National Health Insurance program in 2010. The medical records in the LHID include those from 1996 to 2012 for clinic visits, emergency department visits, and inpatient hospitalizations. To ensure confidentiality, the enrollees' personal information is protected using anonymous unique identification numbers. We extracted data based on the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes.

Study Design

We conducted a population-based retrospective cohort study from the LHID using ICD-9-CM discharge diagnoses across clinical settings (clinic, emergency department, inpatient ward). We defined 3 cohorts for the primary analysis: (1) *SHL with vertigo* (SHL with temporally proximate vertigo), (2) *SHL alone* (SHL without temporally proximate vertigo), and (3) *vertigo alone* (vertigo without any history of SHL). Our primary outcome was a longitudinal follow-up for a first inpatient diagnosis of stroke. The study did not directly involve human subjects and so was exempt from institutional review board oversight.

Study Population

Patients with first-incident SHL (ICD-9-CM 388.2) diagnosed between January 1, 2002, and December 31, 2009, were identified from the LHID. For each member of the SHL cohort, we identified the most proximate visit for a vertigo-related diagnosis (ICD-9-CM 780.4 dizziness and giddiness, 386.x vertiginous syndromes, as used in prior works^{16,17}), if any. We defined our SHL with vertigo cohort as those with a vertigo event temporally proximate to the index SHL event (details in the next paragraph). We defined the SHL-alone cohort as those with either a nonproximate vertigo event or no vertigo event at all. We defined the vertigo-alone cohort as patients with a first-incident vertigo-related diagnosis (ICD-9-CM 780.4 or 386.x) and without an SHL diagnosis (ICD-9-CM 388.2) documented between January 1, 2002, and December 31, 2009. This is shown graphically in Figure 1, A.

We chose to analyze both wide and narrow windows for the temporal relationship between SHL and vertigo because the risk of a major stroke after a minor stroke or TIA varies dramatically over time after the index event; it begins very high (within the first week) and then declines to a base rate by 60-90 days.¹⁸ Because AICA TIAs may present either with SHL or vertigo, we presumed that the order of events (SHL followed by vertigo or the reverse) was not material. We conducted our primary analysis using a *wide window* (vertigo

event $\pm$ 30 days from the index SHL event), trying to encompass the full extent of the elevated short-term stroke risk period for major stroke after minor stroke and matching the window of association between SHL and an increased frequency of vertigo above baseline (“mountain” in Fig 1, B). We conducted a secondary analysis using a *narrow window* (vertigo event $\pm$ 3 days from the index SHL event) to capture the highest-risk period and matching the window of tight association between SHL and an increased frequency of vertigo above baseline (“peak” in Fig 1, B). We defined the *intermediate window* as the patient subgroup within the wide window but outside the narrow window (i.e., vertigo event $\pm$ 4–30 days, inclusive, from the index SHL event).

We were interested in new stroke risk, so we excluded patients with any visit diagnosis of stroke (ICD-9-CM 430–438) before the index visit (i.e., first-incident SHL [SHL with vertigo and SHL-alone cohorts] or vertigo [vertigo-alone cohort]). We also excluded patients with a diagnosis of “vertigo of central origin” (ICD-9-CM 386.2) because this could have been due to stroke.

Outcome Measures

Our primary outcome was first-incident hospitalizations for stroke (ICD-9-CM 430–438). Individuals in any of the 3 cohorts were followed up until stroke or until censored by death, withdrawal from the health insurance program, or the end of the database window for the study (December 30, 2012). We assessed for comorbid vascular risk factors, including hypertension (ICD-9-CM 401.x–405.x), diabetes mellitus (ICD-9-CM 250), dyslipidemia (ICD-9-CM 272.4), cardiovascular diseases (ICD-9-CM 410.x, 411.x, 412, 413, 413.9, 414, 414.0x, 414.8, and 414.9), and migraine (ICD-9-CM 346.x) to support additional analyses.

Statistics

For comparison of demographic data and comorbidities across cohorts, we used either a chi-square test (nominal variables) or 1-way analysis of variance (continuous variables). The long-term stroke incidence (at 1 and 3 years and at the last follow-up) was calculated for each cohort. We compared the stroke incidence across cohorts via pairwise comparisons (SHL with vertigo versus SHL alone and SHL with vertigo versus vertigo alone) using the Kaplan–Meier method and the log-rank test.^{19,20} We used a Cox proportional hazards model²¹ to estimate the hazard ratios of stroke across cohorts with and without adjusting for age, gender, hypertension, diabetes, dyslipidemia, cardiovascular diseases, migraine, urban status, and geographic area.

Results

In total, 218,656 patients were included in our study (Fig 1, A). During the follow-up period, 2342 died, 8457 were diagnosed with stroke, and 207,857 had follow-up data available from the final study year (2009). Among these were 2676 patients with SHL (25% [n = 678] SHL with vertigo [wide window] and 75% [n = 1998] SHL alone) and 215,980 with vertigo alone. Figure 1, B shows the temporal profile of vertigo visits in patients with SHL, which reveals a strong temporal association between the onset of SHL and vertigo that tapers off to a baseline level outside the $\pm$ 30-day window from the SHL index visit. Table 1 shows

demographic data and comorbidities. Age and vascular risk factors were greatest in the SHL with vertigo cohort, intermediate in the SHL cohort, and lowest in the vertigo cohort. The gender distribution varied substantially across groups with the female fraction ranging from 45% (SHL alone group) to 64% (vertigo alone group).

Table 2 reveals the long-term stroke incidence in each cohort. At the end of the study period, stroke was highest in the SHL with vertigo cohort (5.5% versus 3.0% SHL alone and 3.9% vertigo alone). For those with SHL, there appeared to be a “dose–response pattern” for proximity between the SHL and vertigo events—highest stroke rate in the narrow window (± 3 days [6.5% total]), intermediate in the intermediate window (± 4 –30 days [4.8% total]), and lowest outside the wide window ($\pm > 30$ days [3.5% total] and never vertigo [2.6% total]) (Table 2). Subgroup analyses based on the nature of the vestibular diagnosis rendered are in the online supplementary materials (Appendix e-1). In a subgroup analysis from the vertigo-alone cohort, the risk of stroke was slightly higher among patients diagnosed with Menière disease than among those given other vertigo-related diagnoses (appendix e-2).

Kaplan–Meier estimates showed that cumulative stroke incidence was significantly higher in the SHL with vertigo (wide window) cohort than in the SHL-alone (Fig 2, A) or the vertigo-alone cohort (Fig 2, B). Table 3 indicates the hazard ratios (HRs) across the 3 cohorts. The unadjusted hazard for stroke was higher in SHL with vertigo than in SHL alone (HR, 1.93; 95% confidence interval [CI], 1.28–2.91) or vertigo alone (HR, 1.63; 95% CI, 1.18–2.25). The HRs did not change significantly when adjusted for urban status and geographic area (adjusted HR: 1.94, 95% CI: 1.29–2.92 in SHL with vertigo versus SHL alone; adjusted HR: 1.61, 95% CI: 1.16–2.23 in SHL with vertigo versus vertigo alone). After adjusting for age, gender, urban status, geographic area, and cardiovascular risk, SHL with vertigo (wide window) remained a stroke hazard relative to SHL alone (adjusted HR, 1.75; 95% CI, 1.15–2.66) and vertigo alone (adjusted HR, 1.23; 95% CI, .89–1.70), but the latter finding was not statistically significant.

We repeated our hazard analyses using the narrow window definition of SHL with vertigo (vertigo ± 3 days from SHL) (Table 3). Among the 2676 patients with SHL, 10% ($n = 278$) had SHL with vertigo (narrow window) and 90% ($n = 2,398$) had SHL alone. Even after adjusting for age, gender, urban status, geographic area, and cardiovascular risk, the stroke hazard was higher in SHL with vertigo (narrow window) than in SHL alone (adjusted HR, 2.21; 95% CI, 1.31–3.72) and in vertigo alone (adjusted HR, 1.75; 95% CI, 1.10–2.78; Table 3).

Discussion

To our knowledge, this is the first population-based study investigating the impact of vertigo on stroke risk in patients with SHL. Our study shows that temporally proximate vertigo is an independent stroke risk factor among a large cohort of patients with SHL, and suggests that combined audiovestibular presentations (potentially separated in time by up to 30 days, in either order) may portend an even higher stroke risk than vertigo presentations alone. These findings may have important implications for the clinical diagnosis of vertigo and SHL presentations, as well as for future diagnostic and therapeutic research into these problems.

From a clinical standpoint, many physicians still consider acute hearing loss a feature of peripheral vertigo, and so may overlook the possibility of stroke when assessing patients with combined audiovestibular presentations. Even if SHL in vertigo presentations does often indicate an inner-ear lesion site, it appears neither to exclude a cerebrovascular cause nor portend a lower subsequent stroke risk, as shown here.^{4,5} Interestingly, in our subgroup analysis for the vertigo-alone cohort (online supplement), the subsequent risk of stroke was highest among patients diagnosed with Menière disease, perhaps indicating that patients with combined audiovestibular presentations due to stroke are more likely to be incorrectly diagnosed with Menière disease rather than other vestibular disorders that do not usually have associated hearing symptoms (e.g., benign paroxysmal positional vertigo or vestibular neuritis). This explanation would be consonant with recent evidence suggesting stroke misdiagnosis as “benign” vertigo is fairly frequent, and combined audiovestibular presentations of stroke may mimic Menière disease closely.^{1,22}

SHL has been attributed to various etiologies. The most common two may be viral infection and microvascular ischemic disease. Some experts favor viral infection as the main cause of SHL on the basis of viral polymerase chain reaction²³ and pathological findings.²⁴ However, other lines of evidence suggest a vascular etiology, including mechanisms (increase of prothrombin factors in patients with SHL²⁵) and an epidemiological association with stroke (history of stroke as a risk factor for SHL²⁶ and increased risk of stroke during 5-year follow-up [HR = 1.64]¹¹). Case reports and case series data suggest SHL can be a prodromal warning sign for a large-vessel disease (AICA infarction,²⁷ basilar artery occlusion,²⁸ or, rarely, even posterior inferior cerebellar artery [PICA] infarction²⁹). However, only 3% of AICA infarctions present initially with *isolated* SHL, compared with 60% with combined audiovestibular symptoms.⁹ Our present findings that stroke risk is lowest in the SHL-alone cohort are consistent with the possibility that SHL alone may be due to viral causes or microvascular ischemia, whereas SHL with a temporally proximate vertigo is probably more closely linked to stroke.

Research in the overlap between SHL and vertigo presentations is sparse. This finding has been attributed to a gap between groups of researchers in different specialty silos, some interested in hearing loss and the others interested in vertigo.¹⁵ Given our findings, which suggest SHL with vertigo might not have the same spectrum of causes as SHL alone, future SHL studies should carefully segregate those with vertigo from those without. Likewise, future prospective vertigo studies should seek to confirm whether SHL is a stroke predictor in unselected acute vertigo populations.

Our study has limitations. This is a retrospective study using administratively coded diagnoses from a national population-based database. We cannot independently verify diagnoses. There could be random or systematic errors in coding of which we are not aware. The lack of access to granular clinical data limits our ability to explore nuances of SHL and vertigo presentations, including exact temporal relationships. We cannot be sure, for instance, whether the date of diagnosis corresponds to the date of symptom onset for either SHL or vertigo. Our findings were partially explained by vascular risk factors (adjusted hazards for subsequent stroke were lower than unadjusted hazards, regardless of which time window was chosen for a “temporally proximate” vertigo). This finding is to be expected if

both SHL with vertigo and stroke are both caused by vascular risk factors; this colinearity, however, does not diminish the clinical relevance of taking caution when SHL and vertigo occur together.

Conclusions

The combination of SHL with vertigo is associated with increased subsequent stroke risk over SHL alone and vertigo alone, with this difference only partially explained by age and vascular risk factors. This finding suggests that SHL in patients with vertigo is not necessarily a benign peripheral vestibular sign, as traditionally suggested. If these associations can be confirmed in prospective studies, they have important clinical implications. Clinicians should be aware of the possibility that combined audiovestibular presentations (even if they are separated in time by up to a month, but especially if they occur within a week of each other) may portend stroke and should consider the possibility of AICA-territory ischemia. An incorrect diagnosis of Menière disease may be a clinical pitfall among such patients. Future studies should seek to prospectively assess the predictive value of hearing loss as a bedside predictor of stroke in patients with acute vertigo. Future studies of SHL should consider that clinical populations of “SHL with vertigo” and “SHL alone” may be etiologically distinct.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: Supplementary Material

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2017.09.033.

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Figure 1.

Study population derivation (clinical subgroups and temporal relationship between SHL and vertigo). (A) Venn diagram showing the study populations for the primary analysis (wide window definition [± 30 days] for “SHL with vertigo”). Note that the Venn diagram areas are not precisely proportional to the study populations. (B) Histogram (rendered as a line graph) of the SHL population arranged by time between SHL and vertigo events in days. Positive numbers reflect SHL followed by vertigo and negative numbers, the reverse. Case numbers were highest when the interval between SHL and vertigo diagnosis was ± 1 day, and precipitously declined within ± 3 days, leveling out by ± 30 days. This pattern suggests that SHL and vertigo, when they co-occur, tend to cluster together as related events, rather than random, unassociated events. This graph does not distinguish between those with peripheral and central vestibular disorders. Abbreviation: SHL, sudden hearing loss.

Figure 2.

Stroke-free survival using Kaplan–Meier analysis. (A) Kaplan–Meier curve showing stroke-free survival for SHL with vertigo and SHL alone. Case numbers of noncensored observations are listed above the x -axis. There is a statistically significant difference in stroke-free survival, lower among those with SHL with vertigo (log-rank test: $P = .001$). (B) Kaplan–Meier curve showing stroke-free survival for SHL with vertigo and vertigo alone. Case numbers of noncensored observations are listed above the x -axis. There is a statistically significant difference in stroke-free survival, lower among those with SHL with vertigo (log-rank test: $P = .003$). Abbreviation: SHL, sudden hearing loss.

Table 1

Population demographic data and comorbidities using the “wide window” definition for SHL with vertigo (± 30 days)

Characteristics	SHL with vertigo	SHL alone	Vertigo alone	<i>P</i>
Patient number, n	678	1,998	215,980	
Onset age, mean $\pm$ SD	53 $\pm$ 16	48 $\pm$ 18	46 $\pm$ 19	<.001
Female (%)	377 (55.6)	907 (45.3)	138,339 (64.1)	<.001
Comorbidities				
Hypertension (%)	144 (21.2)	320 (16.0)	30,915 (14.3)	<.001
Diabetes mellitus (%)	75 (11.0)	202 (10.1)	12,788 (5.9)	<.001
Hyperlipidemia (%)	4 (.6)	13 (.7)	485 (.2)	<.001
Cardiovascular disease (%)	41 (6.0)	99 (5.0)	8,302 (3.8)	<.001
Migraine (%)	3 (.4)	9 (.5)	1,193 (.6)	.77
Urbanization				
Urban	217 (32.0)	618 (30.9)	59,841 (27.7)	<.001
Nonurban	461 (68.0)	1,380 (69.1)	156,139 (72.3)	<.001
Geographic area				
Northern Taiwan	471 (69.5)	1,363 (68.2)	136,925 (63.4)	<.001
Southern Taiwan	207 (30.5)	635 (31.8)	79,055 (36.6)	<.001

Abbreviations: SD, standard deviation; SHL, sudden hearing loss.

Table 2

Stroke incidence at 1 and 3 years and at study end by study population

Groups	Case number, N	Stroke at 1 y, n (%)	Stroke at 3 y, n (%)	Stroke at study end, n (%)
SHL with vertigo (± 30 d) (wide window)	678	10 (1.5)	16 (2.4)	37 (5.5)
SHL with vertigo (± 3 d) (narrow window)	278	6 (2.2)	10 (3.6)	18 (6.5)
SHL with vertigo (4-30 d) (intermediate window)	400	4 (1.0)	6 (1.5)	19 (4.8)
SHL alone	1,998	11 (.6)	23 (1.2)	59 (3.0)
Vertigo remote from SHL (>30 d) *	870	5 (.6)	11 (1.3)	30 (3.5)
No vertigo at all †	1,128	6 (.5)	12 (1.1)	29 (2.6)
Vertigo alone ‡	215,980	1,763 (.8)	3,557 (1.7)	8,361 (3.9)

Abbreviation: SHL, sudden hearing loss.

* These patients with SHL had a vertigo-related diagnosis that was temporally remote (beyond ± 30 days) from the SHL diagnosis; the index date was the SHL diagnosis date.

† These patients with SHL did not have any vertigo-related diagnosis during the study period.

‡ These patients with vertigo did not have an SHL diagnosis during the study period.

Table 3

Hazard ratios and adjusted hazard ratios for stroke across study populations, using 2 different definitions (wide and narrow) for SHL with vertigo

Groups	HR	95% CI	aHR*	95% CI
SHL with vertigo (wide window definition, vertigo ± 30 d from SHL)				
SHL with vertigo versus SHL alone	1.93	1.28-2.91	1.75	1.15-2.66
SHL with vertigo versus vertigo alone	1.63	1.18-2.25	1.23	.89-1.70
SHL with vertigo (narrow window definition, vertigo ± 3 d from SHL) [†]				
SHL with vertigo versus SHL alone	2.16	1.30-3.61	2.21	1.31-3.72
SHL with vertigo versus vertigo alone	2.01	1.27-3.10	1.75	1.10-2.78

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, unadjusted hazard ratio; SHL, sudden hearing loss.

* Adjusted hazard ratio adjusted for age, gender, urban status, geographic area, hypertension, diabetes, hyperlipidemia, cardiovascular diseases, and migraine.

[†] Note that the narrow window definition for “SHL with vertigo” also affects the “SHL alone” population definition. Thus, the union of the SHL with vertigo and SHL-alone populations is always equal to the total study SHL population (N = 2676), regardless of whether the wide window or the narrow window is being used to define SHL with vertigo.