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MISCELLANEOUS

Age-related hearing loss and dementia: a 10-year national population-based study

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Abstract Age-related hearing loss (ARHL) is postulated to affect dementia. Our study aims to investigate the relationship between ARHL and the prevalence, and 10-year incidence of dementia in the Taiwan National Health Insurance Research Database (NHIRD). We selected patients diagnosed with ARHL from the NHIRD. A comparison cohort comprising of patients without ARHL was frequency-matched by age, sex, and co-morbidities, and the occurrence of dementia was evaluated in both cohorts. The ARHL cohort consisted of 4108 patients with ARHL and the control cohort consisted of 4013 frequency-matched patients without ARHL. The incidence of dementia [hazard ratio (HR), 1.30; 95% confidence interval (CI 1.14–1.49); $P=0.002$] was higher among ARHL patients. Cox models showed that being female (HR, 1.34; 95% CI 1.07–1.68), as well as having co-morbidities, including chronic liver disease and cirrhosis, rheumatoid arthritis, hypertension, diabetes mellitus, stroke, head injury, chronic kidney disease, coronary artery disease, alcohol abuse/dependence, and tobacco abuse/dependence (HR, 1.27; 95% CI 1.11–1.45), were independent risk factors for dementia in ARHL patients. We found ARHL may be one of the early characteristics of dementia, and patients with hearing loss were at a higher risk of subsequent dementia. Clinicians should be more sensitive to dementia symptoms within the first 2 years following ARHL diagnosis. Further clinical studies of the relationship between dementia and ARHL may be necessary.

Keywords Presbycusis · Age-related hearing loss · Dementia · NHIRD · Sensory hearing loss

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Introduction

Hearing loss is common in older adults, but the relationship between dementia and age-related hearing loss (ARHL) is unclear. Deficits in peripheral hearing and central auditory processing can be attributed to ARHL [1, 2]. The prevalence of hearing loss increases with patient age; approximately 1 in 3 people over 65 years of age have disabling hearing loss (http://data.worldbank.org/). Dementia is one of the most common health problems among older adults. The World Alzheimer Report estimated that 35.6 million people were living with dementia worldwide in 2010, and that this figure may reach 65.7 million by 2030, and 115.4 million by 2050 [3]. Notably, central auditory dysfunction is prevalent in Alzheimer dementia, but the mechanism has not been established [4, 5]. Several population-based studies have determined the association of hearing loss and cognitive decline [4–6]. Previous studies even proved some conflicting results of gene influence in dementia and hearing loss [7, 8]. However, a statistically significant relationship between dementia and ARHL was reported in some published cross-sectional studies [9–12] and several supportive longitudinal studies [13–16] while some only focus on central auditory dysfunction [17]. More focused research is needed to understand the mechanism and association between ARHL and dementia. To our knowledge, no large-scale nationwide population-based longitudinal study has ever investigated this association.

Alzheimer's disease (AD) is the most common subtype of dementia. The increasing prevalence of AD is a serious public health problem [3]. Early diagnosis of dementia or AD enables the progression of the disease to be managed. Nonetheless, because of the insidious onset of AD, it is difficult to differentiate between normal aging-related cognitive decline and the pathologic dysfunction of the early stages of AD. We hypothesized that ARHL is an early sign of dementia and could be used as a marker for early diagnosis.

In this 10-year nationwide population-based cohort study, we explored the relationship between ARHL and the incidence of dementia in Taiwan by comparing patients with and without ARHL.

Methods

Data source

The National Health Insurance (NHI) program, established in 1995, is a mandatory, state-run health insurance program that provides comprehensive medical care coverage for outpatient, inpatient, emergency, and traditional Chinese medicine treatments to all residents of Taiwan (23.72 million people). The coverage rate is more than 99% (http://www.nhi.gov.tw/english/index.aspx). The National Health Research Institutes (NHRI) is responsible for managing all reimbursement claim data in the National Health Insurance Research Database (NHIRD); patient confidentiality is maintained in accordance with the directives of the National Health Insurance Administration. To protect the privacy of all insures, the NHRI anonymizes the identification numbers of all NHIRD records. Data for this population-based retrospective study were taken from the 2000 Longitudinal Health Insurance Database (LHID2000), which is a subset of the NHIRD. The LHID2000 contains claims data of 1 million people randomly selected from the 2000 Registry of Beneficiaries. All clinical diagnoses were recorded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Sampled participants

We collected data on patients who had at least three diagnoses of ARHL (ICD-9-CM codes 389.10–389.12 and 388.01) within 4 months during the period of 2010–2012 for the ARHL cohort. The dates of ARHL diagnosis were used as the index date. Patients who had a history of dementia (ICD-9-CM codes 290, 294.1 and 331.0–331.2) before the index date, were younger than 50 years of age, had other types of hearing loss(388.2, 389.0, 389.2), sudden hearing loss, conductive hearing loss, mixed conductive and sensorineural hearing loss or had incomplete age or gender information were excluded. Moreover, dementia patients were only enrolled with at least 3 times dementia diagnosis within 4 months and confirmed by psychiatrist. Control patients without dementia or ARHL at the baseline were randomly selected from the LHID2000 and frequency-matched with each dementia case by age (every 5-year span), gender, and year of dementia diagnosis. The controls were subject to the same exclusion criteria as the ARHL group.

Outcome and comorbidities

All patients were followed until they were diagnosed with dementia, were censored for failure to follow-up, withdrew from the NHI, or until December 31, 2011. The comorbidities examined for were the following: chronic liver disease and cirrhosis (CLD; ICD-9-CM code 571), rheumatoid arthritis (RA; ICD-9-CM code 714), hypertension (HTN; ICD-9-CM codes 401–405), diabetes mellitus (DM; ICD-9-CM code 250), stroke (ICD-9-CM codes 430–438), head injury (ICD-9-CM codes 850–854), chronic kidney disease (CKD; ICD-9-CM code 585), coronary artery disease (CAD; ICD-9-CM codes 410–414), alcohol abuse/dependence (ICD-9-CM codes 305.0 and 303), tobacco

abuse/dependence (ICD-9-CM codes 305.1), and chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 490–492, 494, and 496). All comorbidities were defined before the index date. To increase the credibility of dementia diagnosis, only those patients with at least 3 times of dementia diagnosed in psychiatric clinics within 4 months were enrolled in our data.

Data availability statement

All data and related metadata were deposited in an appropriate public repository. The data from the NHIRD on the study population (http://w3.nhri.org.tw/nhird//date_01.html) were maintained in the NHIRD (http://nhird.nhri.org.tw/). The NHRI is a nonprofit foundation established by the government of Taiwan.

Statistical analysis

We tested the categorical variables of the ARHL cohort, and control cohort by performing Pearson's chi-squared test and 2-sample *t* tests to test continuous variables such as age distribution. We calculated the incidence density rate of dementia (person-years) for each subgroup and conducted univariate and multivariate Cox proportional hazard regression analyses to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of dementia. The multivariate models were adjusted for age, gender, and comorbidities (see subsection 2.3). We used the Kaplan–Meier method to assess the cumulative incidence of dementia between the two cohorts, and the log-rank test to test the differences.

Results

We enrolled 4108 ARHL patients and 4013 controls. Frequency matching ensured that age and sex distribution was similar in both groups. The prevalence of dementia, CLD, RA, HTN, DM, stroke, head injury, and CKD was higher in the ARHL cohort than in the control cohort (Table 1).

Table 2 lists the incidences and HRs for dementia and related risk factors. Risk of dementia increased with age [range of adjusted HR (aHR) = 1.00–7.00]. Compared with the control cohort, the risk of dementia was significantly higher in the ARHL cohort (aHR = 1.30, 95% CI 1.14–1.49). Patients with comorbidities exhibited a 3.57-fold higher risk of developing dementia compared with patients without comorbidities (95% CI 2.18–5.87). ARHL remained independently associated with dementia after adjustment for multiple dementia risk factors, including age, sex, and comorbidities (Table 2). Our results also revealed that female patients with ARHL were at higher risk of dementia than were male patients (aHR = 1.17, 95% CI 1.01–1.34).

The overall incidence rate of dementia was approximately 1.33 per 100 person-years for the control group and 1.76 per 100 person-years for the ARHL group (Table 3). In the multivariate analysis, age was treated as a continuous variable. We found that the risk of

Table 1 Characteristics of patients between patients with ARHL and control group

	Control ($n=4013$)		ARHL patients ($n=4108$)		p
Age (mean ± SD)	68.64 ± 10.26		68.96 ± 10.31		0.157
Age stage					0.461
<65	1476	36.8%	1469	35.8%	
65–74	1198	29.9%	1217	29.6%	
≥75	1339	33.4%	1422	34.6%	
Male	2443	60.9%	2507	61.0%	0.908
Dementia	386	9.6%	483	11.8%	0.002
Co-morbidities					
Chronic liver disease and cirrhosis, CLD	1426	35.5%	1787	43.5%	<0.001
Rheumatoid arthritis, RA	303	7.6%	389	9.5%	0.002
Hypertension, HTN	2931	73.0%	3188	77.6%	<0.001
Diabetes mellitus, DM	1634	40.7%	1853	45.1%	<0.001
Stroke	1399	34.9%	1781	43.4%	<0.001
Head injury	504	12.6%	774	18.8%	<0.001
Chronic kidney disease, CKD	425	10.6%	519	12.6%	0.005
Coronary artery disease, CAD	56	1.4%	77	1.9%	0.107
Alcohol abuse	31	0.8%	40	1.0%	0.393
Tobacco abuse	86	2.1%	106	2.6%	0.221

Table 2 Incidence and hazard ratio for dementia and related risk factor

	Event	PY	Rate	IRR	Adj. HR	(95% CI)
Age (year)						
<65	82	20446.59	0.40	1.00	1.00	
65–74	255	17496.46	1.46	3.59	3.43	(2.67–4.40)
≥75	532	18540.14	2.87	7.21	7.00	(5.54–8.85)
ARHL						
Control	386	29050.08	1.33	1.00	1.00	
ARHL	483	27433.10	1.76	1.35	1.30	(1.14–1.49)
Gender						
M	561	35373.73	1.59	1.00	1.00	
F	308	21109.45	1.46	0.93	1.17	(1.01–1.34)
Co-morbidities						
N	16	4961.66	0.32	1.00	1.00	
Y	853	51521.53	1.66	5.02	3.57	(2.18–5.87)

Rate incidence rate, per 100 person-years, *IRR*, relative hazard ratio, *Adj. HR* adjusted hazard ratio multivariable analysis including age, gender, ARHL, and co-morbidities; *Co-morbidity* patients with any one of the comorbidities (including CLD, RA, HT, DM, stroke, head injury, CKD, CAD, Alcohol abuse and tobacco abuse) were classified as the co-morbidity group

Table 3 Incidence and hazard ratio of dementia between patients with ARHL and control group

	Control			ARHL			IRR	Adj. HR	(95% CI)
	Event	PY	Rate	Event	PY	Rate			
All	386	29050.08	1.33	483	27433.10	1.76	1.35	1.29	(1.13–1.48)
Age (year)									
<65	30	10675.04	0.28	52	9771.55	0.53	2.00	1.96	(1.25–3.08)
65–74	113	8988.71	1.26	142	8507.75	1.67	1.36	1.33	(1.04–1.70)
≥75	243	9386.33	2.59	289	9153.80	3.16	1.24	1.20	(1.01–1.42)
Gender									
M	249	18135.09	1.37	312	17238.65	1.81	1.34	1.26	(1.07–1.49)
F	137	10915.00	1.26	171	10194.46	1.68	1.38	1.34	(1.07–1.68)
Co-morbidities									
N	6	3214.18	0.19	10	1747.48	0.57	3.21	3.18	(1.15–8.81)
Y	380	25835.90	1.47	473	25685.63	1.84	1.28	1.27	(1.11–1.45)

PY person-years, *Rate* incidence rate per 100 person-years, *IRR* relative hazard ratio, *Adjusted HR* hazard ratio adjusted for age, and comorbidities, *Co-morbidity* patients with any one of the comorbidities (including CLD, RA, HTN, DM, stroke, head injury, CKD, CAD, Alcohol abuse and tobacco abuse) were classified as the co-morbidity group

dementia was significantly higher in the ARHL cohort (adjusted HR = 1.29, 95% CI 1.13–1.48). The incidence rate of dementia increased with age. In the stratifications by sex and comorbidities, the risk of developing dementia was always higher in the ARHL cohort.

Figure 1 illustrates the Kaplan–Meier analysis results. The cumulative incidence curves for dementia were significantly higher in the ARHL cohort than in the control cohort (log-rank test $P < 0.001$).

Discussion

This study is considered the first nationwide population-based study using a matched cohort with a 10-year follow-up period to examine ARHL as a risk factor for dementia. The major discovery of our study was a higher incidence of subsequent dementia among the patients with ARHL, while oppositely in the first 2.5 years after diagnosis than among the patients with ARHL. In addition, we suggest

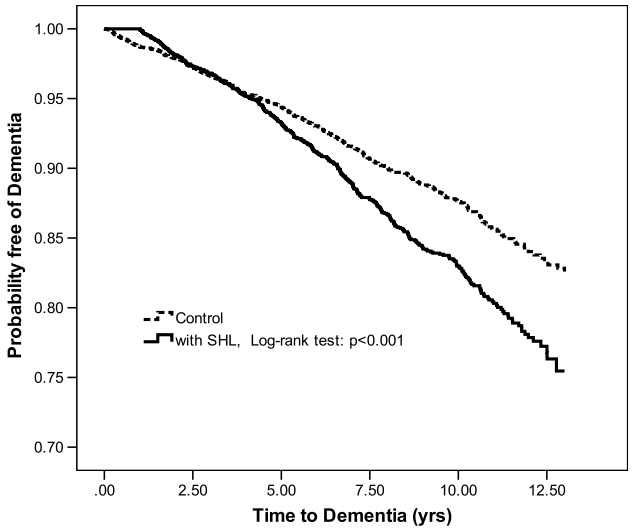

Fig. 1 Cumulative incidence of ARHL compared between patients with and without dementia

that hearing impairments in older adults should be used as a marker for the early diagnosis of cognitive disorders such as dementia.

In a previous study, the incidence of dementia was found to double with every 5.9-year increase in age, from 3.1 per 1000 person-years at age 60–64 years to 175.0 per 1000 person-years at age >95 years [18]. An epidemiological study reported that women have higher rates of AD than men do [19]. Age, as well as diabetes, smoking, and cardiovascular disease are also known risk factors [20]. A longer-term cohort study found raised cholesterol and hypertension in midlife to be related to the onset of AD in later life [21]. In our study, female patients were at higher risk of developing dementia regardless of hearing loss, and comorbidities, such as CLD, RA, HTN, DM, stroke, head injury, and CKD, were potential risk factors for dementia in the ARHL group, but not in the control group (Table 1).

In the older population, hearing loss contributes relatively less to dementia than did well-known risk factors such as comorbidities and unmodifiable factors such as age (Table 2). However, the effect of hearing impairment on people with dementia is likely to be substantial combined with the frequency of other sensory impairments. Visual impairment has been shown to be associated with AD [6, 22]. The combined effect of visual and hearing impairments could have a severe debilitating effect on functional status.

Previous longitudinal studies have also shown a relationship between dementia and hearing loss. Peters et al. [15] found that, in patients with dementia, the decline in cognitive function was greater for those with impaired hearing. Further analyzing the diagnoses revealed that only in subjects with AD could hearing impairment be used to predict more rapid cognitive decline at follow-up [15]. In another longitudinal study, 836 older adults with hearing loss manifested an increased rate of dementia and more rapid decline on the mini-mental state examination scores than their non-hearing impaired counterparts [13]. Another investigation also revealed a clinically significant relationship between central auditory function and cognition test scores [5]. Hearing loss in older adults was found to be independently associated with poorer cognitive function, incident dementia, and falls. These findings suggest that hearing impairment may be an indicator for declined cognitive function in adults aged 65 years and older.

ARHL affects most people aged 65 years and older and represents the predominant neurodegenerative disease of aging. According to the World Health Organization, 278 million people worldwide experience moderate-to-profound hearing loss bilaterally (WHO 2010). There are currently 360 million people with disabling hearing loss (5.3% of the world's population), and 91% of them are adults (http://data.worldbank.org/). Disabling hearing loss is currently defined as a loss of hearing greater than 40 dB HL (0.5–4 kHz) in the better-hearing ear. The following findings were drawn from a representative sample of older people in the Blue Mountains Hearing Study [23]: (1) According to four-frequency pure tone audiometry (PTA) testing, 39% of adults aged 55 or older have hearing loss; (2) the frequency of hearing loss almost doubles every 10 years of age among older adults, increasing from 10.5% in those aged under 60 years to approximately 80% in those aged 80 or older; and (3) Hearing loss occurs more frequently in men. Most people with hearing loss do not seek help. Risk factors for hearing loss include age, sex (male), DM, noise-exposure history, smoking, and impaired vision. In a cross-sectional study, a history of falls, HTN, broken hips, and heart disease were common among both hearing and visual impairment groups [24]. Age has the highest association with declining hearing loss [25]. Men decline as early as at the age of 30, while in women it occurs somewhat later [26]. Hearing levels differ between the sexes, with men having significantly poorer hearing at higher frequencies than women do [27].

Our results in Table 1 demonstrate that age, sex (male), DM, HTN, CLD, and stroke are risk factors for ARHL, whereas smoking (though higher in the ARHL group) is not a significant risk factor. Although one cross-sectional study found cardiovascular disease to be significantly related with the hearing status of older adults, the significance was stronger among women and for low frequencies [28]. Low-frequency presbycusis is typically associated with microvascular disease leading to atrophy of the stria vascularis [29]. Endothelial dysfunction and cardiovascular risk factors were reported highly related to sensory hearing loss [30].

The strengths of our study stem from the representative population-based cohort and large data sets. In the current longitudinal analysis, we found that ARHL may be used to predict the incidence of dementia in this population (Fig. 1). Our results revealed that, compared with the risk of patients without hearing loss, the patients diagnosed with hearing loss had, in the first 2.5 years after diagnosis, a significantly lower chance of dementia. This effect is probably related to delayed diagnosis of dementia in ARHL patients, and not to a lower risk of developing dementia. These findings have not been previously reported, which suggests that patients in the early stages of dementia may be ignored, neglected, or confused after hearing loss was noted in advance. Early signs of dementia, such as memory impairment, slow reaction time, and mild cognitive dysfunction, may be mistaken as a consequence of ARHL in outpatient clinic. Obvious symptoms of dementia as the illness progresses are easier to identify and diagnose. Our findings must be interpreted with caution because the small sample of patients with dementia at follow-up limited the statistical power of our results. In addition, because we used a survivor cohort, there could have been an underestimation of the number of new cases with impaired hearing.

We hypothesized that the processes of dementia and hearing loss are closely related; age-related changes in circulating levels of glucocorticoid and the hypothalamus–pituitary–adrenal (HPA) axis could act in combination with the processes underlying ARHL, thus resulting in the further worsening of dementia. In particular, hippocampal damage may cause HPA axis disturbances, which have been reported in patients with dementia [31, 32]. Furthermore, dementia has been associated with chronic neuroinflammation [33–35]. Neuroinflammation induces glucocorticoid resistance [36, 37]. Notably, HPA and glucocorticoid resistance have been associated with sensorineural hearing loss [38, 39]. Thus, ARHL may increase the risk of dementia by disturbing the HPA axis and glucocorticoid resistance. We found that age was the most crucial risk factor for dementia (Table 2), followed by comorbidities, hearing loss, and gender.

However, the relatively small number of patients in the matched 10-year follow-up cohort presented a limitation. Therefore, changes in dementia over time could have been underestimated due to the lack of statistical power. Another limitation was that our study was a longitudinal study with diagnoses collected only from the NHIRD, risking potential bias resulting from differing diagnosis standards among individual clinicians. We identified patients with hearing loss in the NHIRD according to ICD-9-CM codes and pure tone audiometry (PTA) results were not available in NHIRD. Thus, the actual severity of hearing loss as a risk factor for subsequent dementia was not explored. An additional limitation was the lack of other demographic variables such as socioeconomic status, years of education, mood status, living arrangement, occupation, noise-exposure history, lifestyle, and family medical history, which could have provided useful information regarding other potential risk factors for hearing loss and dementia. Diagnosis of dementia has been known a big challenge for clinicians due to some unspecified symtpoms and different etioloigies. The disease is usually finally confirmed in specialist clinics. Since Data like MMSE and CDR are not available in NHIRD. In our study, we therefore narrowed the group and only selected dementia patient (ICD-9-CM codes 290, 294.1 and 331.0–331.2) with at least 3 times within 4 months and diagnosed by psychiatrists. Finally, this study used an observational design rather than an experimental one. Data on the relationship between the severity of dementia and severity (and frequency range) of hearing loss were unavailable.

Conclusion

Current recommendations for patients with ARHL include regular exams to monitor changes in PTA. As our study indicates, evidence of a possible link between ARHL and dementia exists. Physicians should be more alert of early signs of dementia which may be mistaken as a sequence for ARHL following the first 2 years of diagnosis and pay more attention to those constituing the group of high-risk dementia. These findings can potentially be used to modify the treatment of patients suffering from ARHL, especially in the first 2 years following diagnosis. Clinicians may inquire about cognitive function during preventive care protocol and could refer patients to a cognitive specialist for further evaluation and maintain their cognitive ability if a cognitive decline is reported.

Compliance with ethical standards

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Conflict of interest Every author declares that he/she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. The NHIRD contains only encrypted patient information; it provides anonymous identification numbers and corresponding claims information, including gender, date of birth, administered medical services, and prescriptions given. Patient consent is not required to access the data stored in NHIRD. This study was approved by the Institutional Review Board (IRB) of China Medical University Hospital (CMUH104-REC2-115). The IRB waived the consent requirement.

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