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Short communication

Depression and cholesteatoma: Preliminary findings from a nationwide population-based retrospective cohort study

Chin-Lung Kuo [a,d,e,f,g,h], Nancy HsaoYen Chang [c], An-Suey Shiao [d,e], Chiang-Feng Lien [d,e], Hsiao-Ling Huang [b], Szu-Hai Lin [b], Wei-Pin Chang [i,*]

[a] Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan, ROC
[b] Department of Health Care Administration, Taipei Medical University, 250 Wu-Hsing Street, Taipei, Taiwan
[c] University of Texas at Austin, Austin, TX, USA
[d] Department of Otolaryngology-Head and Neck Surgery, Taipei Veterans General Hospital, Taipei, Taiwan, ROC
[e] Department of Otolaryngology, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC
[f] Department of Otolaryngology, HsinChu Armed Forces General Hospital, HsinChu, Taiwan, ROC
[g] Department of Otolaryngology, Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan, ROC
[h] Department of Otolaryngology-Head and Neck Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
[i] School of Health Care Administration, Taipei Medical University, Taipei City, Taiwan, ROC

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ABSTRACT

Objective: To estimate the risk of developing depressive disorder (DD) following diagnosis with cholesteatoma.
Methods: In the study, we analyzed data from the Longitudinal Health Insurance Database of Taiwan. A total of 599 patients newly diagnosed with cholesteatoma between 1997 and 2007 were included with a comparison cohort of 2995 matched non-cholesteatoma enrollees. Each patient was followed for 3 years to identify the subsequent development of DD. Cox proportional hazard regression analysis was performed to compute adjusted 3-year hazard ratios.
Results: The incidence of DD per thousand person-years was approximately twice as high among patients with cholesteatoma (11.32) as among those without cholesteatoma (5.85). After adjusting for potential confounders, patients with cholesteatoma were 1.99 times (95% CI=1.18–3.34, P=0.010) more likely to suffer from DD within 3 years compared to those without cholesteatoma.
Conclusions: This is the first study to demonstrate a link between cholesteatoma and subsequent DD within a three-year followup. We suggest that clinicians keep this critical but neglected issue in mind and carefully investigate the possibility of subsequent psychological problems among cholesteatoma patients.
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1. Introduction

Cholesteatoma is a histologically benign but behaviorally malignant lesion which develops from an abnormal growth of keratinizing squamous epithelium in the temporal bone (Kuo, 2015). Patients with cholesteatoma are susceptible to frequent recurrence of foul-smelling otorrhea, hearing impairment, and tinnitus (Kuo et al., 2015a). It is reasonable to assume that the psychological burden associated with cholesteatoma could cause a patient to become socially withdrawn and potentially lead to the development of depressive disorder (DD).

Nevertheless, the relationship between cholesteatoma and depression remains unclear. Hence, we sought evidence to support our hypothesis that patients with cholesteatoma may face an elevated risk of developing DD.

2. Methods

2.1. Data source

The Institutional Review Board of Taipei Veterans General Hospital exempted this study from review because it used existing, de-identified public use data (VGHIRB no. 2015-04-002AC). The National Health Insurance (NHI) program was implemented in 1995 and currently covers 99% of the Taiwanese population. Claims data are maintained in the National Health Insurance Research Database (NHIRD), which is managed and audited by the National Health Research Institutes (NHRI). The NHIRD includes data related to demographics, clinical visits, diagnostic codes,

* Corresponding author.
E-mail address: wpchcang@gmail.com (W.-P. Chang).

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prescriptions, and expenditures. To validate the completeness and accuracy of the claims data, the NHRI conducts random patient interviews, annually reviews medical records, and employs random sampling of claims from every hospital. This retrospective study used a subset of the NHIRD, the Longitudinal Health Insurance Database (LHID2005), which enables researchers to follow-up on all medical service utilization by 1 million enrollees randomly selected from the NHIRD in 2005. In the LHID 2005, the 359 towns/cities in Taiwan are stratified into 8 urbanization categories according to criteria established by the NHRI, with 1 indicating the highest level of urbanization and 8 indicating the lowest. The number of cholesteatoma cases in levels 4, 5, 6, 7, and 8 were low; therefore, these levels were combined into a single urbanization group, level 4. In the study, we examined ambulatory and inpatient care data for patients in the LHID2005 from 1997 to 2007.

2.2. Participants

A study group and a comparison group were assembled for a retrospective cohort examination of the relationship between cholesteatoma and depression. Patients newly diagnosed with cholesteatoma between January 1, 1997 and December 31, 2007 were identified according to diagnostic criteria from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM code 385.3, 385.30, 385.31, 385.32, 385.33). The date of the first cholesteatoma surgery was assigned as the index date for each patient in the study. To ensure the accuracy of data, only patients who have undergone surgery to treat the disorder were included. We adopted the surgical procedures in the recruitment of cholesteatoma patients (surgical procedure code 84018B, 84019B, 84021B, 84022B, 84033B, and 84034B). Five patients without cholesteatoma were randomly matched to each patient in the cholesteatoma cohort based on age, sex, and index year. Patients with a history of depression (A-Codes A212, A214, and A219 before year 2000; ICD-9 CM codes 296.2, 296.3, 300.4, and 311 after year 2000) were excluded from this study. The criteria used for depressive disorders (ICD-9 CM codes 296.2, 296.3, 300.4, and 311) were consistent with those applied in several population-based studies published in peer reviewed journals (Chang et al., 2009; Chen et al., 2013a; Chen and Lin, 2011; Chung et al., 2011; Huang et al., 2011). To enhance the precision of inclusion criteria related to depressive disorders, we only considered patients whose depressive disorder had been diagnosed by a psychiatrist; and patients with ≥ 2 ambulatory visits or ≥ 1 inpatient visits for depressive disorder. In addition to ICD-9 CM codes, furthermore, the revised inclusion criteria for depression also includes A-Codes (A212, A214, and A219) before year 2000. We determined the number of patients who had been assigned A-Codes or ICD-9 CM codes for depression after being diagnosed with cholesteatoma.

2.3. Statistical analysis

DD-free survival was calculated for all patients diagnosed with depression between the date of the first hospitalization or ambulatory visit for cholesteatoma and the end of the study period (December 31, 2010) or death, whichever came first. We calculated the three-year DD-free survival rates using the Kaplan–Meier method. We also applied the log-rank test to examine differences in DD-free survival rates between cohorts. Cox proportional-hazard regression analysis stratified by follow-up period and relative confounders was used to examine the risk of DD in cholesteatoma and comparison cohorts during the 3-year follow-up period. Current evidence suggests that, compared to the general population, depression is more prevalent among patients with chronic medical conditions, such as hypertension (Kretchy et al., 2014), hyperlipidemia (Chuang et al., 2014), diabetes (DeJean et al., 2013), and obesity (Luppino et al., 2010). We included these potential confounders in the Cox proportional-hazard regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to represent the risk of depression in the cohorts before and after stratification based on follow-up period. Comparison results had to have a 2-sided P value of <0.05 to be considered statistically significant.

3. Results

A total of 599 and 2995 patients were included in the cholesteatoma and comparison cohorts, respectively. Cholesteatoma patients presented a lower rate of hypertension ($P=0.024$) than did the comparison cohort. No statistically significant differences in hyperlipidemia ($P=0.698$), diabetes ($P=0.425$) or obesity ($P=0.957$) were observed.

During the 3-year follow-up, 20 (3.3%) of the cholesteatoma patients and 52 (1.7%) of the patients in the comparison group developed DD (Table 1). Cox regression analysis revealed that the crude HR of DD was 1.94 times higher (95% CI = 1.16–3.25; $P<0.05$) among cholesteatoma patients than among the comparison cohort. The risk of DD remained significant even after adjusting for potential confounders (adjusted HR: 1.99, 95% CI: 1.18–3.34; $P<0.05$), and cholesteatoma patients presented a significantly lower 3-year DD-free survival rate ($P=0.010$; Fig. 1).

4. Discussion

4.1. Potential biological mechanisms

Some plausible biological and psychosocial factors could play a role in the underlying mechanisms linking depression to cholesteatoma. First, cholesteatoma can have profound and far-reaching consequences for daily life, such as the frequent occurrence of foul-smelling otorrhea, hearing loss, tinnitus, vertigo, and even the possibility of facial paralysis or intracranial fatal complications (Kuo et al., 2014a). Patients who are not candidates for surgery require frequent visits to the clinic for ear cleaning, which can be highly inconvenient, particularly for busy patients and those who live in rural or remote areas (Kuo et al., 2015b). Patients with

Table 1
Hazard ratios (HRs) of depressive disorders among cholesteatoma patients during the 3-year follow-up period from the index ambulatory visits or inpatient care from 1997 to 2007.

Development of Depressive disorders	Total		Patients with cholesteatoma		Patients without cholesteatoma	
	NO.	(%)	NO.	(%)	NO.	(%)
3-year follow-up period						
Yes	72	2.0	20	3.3	52	1.7
No	3522	98.0	579	96.7	2943	98.3
Crude HR (95% CI)				1.94 (1.16 – 3.25)*	1	
Adjusted HR (95% CI)				1.99 (1.18 – 3.34)*	1	

Total sample number = 3594; both crude and adjusted HRs were calculated by Cox proportional hazard regressions, and stratified by age and sex.
Adjustments were made for urbanization level, geographic region, and hypertension.
* Indicates $p<0.05$.

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