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Age-Related Macular Degeneration and Risk of Degenerative Dementia among the Elderly in Taiwan

A Population-Based Cohort Study

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Purpose: To investigate the relationship between age-related macular degeneration (AMD) and future development of Alzheimer's disease (AD) or senile dementia.

Design: A longitudinal case-control study using the Taiwan National Health Insurance Research Database.

Participants: From 2001 to 2009, the newly diagnosed AMD cases aged ≥65 years in the database were recruited as the AMD cohort (n = 4993). Of those, there were 540 with and 4453 without exudative AMD diagnoses. Subjects without any AMD, matched for age, gender, and time of enrollment, were randomly sampled as the control cohort (n = 24 965) for comparison.

Methods: Alzheimer's disease/senile dementia-free survival analysis was assessed using a Kaplan–Meier method. Cox proportional hazard regressions were performed to calculate the hazard ratios (HR) of AD or senile dementia for the 2 cohorts after adjusting for preexisting comorbidities and number of clinical visits.

Main Outcome Measures: The first-ever diagnosis of AD or senile dementia during the observation period.

Results: Of the 29 958 sampled subjects, 1589 (5.3%) were diagnosed with AD or senile dementia during a mean follow-up period of 4.4 years, including 294 (5.9%) from the AMD cohort and 1295 (5.2%) from the control cohort. The incidence of AD or senile dementia was higher in patients with AMD than in the controls ($P = 0.044$), with an HR of 1.44 (95% confidence interval [CI], 1.26–1.64) after adjusting for covariates. The stratified analysis showed that the adjusted HR for AD or senile dementia was 1.35 (95% CI, 0.89–2.06) for exudative AMD versus the controls and 1.44 (95% CI, 1.26–1.65) for nonexudative AMD versus the controls.

Conclusions: This study provides large-scale, population-based evidence that AMD, especially nonexudative AMD, is independently associated with an increased risk of subsequent AD or senile dementia development. *Ophthalmology 2015;122:2327-2335 © 2015 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Rapidly aging populations worldwide have resulted in an increasing prevalence of both age-related macular degeneration (AMD) and senile dementia. In Taiwan, reports place the prevalence of AMD and senile dementia among the elderly aged 65 years or more at 11.1% and 4.4%, respectively,[1,2] whereas the annual incidence of senile dementia is estimated at 1.28%.[3] These degenerative disorders of eye and brain may cause an exponential increase in financial burden and are major public health issues. Alzheimer's disease (AD), the leading cause of senile dementia, is an incurable neurodegenerative disease characterized by progressive deterioration in memory and cognitive function.[4] Thus, there is a great need for early detection and intervention for senile dementia among high-risk individuals to delay the progression of irreversible brain pathologies.

The retina is an extension of the brain. With advances in retinal imaging, researchers have identified certain retinal abnormalities as potential biomarkers for AD diagnosis and progression.[4] There are several clinical and pathologic similarities between AD and AMD. For example, aging is the principal risk factor for both multifactorial degenerative disorders of the central nervous system. Furthermore, extracellular amyloid β-peptide deposition, the primary pathologic hallmark of AD, is also a component of the drusen that is an early sign of AMD.[5] However, the association between AMD and AD, senile dementia, or cognitive impairment remains inconclusive in the literature.[6–17] The conflicting results across observational studies may result partially from differences in study design and sample size. Several studies also made no

http://dx.doi.org/10.1016/j.ophtha.2015.07.033
ISSN 0161-6420/15

distinction between exudative and nonexudative subtypes among patients with late AMD.[6–10,12,13]

It is suggested that different subtypes of AMD may have different levels of association with cognitive impairment and pathogenic similarities with AD.[11] Some studies reported that AMD, especially its late nonexudative subtype, is independently associated with cognitive impairment.[11,15] With the use of record linkage analysis in England, a study of patients with AMD admitted for intravitreal injection treatment was unable to demonstrate a positive association with AD or dementia.[14] On the contrary, a cross-sectional database study in Taiwan found that patients with dementia, including vascular, presenile and senile dementia, and AD, were associated with a higher proportion of prior exudative AMD than the controls.[17] Because both AMD and AD are the degenerative disorders of central nervous system, additional large-scale longitudinal studies, stratifying AMD into exudative and nonexudative subtypes and focusing on the relationship between AMD and degenerative dementia, may be helpful to further clarify this controversial issue. Therefore, we used the Taiwan National Health Insurance Research Database (NHIRD) in this nationwide study with a retrospective cohort and case-control design to investigate the relationship between AMD subtypes and subsequent AD or senile dementia.

Methods

Database

The NHIRD, a large and comprehensive nationwide population-based database published annually by Taiwan National Health Research Institute in an electronically encrypted form, contains all the original claims data from the Taiwan National Health Insurance (NHI) program. This mandatory, single-payer social health insurance system has been in operation since 1995 and currently has more than 22 million enrollees, representing approximately 99% of the Taiwanese population. Among the subsets of the NHIRD, there are 2 cohort datasets each composed of all the original claims data of 1 000 000 beneficiaries who were randomly sampled from the year 2000 and 2005 Registry of Beneficiaries of the NHIRD, respectively. These cohort datasets have been confirmed by the National Health Research Institute to be representative of the Taiwanese population under the NHI program, and all of their claims data are available from 1996 onward. Therefore, we analyzed these representative longitudinal datasets to examine the occurrence of AD or senile dementia among AMD cases and the matched controls. The Institutional Review Board of National Yang-Ming University Hospital approved the study (2013A007) and waived the requirement of informed consent, because the analyzed datasets were from a database devoid of identifiable personal information.

Study Sample

In this study, we identified subjects who were aged ≥65 years and had ≥2 clinical visits with a diagnosis of AMD (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code 362.50, 362.51, and/or 362.52) from January 1, 2001, to December 31, 2009, as patients with AMD. We excluded those who had been diagnosed with AMD before 2001 to increase the likelihood of recruiting patients with incident AMD. The control group was selected from those enrollees aged ≥65 years and without AMD throughout the whole course of follow-up in the same dataset. By using stratified random sampling, we randomly selected 5 matched controls for each identified patient with AMD. Matching characteristics included age (±5 years), gender, and the year of index date. The index date was taken as the date of the outpatient visit for the first diagnosis of AMD. The matched controls received the same index date as their corresponding cases and had used NHI healthcare during the year of index date. We excluded subjects who had been diagnosed as AD (331.0) or dementia (290.xx) cases before enrollment and further separated AMD patients into exudative and nonexudative subgroups based on the presence of exudative AMD claims (ICD-9-CM codes 362.52). Stroke is a primary risk factor for vascular dementia or post-stroke dementia. To investigate the association between AMD and the occurrence of degenerative dementia, subjects with a history of stroke (ICD-9-CM codes 430-438) were also excluded. The main outcome of our study was the first occurrence of AD (ICD-9-CM codes 331.0) or senile dementia (290.0, 290.2, 290.20, 290.21, 290.3) identified by the insurance claims during the follow-up period. To improve the identification accuracy, those who received an AD or senile dementia diagnosis only once were not identified as incident AD or senile dementia cases. All of the subjects were followed up until the study end point, disenrollment from the NHI program, or December 31, 2009, whichever came first.

Statistical Analysis

We used Microsoft SQL Server 2008 (Microsoft Corp, Redmond, WA) for data management and computing and performed statistical analysis with SPSS software (Version 17.0, SPSS Inc, Chicago, IL). All data were expressed as mean (standard deviation [SD]), median (interquartile range), or percentage. The differences between the 2 groups in terms of demographic characteristics, follow-up time, number of NHI claims for outpatient visits during the follow-up period, and preexisting comorbidities, including hypertension (ICD-9-CM codes 401.xx–405.xx), diabetes mellitus (250.xx), hyperlipidemia (272.xx), coronary artery disease (411.xx–414.xx), dysrhythmia (427.xx, 785.0, 785.1), and thyroid disease (240.xx–246.xx) were determined by the independent Student t test, Mann–Whitney U test, or Pearson's chi-square test as appropriate. Survival analysis was assessed using a Kaplan–Meier analysis, with the significance based on the log-rank test. Multivariable regression analysis was carried out using Cox proportional hazard regression analysis with adjustment for chronic comorbidities at baseline, such as Parkinson's disease, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, dysrhythmia, and thyroid disease, and number of NHI claims for outpatient visits during the follow-up period. The log minus log plot of survival was used to verify that the explanatory variables analyzed satisfy the proportionality assumption of the Cox regression model. Statistical significance was inferred at a 2-sided P value < 0.05.

Results

The final analysis included 4993 patients with AMD and 24 965 matched controls (Fig 1). Of these patients with AMD, only 540 (10.8%) cases had claims for exudative form (ICD-9-CM codes 362.52). We matched patients with AMD and the controls in terms of age (mean age, 74.5 years), gender (53.0% male), and the year of index date. The distributions of demographic characteristics, comorbidities, and number of clinical visits for these 2 cohorts are shown in Table 1. Patients with AMD were more likely to have claims for chronic comorbidities at baseline, including