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Clinical Study

Increased risk of ischemic stroke in patients with pneumoconiosis

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ABSTRACT

Although past studies have confirmed that chronic dust exposure is a risk factor for cardiovascular disease, the relationship between it and cerebrovascular disease is still unclear. We aimed to determine whether pneumoconiosis is related to increased incidence of ischemic stroke in the following 5 to 11 years. We selected 1238 patients with pneumoconiosis from Taiwan's National Health Insurance database as our study cohort. After matching for age, sex and the date of ambulatory care visit, another 4952 patients without pneumoconiosis were selected as the comparison cohort. Each patient was individually followed up until the end of 2010 to track the incidence of stroke, and Cox proportional hazard regression analysis was performed to compute the relative hazard ratio of stroke. Our results showed 19.6% of pneumoconiosis patients and 15.8% of non-pneumoconiosis patients developed stroke. After statistically adjusting for age, sex, and medical comorbidities, the hazard of developing stroke was 1.36 times greater for those with pneumoconiosis compared to those without. Even in those with pneumoconiosis excluding chronic obstructive pulmonary disease, the hazard of developing stroke was still 1.31 times greater than those without pneumoconiosis. Our study revealed that pneumoconiosis patients are at a higher risk of ischemic stroke, and primary prevention of stroke is particularly important in this group of patients.

1. Introduction

Pneumoconiosis is a chronic occupational lung disease caused by long term inhalation of dust. The dust accumulated in the airway can result in deposits of fibrous tissue, mineral pigment, and inflammatory cells in the walls of respiratory bronchioles and alveoli, which is pathologically different from lung diseases caused by tobacco smoking [1]. The chronic inflammatory stimulus related to the deposition of fine dust increases the risk of lung cancer [2], which leads to significant mortality in pneumoconiosis patients. Decreased lung function with either a restrictive or obstructive pattern caused by dust related fibrosis and inflammation [3] causes dyspnea, which also impairs quality of life and causes significant morbidity. Therefore, pneumoconiosis related pulmonary morbidity and mortality is a concern for medical workers and governments in the field of occupational medicine.

In addition to the pulmonary hazard, chronic dust exposure is also related to cardiovascular diseases. Long term dust inhalation can result in a prothrombotic tendency via an interleukin-6 dependent pathway, leading to reduced clotting times, intravascular thrombin formation, and accelerated arterial thrombosis [4]. In animal studies, dust exposure has been related to increased plasminogen activator inhibitor-1 and suppressed tissue plasminogen activator, which can cause deficient fibrinolysis [5]. Furthermore, tissue factor pathway inhibitor is also suppressed in animals exposed to dust, and an enhanced extrinsic coagulation pathway exacerbates intravascular thrombosis [6]. Due to the above reasons, chronic dust exposure has been confirmed to be a risk factor for cardiovascular disease by the American Heart Association [7].

It would be expected that the impact of dust exposure on the development of cerebrovascular disease would be similar to cardiovascular disease. Nevertheless, studies on the relationship between dust exposure and cerebrovascular diseases are few and conflicting. One study confirmed that fine dust exposure (diameter less than 2.5 μm) increased the risk of ischemic stroke [8]. However, another study concluded that fine dust exposure was not associated with the occurrence of ischemic stroke in the general population. Only patients with diabetes mellitus showed an 11% increase in ischemic stroke risk [9]. A meta-analysis included 12 studies investigating the association between dust exposure and risk of stroke, but the result showed only particles less than 2.5 μm in diameter were related to stroke occurrence in time series studies. Larger particle exposure was not related to an increased

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risk of daily stroke occurrence [10]. In addition to dust exposure studies, cohort based occupational studies also showed conflicting results. In one study, increased stroke mortality was observed in asbestos workers [11]. On the contrary, another study showed significantly lower cerebrovascular disease related mortality in pneumoconiosis patients [12].

Despite the controversies described above, we hypothesize that pneumoconiosis is related to elevated risk of ischemic stroke due to extensive reports of the prothrombotic tendency caused by dust exposure in the literature [4–6]. The aim of our study was to determine whether pneumoconiosis may increase the risk of stroke, and we have conducted this retrospective cohort study using a database containing the most representative medical care samples in Taiwan, which can provide significant value for health workers in Eastern countries.

2. Materials and methods

2.1. Database

This study utilized the database provided by the Taiwan National Health Research Institute, which contains the original medical data, including diagnosis and drug prescriptions, from a systematically selected 1,000,000 people under the program of Taiwan's National Health Insurance (NHI) between the years 2000 and 2010. The NHI is the single largest medical health insurance company in Taiwan, and more than 98% of Taiwanese residents are included as beneficiaries of this program [13]. Therefore, the data derived from the NHI program are representative of the general medical health status of the entire Taiwanese population. The Taiwan National Health Research Institute claims that there were no statistically significant differences in age, sex, or health care costs between the sampled 1,000,000 people in the database and all beneficiaries under the NHI program. Therefore, it provided a valuable resource for us to study the relationship between pneumoconiosis and stroke incidence in Taiwan. Furthermore, because the database consists of de-identified secondary data released to the public for research purposes, this study was exempt from Institutional Review Board approval.

2.2. Study sample

This was a retrospective cohort study. In Taiwan, patients with a strictly confirmed diagnosis of pneumoconiosis receive a catastrophic illness card (CIC) which allows them to be exempt from most of the cost related to pneumoconiosis when they visit healthcare facilities. In order to prevent mistaken diagnosis, only the patients with a CIC for pneumoconiosis (International Classification of Diseases-Ninth Revision-Clinical Modification [ICD-9-CM] code 500 to 505) during the 6 year period from 1 January 2000 to 31 December 2005 were selected as the study cohort. Patients younger than 30 years were excluded due to the incidence of pneumoconiosis being too low. In addition, patients with a history of stroke (ICD-9-CM code 434 to 436) before the diagnosis of pneumoconiosis were also excluded to avoid wrong causal-response relationships. As a result, a total of 1238 patients were included.

The subjects for a comparison cohort were then randomly selected from the remaining patients in the database by matching number, age, sex, and the date of their ambulatory care visit. We again excluded patients younger than 30 years and those with a diagnosis of stroke before the day of index ambulatory care visit. A total of 4952 subjects were selected as our comparison cohort. All cases in both cohorts were followed up until 31 December 2010 to track the incidence of stroke (ICD-9-CM code 434 to 436). In order to prevent erroneous diagnosis of stroke, the diagnosis was confirmed only if the patient was given the same diagnosis three times during ambulatory healthcare visits, and brain CT scan or brain MRI was done at least once to confirm the diagnosis, or the patient had one instance of stroke diagnosis as an in-patient. Furthermore, several medical comorbidities were also taken into consideration, including hypertension (ICD-9-CM code 401 to 405), diabetes mellitus (DM) (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 491, 492 and 496) and chronic kidney disease (CKD) (ICD-9-CM code 585). These diagnoses were confirmed by the same criteria for stroke diagnosis mentioned previously, and these risk factors for stroke would be statistically adjusted for in the subsequent regression model.

2.3. Statistical analysis

After formulating the study and comparison cohorts, subsequent statistical analysis was done using SAS software, version 9.2 (SAS Institute, Cary, NC, USA). Student's *t*-test and the chi-squared test were used to compute the statistical differences of age, sex, and medical comorbidities including hypertension, DM, hyperlipidemia, COPD, and CKD between the study and comparison cohorts. We then used the Cox proportional hazards regression model to compute the hazard ratio of stroke between the two cohorts with adjustment for the variables mentioned above. As the incidence of COPD was much higher in pneumoconiosis patients, further stratified analysis according to the presence of COPD was carried out. Finally, the Kaplan–Meier method with log rank test was used to examine the stroke-free survival rate. A p value of 0.05 was considered significant in our models.

3. Results

Comparisons of clinical characteristics between the two cohorts are shown in Table 1. Because the study subjects were matched during case selection, there were no statistical significant differences in age or sex distribution between the 2 groups. In addition, there were no significant differences in the prevalence of hypertension, DM and CKD between them. However, higher prevalence of hyperlipidemia ($p = 0.039$) and COPD ($p < 0.001$) were observed in pneumoconiosis patients compared to patients in the comparison cohort.

Each of the study subjects were individually tracked for the incidence of stroke during the next 5 to 11 years until 31 December 2010. The mean and median follow-up duration was 7.5 years and 8.4 years, respectively. Three hundred and thirty-one subjects died from diseases other than stroke in the follow-up period, and they were taken as censored data in our study. Table 2 shows the incidence and hazard ratio of stroke in subjects with pneumoconiosis and those without, stratified by age and sex. Overall 19.6% of pneumoconiosis patients developed stroke, while 15.8% of the comparison cohort subjects developed stroke. Patients with pneumoconiosis were more likely to develop stroke compared to those without pneumoconiosis. Because there were too few patients aged 30 to 49 years, there was no statistically significant difference in hazard ratio of stroke detected between the two cohorts. The hazard ratio of stroke brought on by pneumoconiosis increased in the study subjects as age increased. Furthermore, the hazard ratio of stroke was also higher in females.

Considering the pneumoconiosis cohort patients were more prone to have COPD, and COPD was found to have increased risk of stroke [14–16], further stratified analysis according to the presence of pneumoconiosis and COPD was done. As shown in Table 3, patients with both pneumoconiosis and COPD had the highest incidence and hazard ratio of stroke. It is worth noting that patients