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Ambient Air Pollution and the Risk of Central Retinal Artery Occlusion

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Purpose: To investigate whether daily changes in ambient air pollution were associated with an increased risk of central retinal artery occlusion (CRAO).

Design: Retrospective population-based cohort study.

Participants: We identified patients newly diagnosed with CRAO between 2001 and 2013 in a representative database of 1 000 000 patients that were randomly selected from all registered beneficiaries of the National Health Insurance program in Taiwan. We identified air pollutant monitoring stations located near these patients' residences in different administrative areas in Taiwan to determine the recorded concentrations of particulate matter $\leq$2.5 μm ($PM_{2.5}$), particulate matter $\leq$10 μm (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3). Patients without corresponding monitoring stations were excluded.

Methods: We used a time-stratified case-crossover study design and conditional logistic regression analysis to assess associations between the risk of CRAO and the air pollutant levels in the days preceding each event.

Main Outcome Measures: Odds ratios (ORs) and 95% confidence intervals (CIs).

Results: We enrolled 96 patients with CRAO in this study. The mean age was 65.6 years (standard deviation, 12.7 years) and 67.7% of patients were male. The risk of CRAO onset was significantly increased (OR, 1.09; 95% CI, 1.01−1.17; $P = 0.03$) during a 5-day period following a 1 part per billion increase in NO_2 levels. After multipollutant adjustment, the increase in risk was most prominent after 4 days (OR, 1.40; 95% CI, 1.05−1.87; $P = 0.02$) to 5 days (OR, 2.16; 95% CI, 1.10−4.23; $P = 0.03$) of elevated NO_2 levels in diabetic patients. The risk of CRAO onset also significantly increased in patients with hypertension and in patients $\geq$65 years old, after 1 day of elevated SO_2 levels (OR, 1.88; 95% CI, 1.07−3.29; $P = 0.03$ and OR, 1.90; 95% CI, 1.13−3.21; $P = 0.02$, respectively). The transient concentration of the other air pollutants, including $PM_{2.5}$, PM_{10}, and O_3, did not significantly affect the occurrence of CRAO in this study.

Conclusions: These results demonstrated a positive association between air pollution and CRAO onset, particularly in patients with diabetes or hypertension and those older than 65 years. *Ophthalmology 2016;■:1−7 © 2016 by the American Academy of Ophthalmology*

Supplementary material is available at www.aaojournal.org.

Central retinal artery occlusion (CRAO) is one of the leading causes of acute permanent loss of vision, with an incidence of approximately 1 per 100 000 people.[1,2] Despite its rarity, the visual outcome of CRAO is typically dire. In addition, these patients had shorter life spans, higher risk of stroke, and more cardiovascular risk factors compared with controls.[3−6] Similar to ischemic cerebral stroke, CRAO is caused by thrombotic or embolic occlusion of the central retinal artery, which leads to ischemia of the retina and optic nerve head with profound loss of vision.[7,8] In addition, CRAO and ischemic stroke have similar risk factors.[6,9] Moreover, the risk of ischemic stroke was significantly increased both before and after the occurrence of CRAO.[10]

Growing evidence has indicated that gaseous and particulate air pollutants were markedly temporally associated with hospital admissions for stroke and stroke-related mortality.[11,12] It has been shown that the risk of stroke was significantly associated with daily increases in both particulate matter (PM), measured in terms of particles $\leq$2.5 μm or $\leq$10 μm in diameter ($PM_{2.5}$ and PM_{10}, respectively), and gaseous air pollutants, including carbon monoxide, sulfur dioxide (SO_2), and nitrogen dioxide (NO_2), but not ozone (O_3).[11,12] These associations were stronger in patients with recurrent ischemic stroke, a history of stroke, diabetes mellitus (DM), and $\geq$1 cardiovascular risk factor.[12] Short-term exposure to these air pollutants may also trigger a myocardial infarction, which is also a thromboembolic event.[13] Given the similarities in the pathophysiology of CRAO, ischemic stroke, and myocardial infarction, it is plausible that air pollution may be an important, modifiable risk factor for CRAO.

This study aimed to investigate whether daily changes in the level of ambient air pollution were associated with an increased risk of CRAO.

Methods

This retrospective, population-based cohort study was based on data retrieved from January 1, 2000, to December 31, 2013, using the Taiwan National Health Insurance Research Database

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(NHIRD). We included patients newly diagnosed with CRAO between 2001 and 2013. Patients aged <20 years or those with antecedent CRAO were excluded. CRAO was defined according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic code 362.31. We defined the onset of CRAO as the first date that the diagnostic code was recorded. The patient's area of residence was defined as the location of the corresponding clinic/hospital in Taiwan, assuming that patients sought medical help at the closest clinic/hospital. We collected data on the patient's comorbidities, including DM, hypertension (HTN), coronary artery disease, hyperlipidemia, cerebral infarction, arrhythmia, heart failure, carotid artery stenosis, rheumatic heart disease, and glaucoma, except for normal tension glaucoma. Each patient's comorbidities were identified using the claims 1 year before the date of incident CRAO (the index date). The study protocol adhered to the tenets of the Declaration of Helsinki, and the study was approved by the institutional review board of the hospital.

The National Health Insurance (NHI) program in Taiwan is a mandatory general health insurance that covers up to 99% of Taiwan residents.[14] It covers emergency, inpatient, and outpatient care. The NHIRD contains encrypted data to prevent identification of individual patients; these data are maintained and released by the National Health Research Institutes for scientific research. In this study, we analyzed data in a representative database of 1 000 000 patients that were randomly selected from the registered beneficiaries of the NHI program. This selected patient group was termed the Longitudinal Health Insurance Database of the NHIRD.

The ambient concentrations of $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 were measured hourly and averaged from 78 local monitoring stations operated by the Environmental Protection Administration Executive Yuan of Taiwan (Fig 1, available at http://www.aaojournal.org). We obtained averaged hourly meteorological data, including temperature, from 603 local monitoring sites operated by the Central Weather Bureau of Taiwan. The patients were paired with monitoring stations located in the same administrative division as their area of residence (taken as the hospital location). The individualized exposure to ambient air pollution was then defined according to the date of CRAO onset and the patient's residential location. We excluded subjects that lived in areas that had no monitoring station in the same administrative division.

We used a time-stratified case-crossover study design[15] to assess the association between the risk of CRAO onset and the concentration of each kind of air pollution in the days preceding the event. In brief, each patient's exposure before a case-defining event (case period) was compared with the patient's exposure during a control period, when the patient did not experience a case-defining event. The control period was selected from other days of the same month, on the same day of the week, as the case period. The control period was selected from days both before and after the event, because individual events were not expected to impact the distribution of exposure (Fig 2, available at http://www.aaojournal.org).[16,17] Because the case and control periods were on the same day of the week in the same calendar month for a given individual, this study design controlled for seasonality, effect of the day of the week, time trends, and slowly varying potential confounders.[15,17] Moreover, the personal factors such as lifestyle, activity pattern, working area, and comorbidity were also controlled because the patients themselves were their own control.

Statistical Analysis

We used conditional logistic regression to analyze associations between CRAO events and air pollution factors. These results are expressed as estimated odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Exposure to each air pollution factor was assessed relative to the time of CRAO onset. We first examined the risk of CRAO onset for each pollutant based on 1-day interval (single-day lag analysis). The risk of CRAO onset for each air pollutant was then identified based on average levels in the 0 to 2 days, 0 to 4 days, and 0 to 6 days preceding onset to check if there is an effect of increment of air pollution (multiday lag analysis). Additionally, we also stratified the pollutant levels into <25th, 25th to 75th, and >75th percentile of mean daily pollutant levels to examine the effect of high levels or low levels of pollution. At the end of this section, we used a multivariable conditional logistic regression model, adjusted for all pollutants and daily temperatures, to examine our results (multipollutant model).

On the second part, we conducted sensitivity analyses to test the stability of the overall analyses. Because each air pollutant had a different basal concentration, we used the mean pollutant levels of all of the control days in the same patient as his or her baseline. Each value in the case and control period was then divided by the baseline value and entered the subsequent conditional logistic regression analysis. We also set another model with longer buffer periods between the case period and control periods to check the stability of our results. In addition, studies have shown that temperature affects the occurrence of stroke significantly.[18] Therefore, we built another model with ±1° C daily temperature-matched control days in the same month to examine our results.

In the final section of analyses, we performed risk-stratified analyses according to relevant comorbidities, age, and gender to identify effect modification. A multivariable conditional logistic regression model, adjusted for all pollutants and daily temperatures (multipollutant model), was used in this analysis.

Data extraction, processing, and sampling were performed with Microsoft SQL Server 2012 (Microsoft Corporation, Redmond, WA). We used STATA version 12.1 (StataCorp LP, College Station, TX) for statistical analyses. All reported P values were based on 2-sided tests; P values <0.05 were considered statistically significant.

Results

We identified 266 patients newly diagnosed with CRAO. Of these, 170 were excluded owing to the absence of an air monitoring station in the corresponding residential area or owing to incomplete pollutant or meteorological data. Thus, the study included a total of 96 patients newly diagnosed with CRAO. The mean age of all study subjects was 65.6 years (standard deviation, 12.7 years; range, 30−100 years), and 67.7% of the subjects were male. All eligible patients lived within 20 km of the monitoring stations. The major comorbidity was HTN, followed by DM and hyperlipidemia (Table 1). The distributions of mean daily pollutant and temperature levels in Taiwan are shown in Table 2 (available at http://www.aaojournal.org). The changes of air pollutant levels in Taiwan during the 13-year study period are shown in Figure 3 (available at http://www.aaojournal.org).

In the single-day lag analyses, NO_2 levels on the fifth day before CRAO onset (OR, 1.09; 95% CI, 1.01−1.17; $P = 0.03$) and daily temperature on the second day before CRAO onset (OR, 1.23; 95% CI, 1.03−1.47; $P = 0.02$) showed significant impacts on the occurrence of CRAO (Fig 4). In the multiday lag analyses, NO_2 levels (OR, 1.13; 95% CI, 0.99−1.28; $P = 0.06$; 0−6 days before CRAO onset), SO_2 levels (OR, 1.31; 95% CI, 1.00−1.72; $P = 0.05$; 0−2 days before onset), and daily temperature (OR, 1.21; 95% CI, 1.00−1.47; $P = 0.05$ 0−2 days before onset and OR, 1.25; 95% CI, 1.00−1.56; $P = 0.05$ 0−4 days before onset)