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Incidence of nonarteritic anterior ischemic optic neuropathy: increased risk among diabetic patients

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Abstract

Objective—Previous studies have identified a higher prevalence of diabetes mellitus (DM) among patient cohorts with non-arteritic anterior ischemic optic neuropathy (NAION). We sought to determine the development of incident NAION among a group of newly diagnosed patients with DM and to estimate the incidence of NAION among the elderly.

Design—Medicare 5% database study.

Participants—25,515 patients with DM and an equal number of age- and gender-matched non-diabetics.

Methods—Query of Medicare 5% claims files identified patients with new diagnosis of DM in 1994. A randomly selected control group was created using one-to-one propensity score matching. Patients with a diagnosis of giant cell arteritis, pre-existing DM, and age < 68 years or > 95 years were excluded. Patients with DM and controls were followed for the development of NAION over the following 4,745 days.

Main Outcome Measures—Incidence of anterior ischemic optic neuropathy (AION) among patients with and without DM.

Results—Each group was 85% White, 11% Black, and 4% other race, aged 76.4 years, and 40% male with a mean followup time of 7.6 years. In the diabetes group, 188 individuals developed AION (0.7%) compared to 131 individuals (0.5%; $p < 0.01$) in the control group. In unadjusted Cox regression analysis, having diabetes mellitus was associated with a 43% increased risk (Hazard ratio [HR]: 1.431; 95% confidence interval [CI]: 1.145, 1.789) of developing AION. After adjusting for other covariates, the risk of developing AION among individuals with DM was reduced to 40% (HR: 1.397; 95% CI: 1.115, 1.750). Male gender increased an individual's risk of developing AION by 32% (HR: 1.319; 95% CI: 1.052, 1.654). No other covariate was statistically

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significantly associated with developing AION. The annual incidence of NAION was 82 per 100,000.

Conclusions—DM significantly increased the risk of the diagnosis NAION. The incidence of NAION among patients older than 67 years may be higher than previously reported.

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common acute, optic neuropathy among individuals over the age of 50 years with an estimated annual incidence of 2.3 – 10.2/100,000 in the United States (U.S.).^{1,2} These estimates are based on small local studies and then extrapolated to the U.S. population.

The exact pathophysiology of NAION remains unknown, but numerous risk factors have been proposed based on retrospective observations of relatively small groups of patients. The most commonly cited risk factors suggest vasculopathic disorders such as diabetes mellitus (DM),³⁻⁶ systemic hypertension,⁴⁻⁷ hyperlipidemia,⁷⁻⁹ and smoking.^{8,10,11} Each of these factors has been disputed,¹² and, in many cases, a study identified one risk factor and discounted another.³⁻⁹ Diabetes mellitus has the highest prevalence among patients with NAION, however to our knowledge, the incidence of NAION among a group of patients with a particular risk factor has not been studied.

This paper analyzes the likelihood of developing an incident diagnosis of NAION among Medicare beneficiaries after receiving a new diagnosis of diabetes mellitus (DM) compared to a matched control group. A secondary aim identified the incidence of NAION over a 13-year period.

Methods

Institutional review board approval was obtained for this study from Duke University.

Data

Medicare 5% inpatient, outpatient, and Part B claims files were used to identify a nationally-representative sample of Medicare beneficiaries aged 65 or older who were diagnosed with DM, NAION, and health and eye related comorbidities from 1991-2007. The data contained information on diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification, ICD-9-CM) and procedure codes (Current Procedural Terminology, CPT-4; Healthcare Common Procedure Coding System, HCPCS) submitted with each claim and were merged with Medicare denominator files for information on enrollment dates in fee-for-service Medicare, death, and beneficiary demographic characteristics.

Sample Selection

We composed a sample of individuals first diagnosed with diabetes mellitus (DM: ICD-9-CM code 250.xx) in 1994. To ensure these were incident cases of DM and to identify other comorbidities, we employed a 3-year look back period, which necessitated all individuals to be age 68+ in 1994 in order to have a full look-back. We also excluded all individuals ever diagnosed with giant cell arteritis (ICD-9-CM: 446.5), individuals age 95+ in 1994, and persons who entered a Medicare risk plan (HMO) or lived outside of the U.S. for 12 months or more during the look back period. To ensure that an anterior ischemic optic neuropathy (AION) diagnosis occurred after the diagnosis of DM, we excluded any individual initially diagnosed with AION prior to DM diagnosis in 1994.

We then created a control pool of persons never diagnosed with DM, with the same exclusion restrictions described above. Using propensity score matching, we created a control sample of equal number to the DM sample based on observable covariates. We

describe this method in greater detail below. The matched samples consisted of 25,515 DM individuals and an equal number of controls.

Sample individuals were followed for 4,745 days (13 years) or until censored. Individuals were censored as of their date of death, the date they joined an HMO, or the date they moved outside of the U.S. Individuals living in a foreign country were censored as of January 1 of the year in which they first reported living outside of the U.S.

Propensity Score Matching

Using logit analysis, we predicted the probability of an individual having DM, considering the full DM sample and a control pool composed of all individuals satisfying the exclusion criteria. Covariates were binary variables for male gender, black race, other race, prior diagnosis of: Charlson comorbidity index,¹³ an indicator of general health, hypertension, and lipidemia.

All prior diagnoses were collected during the 3-year look-back period. The Charlson comorbidity index was calculated from diagnoses included on Medicare claims in the calendar year 1993, the year prior to entry into the sample.

The propensity score calculated the probability of developing DM, conditional on observed covariates. Matching on propensity score reduces selection bias between individuals with a diagnosis, in this case, of DM, and those without.¹⁴⁻¹⁵ From logit analysis, we used the predicted probability an individual had DM to match a person with DM to his/her nearest match never diagnosed with DM. We used a SAS Greedy 5 to 1 digit match macro to perform 1 to 1 propensity score matching.¹⁶ This program initially matched individuals with DM to persons with no DM based on an exact match to the fifth decimal place of their propensity score in order to find the “optimal” match first. If an individual did not have a match to the fifth decimal place, the program then attempted to match individuals by propensity score to the fourth decimal place. It continued to match individuals down to 1 decimal place. All individuals with DM were matched with a unique control person.

Analysis

We calculated standardized differences for covariates used in the propensity score analysis to ensure we had created a well-matched sample. We also performed student T-tests to compare all covariates in the full model. We then used Cox proportional hazards models to calculate unadjusted and adjusted time-to-NAION considering a binary variable for DM. Covariates in the adjusted model included all those listed above for the logit analysis, as well as prior diagnosis of: ischemic heart disease; chronic heart failure; stroke; blindness or low vision; age-related macular degeneration; cataract; and diabetic retinopathy.

Results

After propensity score matching, there were 25,515 controls and 25,515 persons with DM. Covariates used for matching had no standardized differences >10% making the samples well matched (Table 1).¹⁷⁻¹⁸ Each group was 85% White, 11% Black, and 4% other race, aged 76.4 years, and 40% male. We followed individuals in each group for a mean time of 7.6 years.

Overall, 319 (0.6%) patients were diagnosed with NAION during the follow-up period. The annual incidence of NAION was 82 per 100,000 persons. Men were more apt to receive a diagnosis of NAION in the control group. In the diabetes sample, the incidence was higher among men aged 68-75 years, but higher among women aged 76-95 years (Table 2). In the

diabetes group, 188 individuals were diagnosed with AION (0.7%) compared to 131 individuals (0.5%; $p<0.01$) in the control group. However, among individuals who were diagnosed with AION, individuals in the control group were diagnosed with AION more than a year earlier than individuals in the DM group ($p=0.005$). Individuals in the diabetes group had higher rates of ischemic heart disease, chronic heart failure, stroke, and diabetic retinopathy and lower rates of cataract than persons in the control group (Table 3).

In unadjusted Cox regression analysis, having diabetes mellitus was associated with a 43% increased risk (Hazard ratio [HR]: 1.431; 95% confidence interval [CI]: 1.145,1.789) of the diagnosis of AION. After adjusting for other covariates, the risk of the diagnosis of AION among individuals with DM was reduced from 43% to 40% (HR: 1.397; 95% CI: 1.115,1.750). Being male also increased an individual's risk of the diagnosis of AION by 32% (HR: 1.319; 95% CI: 1.052,1.654). No other covariate was statistically significantly associated with developing AION (Table 4).

Discussion

We found that DM represents an independent risk factor for the diagnosis of incident NAION among Medicare beneficiaries compared to a control group without DM. In our study, we identified more than 25,000 patients, all of who were first diagnosed with DM within the same year (1994). During the 13-year follow up period, 188 patients were diagnosed with incident NAION. This was significantly greater than the matched control group of more than 25,000 Medicare beneficiaries not diagnosed with DM.

Others have suggested an association between DM and NAION,³⁻⁶ but our study approaches the relationship from the opposite perspective. Previous studies retrospectively identified groups of patients with NAION and determined the prevalence of DM at the time of NAION diagnosis. Determination of cause-and-effect relationship is challenging if one considers prevalence data alone especially among small groups of patients and controls. In contrast, we identified a relatively large population of patients newly diagnosed with DM and determined the incidence of NAION diagnosis.

The prevalence of DM in prior studies has ranged from 5 to 40%. Falavarjani and colleagues described 107 patients with NAION, of these 40% had DM.¹⁹ In the Ischemic Optic Neuropathy Decompression Trial, 24% of 420 patients with NAION had DM at trial entry. 11 Salomon et al. reported an odds ratio for DM of 2.3 (95% CI:1.1-4.8) among 61 patients with NAION. 9 A previous Medicare database study of risk factors in NAION identified DM with an odds ratio of 1.14 (95% CI: 1.05-1.20). (Gordon LK, Yu F, Coleman AL, Arnold AC. Medicare database analysis of prevalence and risk factors for ischemic optic neuropathy. Paper presented Nov 17, 2003, Anaheim, CA). The largest cohort of NAION described 655 patients, of which 206 (31%) had diabetes and 449 did not.²⁰

Others have found a low prevalence of DM among patients with NAION and, in some cases, no significant difference between patients and controls. Recently, Giambene et al compared risk factors for 85 patients with NAION to 107 age and gender matched controls. 7 They found no difference in DM between patients (4.7%) and controls (2.9%). Bogen and Glaser described only 2 of 35 (5.7%) with DM at the time of NAION diagnosis. 21 Another study of 40 patients with NAION revealed only 3 (7.5%) with DM.²² Sawle reported only 5.6% of 71 patients with NAION had DM. 23

Some authors have stratified their diabetes prevalence data by age group. Repka noted that 20 (20%) of 102 patients between ages of 45-64 years had DM, which was significantly higher than Public Health Service data. However, they found no difference in diabetes prevalence among those aged 65 and older only. 6 Another study described 51 patients with

new onset NAION over the age of 45 years and compared them to two randomly selected control groups.³ This study found that diabetes increased the odds of developing NAION. Subgroup analysis showed that diabetes increased the odds ratio of developing NAION among individuals younger 68 years, but that this was not true for patients over 68 years. Our study included only those individuals over the age of 67 years and found that DM raised the risk of NAION by 40%.

It is not clear why patients without DM were diagnosed with NAION significantly earlier than those with DM in our cohort. Since the exact pathophysiology of NAION is not understood, it is possible that the control group contained some other risk factor not accounted for in our assessment. It is possible that this was a statistical anomaly. This may also relate to our cohort restriction of patients 68 years and older.

Historically, the incidence of NAION has been reported as 2.3 to 10.2 per 100,000 persons.¹⁻² Johnson and Arnold mailed monthly surveys to ophthalmologists in Missouri and Los Angeles County over a 6-12 month period to identify new cases of NAION. Based on U.S. Census Bureau data, they estimated an incidence of 2.3 per 100,000 for patients over age 50 years. With more than a 50% nonresponse rate, it is likely that they missed cases of NAION.¹ Since it is unlikely that all patients in Missouri and Los Angeles County received an ophthalmologic examination, the denominator appears overestimated. Therefore, this methodology underestimates the true incidence of NAION. Hattenhauer and colleagues identified 21 patients with NAION over a 10-year period in Olmstead County, MN. Adjusting for the age and gender of the U.S. population, the authors calculated an incidence of 10.2 per 100,000. They assume that all patients with NAION were seen in the Rochester, Minnesota.² With only 21 patients, one or two missed patients with NAION, who either did not seek medical attention or was seen at another institution in Minnesota, would significantly affect their results. It is also difficult to extrapolate this relatively homogenous, rural community to the entire U.S. population. In our study of more than 51,000 patients from across the U.S., there were 319 cases of NAION diagnosis over a 13-year period. We estimate the annual incidence of NAION diagnosis among Medicare beneficiaries over the age of 68 years is 82/100,000. This is significantly higher than previous reports. This may relate to the older age of our cohort or the fact that this study included a national database compared to regional databases. The higher incidence may also relate to misdiagnosis of other optic neuropathies reported by U.S. providers.

We acknowledge the intrinsic limitations of all retrospective studies. However, the low incidence of NAION makes a prospective, observational risk study nearly impossible. This group of more than 50,000 patients represents a large enough cohort to study NAION risk. The Medicare database does not contain any information on smoking status. Although the effect of smoking on NAION is somewhat controversial, it is unclear if either group contained a greater number of smokers and whether this affected the results. We also recognize that not all U.S. providers utilize strict diagnostic criteria when diagnosing NAION. The advantage of this study is that it represents a national sample from real-world practitioners providing routine care, which makes our results generalizable. Our study was limited to patients age 68+ and, although unlikely, may not apply to younger individuals with diabetes. The Medicare database does not contain information regarding socioeconomic status, which may play a role in control of diabetes and conceivably could affect the incidence of NAION. Finally, while propensity score matching reduces selection bias between individuals with and without a specific diagnosis, it does not completely eliminate selection biases related to unobserved covariates and does not replace the value of random assignments in experimental designs in making causal inferences.

This study presents robust data that diabetes mellitus increases the risk for the diagnosis of non-arteritic anterior ischemic optic neuropathy. The annual incidence of NAION is 82 per 100,000 among individuals older than 67 years of age.

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Table 1

Standardized differences of Matched Samples

	Control sample	Diabetes sample	Std Diff
Health comorbidities			
Charlson comorbidity index	0.995	1.001	-0.327
Lipidemia	0.263	0.263	-0.009
Hypertension	0.562	0.562	0.024
Demographic characteristics			
Age (in years)	76.429	76.379	0.786
Male	0.401	0.401	-0.032
Black race	0.110	0.110	-0.038
Other race	0.039	0.039	0.081
Observations	25,515	25,515	

Std diff: Standardized differences $= (100 * (x_{ti} - x_{nti}) / (((s_{ti}^2 + s_{nti}^2) / 2)^{0.5}))_i$

Table 2

Incidence per 100,000 of anterior ischemic optic neuropathy by gender.

Control Sample			
	Male	Female	
	<hr/>		
		Age	
	40.24	28.48	68-75
	48.11	27.18	76-95
Diabetes Sample			
	Male	Female	
	<hr/>		
		Age	
	57.26	48.15	68-75
	33.58	52.16	76-95

Table 3

Descriptive statistics

	Control sample	Diabetes sample
Anterior ischemic optic neuropathy	0.005	0.007**
Health comorbidities		
Charlson comorbidity index	0.995	1.001
Lipidemia	0.263	0.263
Hypertension	0.562	0.562
Ischemic heart disease	0.259	0.318***
Chronic heart failure	0.104	0.138***
Stroke	0.110	0.118**
Demographic characteristics		
Age (in years)	76.429	76.379
Male	0.401	0.401
White race	0.851	0.851
Black race	0.110	0.110
Other race	0.039	0.039
Eye related comorbidities		
Blindness or low vision	0.011	0.012
Age-related macular degeneration	0.095	0.090
Cataract	0.409	0.390***
Diabetic retinopathy	0	0.010***
	25,515	25,515

*p<0.05

**
p<0.01***
p<0.001.

Table 4

Hazard Ratios (95% Confidence Intervals) from Cox Proportional Hazard Analysis Time to Anterior Ischemic Optic Neuropathy for Persons Previously Diagnosed with Diabetes Mellitus

	Unadjusted		Adjusted
Diabetes mellitus	1.431 (1.145,1.789)	1.416 (1.132,1.772)	1.397 (1.115,1.750)
Health comorbidities			
Charlson	0.967 (0.888,1.054)	0.946 (0.861,1.040)	
Lipidemia	1.031 (0.803,1.326)	1.020 (0.793,1.311)	
Ischemic heart disease	1.151 (0.887,1.494)	1.103 (0.847,1.438)	
Hypertension	1.031 (0.813,1.307)	0.995 (0.784,1.263)	
Stroke	1.277 (0.888,1.835)	1.260 (0.876,1.811)	
Chronic heart failure	1.269 (0.850,1.894)	1.274 (0.854,1.901)	
Demographic characteristics			
Male	1.011 (0.991,1.031)	1.005 (0.985,1.025)	
	1.302 (1.038,1.632)	1.319 (1.052,1.654)	
Black	1.000 (0.695,1.439)	1.030 (0.715,1.485)	
Other race	0.694 (0.357,1.350)	0.710 (0.365,1.380)	
Eye related comorbidities			
Blindness or low vision		1.332 (0.547,3.244)	
Age-related macular degeneration		1.310 (0.917,1.870)	
Cataract		1.213 (0.962,1.529)	
Diabetic retinopathy		2.110 (0.781,5.695)	