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Risk of glaucoma among patients with benign essential blepharospasm

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Abstract

Purpose—Debate exists whether intraocular pressure (IOP) fluctuation is a risk factor for glaucoma. Patients with benign essential blepharospasm (BEB) experience intermittent, ultra-short term IOP elevations from frequent blinking and spastic eyelid closure. This paper explores the development of incident glaucoma after BEB diagnosis.

Methods—Medicare claims files were used to identify patients with a diagnosis of BEB from 1994–2000. An equal size control group without BEB was created using one-to-one propensity score matching. BEB patients and controls were followed for the development of one of the following main outcome measures: primary open angle glaucoma (POAG), closed angle glaucoma (CAG), or other glaucoma (besides POAG and CAG) over the following 2,190 days.

Results—There were 1350 persons in each group, consisting of 29% men, 94% of whom were white, with a mean age of 76 years. In the unadjusted model, BEB patients did not develop POAG (HR:1.159; 95% CI:0.876,1.534), CAG (HR:1.477; 95% CI:0.711,3.066), or other glaucoma (HR:1.306; 95% CI: 0.904,1.886) more often than controls. Adjusting for age, gender, race, number of visits to the ophthalmologist and other eye disease, a diagnosis of BEB did not affect the risk of POAG (HR:1.152; 95% CI:0.870,1.525), CAG (HR:1.448; 95% CI:0.696,3.015), or other glaucoma (HR:1.296; 95% CI:0.896,1.873).

Conclusions—Benign essential blepharospasm is not a risk indicator for POAG, CAG, or other forms of glaucoma.

Debate exists whether high IOP variability represents a risk factor for the development of glaucoma.^{1–4} Some studies have shown a positive association while others have not. Meanwhile, a number of factors have been associated with progression of visual field loss among glaucoma patients including older age, elevated intraocular pressure (IOP), and

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fluctuation of IOP. High IOP variability has resulted in an increased rate of glaucoma progression in the Advanced Glaucoma Intervention Study.⁵ Progression of field defects can occur with high IOP fluctuation for intraday and inter-visit measurements.^{6–10}

Benign essential blepharospasm (BEB) is an idiopathic, involuntary disorder characterized by bilateral eyelid closure. It affects approximately 1–5 out of 100,000 in the US and occurs more commonly among women. Onset of symptoms usually begins around the age of 55 years with excessive blinking triggered by stimuli such as bright lights, fatigue, or emotional tension. The condition often progresses slowly to involuntary, spasmodic contracture of the orbicularis oculi lasting seconds to minutes at a time.¹¹

Under physiologic conditions, the intraocular pressure (IOP) varies with external stimuli such as eye movement, blinking, or eyelid squeezing. Reports have described an increase in IOP of 5–10 mmHg with eye movement,^{12–13} 5–10 mmHg with blinking,^{13–15} and as much as 50–100 mmHg with forced eyelid closure.^{12–15}

This paper analyzes the likelihood of developing incident glaucoma among Medicare beneficiaries receiving a diagnosis of BEB compared to a control group matched on demographic characteristics.

Methods

Data Source

Medicare 5% inpatient, outpatient, Part B, and durable medical equipment claims files were used to identify a nationally-representative sample of Medicare beneficiaries aged 65 or older who were diagnosed with benign essential blepharospasm and related adverse outcomes from 1991–2006. The data contained information on demographic characteristics as well as 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. This study was HIPAA-compliant and approval was obtained by the institutional review board of the Duke University Health System.

Sample Selection

Persons were entered into our sample after receiving a diagnosis of benign essential blepharospasm (ICD9 code 333.81) from 1994–2000. We employed a 3-year look back period to ensure that all BEB diagnoses were incident cases. Persons who received a BEB diagnosis prior to 1994 or prior to age 68 were excluded from our analysis to allow a full 3-year look back period. Individuals older than 95 years at the time of diagnosis were also excluded. 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 were also excluded. To ensure that a glaucoma diagnosis occurred after the diagnosis of BEB, we excluded any persons with a previous glaucoma diagnosis. Persons diagnosed as glaucoma suspects were included. Individuals who did not report at least 1 ophthalmologist/optometrist visit during the look back or follow up period were also excluded.

A control pool of persons never diagnosed with BEB was created. The same age, HMO, foreign residence, and no prior glaucoma restrictions were applied to the control pool. Control individuals were also required to have at least 1 eye care visit during the look back period and during the follow up period. Using a random number generator, we selected 5,000 individuals meeting the control restrictions for the control pool. We then matched a control sample based on observable covariates to the BEB sample using propensity score

matching described below. After matching, the sample consisted of 1,350 BEB individuals and an equal number of controls.

Once in the sample, individuals were followed for 2,190 days or until censored. Censoring occurred when an individual died, joined an HMO, moved outside of the U.S. or left the sample. Data on country of residence was collected annually. Any person living outside of the U.S. was censored as of January 1 of the year in which they first reported living outside of the U.S.

Propensity Score Matching

Using the BEB sample and control pool, we predicted the probability of an individual having BEB using logit analysis. Covariates were binary variables for male gender, white race, prior diagnosis of: cataract, age-related macular degeneration, or diabetic retinopathy related complications (background diabetic retinopathy, proliferative diabetic retinopathy, or macular edema), and continuous variables for age and Charlson comorbidity index, a general health indicator.¹⁶

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

In the context of the current study, the propensity score is defined as the probability of developing BEB, conditional on observed covariates. Propensity scores matching reduces selection bias between individuals with a specific diagnosis and those without.^{17,18} Using the predicted probability of an individual having BEB we matched an individual with BEB to his/her nearest match without a BEB diagnosis. SAS Greedy 5 to 1 digit match macro (by Lori S. Parsons, accessed April 20, 2009, at <http://www2.sas.com/proceedings/sugi26/p214-26.pdf>)¹⁹ was used to perform propensity score matching. This program made the “best” match first, matching individuals on 5 digits of the propensity score. For individuals without a match on 5 digits, it then matched BEB individuals to controls by 4 digits. It continued to match individuals down to 1 digit. Those without a match on 1 digit were excluded from the analysis. To check whether individuals were well matched, we calculated standardized differences for all covariates used in the logit analysis. When differences are less than 10% the groups are well matched.^{20–21}

Analysis

Cox proportional hazards models were used to calculate unadjusted and adjusted time-to-POAG (ICD9 365.1x), CAG (ICD9 365.2x), and other glaucoma (see Table 1) between the BEB and control sample. Covariates were the same as from logit analysis listed above.

Results

Both the BEB and control groups were 29% male, 94% white, with an average age of 76 years (Table 2). 30–31% of observations were censored in the control and 27–28% in the BEB group, depending on the glaucoma diagnosis being studied. Differing rates of CAG, POAG, and other glaucoma partly reflect differences in percentages of observations censored. Data on individuals diagnosed with POAG could not be censored since having a POAG diagnosis was an endpoint. Only 3% of each sample group carried a diagnosis of ocular hypertension. There were no standardized differences greater than 10% making the groups well balanced.^{20–21}

Primary open angle glaucoma analysis

One hundred six (7.9%) patients in the BEB group and 91 (6.7%) patients in the control group developed POAG during the study period. In the unadjusted model (Table 3), persons in the BEB group were not significantly more likely to develop POAG (Hazard ratio (HR): 1.159; 95% Confidence Interval (CI): 0.876, 1.534). Adjusting for age, gender, race and other eye disease did not affect the likelihood that persons diagnosed with BEB were more likely to develop POAG (HR: 1.152; 95% CI: 0.870, 1.525). Blacks were more than twice as likely to receive a POAG diagnosis (HR: 2.320; 95% CI: 1.312, 4.103).

Closed angle glaucoma analysis

Eighteen (1.3%) of the BEB cohort developed CAG compared to 12 (0.9%) in the control group. In the unadjusted model, the BEB group was not more likely to develop closed angle glaucoma compared to the non BEB control group (HR: 1.477; 95% CI: 0.711, 3.066). After adjusting for covariates, a diagnosis of BEB did not affect a person's adjusted likelihood of developing CAG (HR: 1.448; 95% CI: 0.696, 3.015).

Other glaucoma (non POAG, non CAG) analysis

Other glaucoma occurred in 66 (4.9%) and 50 (3.7%) persons in the BEB and control samples respectively. In the unadjusted model, patients with BEB were not statistically significantly more likely to develop other glaucoma (HR: 1.306; 95% CI: 0.904, 1.886) compared to controls. Adjusting for additional covariates did not affect a BEB individual's probability of developing other glaucoma (HR: 1.296; 95% CI: 0.896, 1.873) compared to individuals in the control group.

Discussion

We found that BEB does not increase the risk for the development of primary open angle glaucoma among Medicare beneficiaries compared to a control group without BEB. We used CAG and other glaucoma as internal control groups and BEB did not affect the incidence risk of these groups. Reports have demonstrated that high IOP fluctuation results in visual field defect progression among patients with glaucoma.^{5–10} Meanwhile, a report from the Early Manifest Glaucoma Trial disagreed with this finding.²² Some studies have suggested that IOP fluctuation is associated with glaucoma development while others have not.^{1–4} These studies described a small mean variability in IOP of less than 10 mmHg.^{1–10}

Eyelid closure increases the intraocular pressure. Two studies found that the IOP rises by 1.5 to 3.9 mm Hg among normal and glaucomatous eyes when the patient attempts to close the eye held open by an examiner.^{23,24} However these eyes were not permitted to close fully. Miller placed a contact lens balloon attached to a pressure transducer on ten normal subjects.¹³ He found that the IOP rose by 10 mmHg and 51 mmHg with a normal blink and hard eyelid squeeze respectively. Comberg and Stoewer reported that blinking raised the IOP by 10–12 mmHg and forceful eyelid closure raised the IOP to 70 mmHg.¹⁴ Duke Elder stimulated the facial nerve in dogs and found similar results.¹² Coleman and Trokel measured intraocular pressure directly by placing a 23-gauge needle connected to a pressure monitor into the anterior chamber of an eye about to undergo enucleation. Passive blinking resulted in an increase of 5–10 mmHg. Forceful closure showed an average rise to 70 mmHg and a peak IOP of 110 mmHg.¹⁵ These studies indicate that forceful eyelid closure likely raises the intraocular pressure by at least 50 mmHg.

Patients with blepharospasm experience involuntary closure of the eyelids. This may range from increased blinking to sustained, spasmodic eyelid closure.¹¹ This almost certainly results in temporary, ultra-short term increases in IOP and high IOP variability. Patients with

BEB presumably suffer innumerable and substantial swings in IOP. Despite these large fluxes in IOP, glaucoma did not develop more frequently among the BEB group compared to controls.

Why did this study yield negative results? Perhaps IOP variability alone does not result in the development of glaucoma. Another consideration is that the presumptive spikes in IOP are too short lived to cause glaucoma. BEB patients often receive botulinum toxin A, which reduces the frequency and intensity of spastic eyelid closure. Therefore, botulinum treated patients may not suffer wide swings in IOP. Since our study looked at development of glaucoma after the diagnosis of BEB, this may have affected our results. In response to this, we queried the incidence of patients with both diagnoses of glaucoma and BEB at any time point compared to a diagnosis of glaucoma alone (data not shown). Again, no increase in risk was observed.

We acknowledge the inherent limitations of this retrospective study. However, the low prevalence of BEB makes a prospective study of glaucoma development extraordinarily difficult. With more than 1300 persons diagnosed with BEB, the present study provides a cohort large enough to determine glaucoma risk. We also recognize the lack of uniform diagnostic criteria and reporting for diagnosing BEB and various forms of glaucoma among U.S. providers. However, this study represents a national sample from real-world practitioners providing routine care, which makes our results more generalizable to all BEB patients than a rigid hospital-based clinical study. Our study was limited to patients with BEB who were 68 years or older and conceivably may not apply to younger individuals. At a minimum, we believe the results are valid for older persons who comprise the majority of persons with a glaucoma diagnosis and likely apply to younger patients as well. Further, while propensity score matching reduces selection bias between individuals with and without a specific diagnosis,^{17,18} it does not completely eliminate selection biases related to unobserved covariates and does not replace the value of random assignment in experimental designs in making causal inferences.

Despite these limitations, we believe our results are robust. This study suggests that the cumulative effects of frequent, long-term, intermittent and ultra-short term IOP elevations from BEB do not result in glaucomatous damage.

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Table 1

Diagnosis codes

Glaucoma	
Primary Open Angle	365.1x
Closed Angle	365.2x
Other	053.22, 054.44, 363.21, 364.00-2, 364.10, 364.11, 364.2, 364.21, 364.22, 364.3, 365.3x, 365.4x, 365.5x, 365.8x, 365.9, 365.6, 365.60-5, 365.73
Age-related macular degeneration	362.5, 362.50, 362.52-3, 362.57
Blindness or low vision	369.xx, V26.00, V26.10 V26.15, 92392
Cataract	366.xx, 379.31, 743.30-4, V43.1
Diabetic retinopathy	362.01, 362.02, 362.53, 362.83
Charlson comorbidity index	
<u>Charlson Comorbidities</u>	
Cerebrovascular Disease	362.34, 430.x-438.x
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Dementia	290.x, 294.1, 331.2
Chronic Pulmonary Disease	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Rheumatic Disease	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725.x
Peptic Ulcer Disease	531.x-534.x
Mild Liver Disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Diabetes without chronic complications	250.0-250.3, 259.8, 250.9
Diabetes with chronic complications	250.4-250.7
Hemiplegia or Paraplegia	334.1, 342.x, 343.x, 344.0-344.6, 344.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Malignancy	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6
Moderate or Severe Liver disease	456.0-456.2, 572.2-572.8
AIDS/HIV	042.x-044.x
Myocardial Infarction	410.x, 412.x
Peripheral Vascular Disease	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 47.1 557.1, 557.9, V43.4

Table 2

Descriptive Statistics at Baseline

	BEB group	Control group	Std Diff
Male	0.293	0.293	0.465318
Age	75.9	75.9	-0.16269
Black	0.030	0.032	-1.28699
Other race	0.025	0.034	-5.24209
Age-related macular degeneration	1.202	1.256	-3.11312
Cataract	0.133	0.146	-3.85043
Charlson comorbidity index	0.697	0.697	0
Diabetic retinopathy	0.027	0.034	-3.86148
Diabetes mellitus	0.192	0.199	-1.86698
Observations	1350	1350	

Notes: BEB – Benign essential blepharospasm; Std Diff – Standardized difference = $(100 * (x_{ti} - x_{nti})) / ((s_{ti}^2 + s_{nti}^2) / 2)^{0.5}$; i ;

*
p<0.05;

**
p<0.01;

p<0.001.

Hazard Ratios (95% Confidence Intervals) from Cox Proportional Hazard Analysis Time to Glaucoma for Persons Previously Diagnosed with BEB.

Table 3

	POAG			Closed angle glaucoma			Other glaucoma			Any Glaucoma		
	Unadjusted	Adjusted		Unadjusted	Adjusted		Unadjusted	Adjusted		Unadjusted	Adjusted	
Benign essential blepharospasm	1.159 (0.876,1.534)	1.152 (0.870,1.525)		1.477 (0.711,3.066)	1.448 (0.696,3.015)		1.306 (0.904,1.886)	1.296 (0.896,1.873)		1.156 (0.912,1.466)	1.149 (0.905,1.457)	
Age		1.005 (0.980,1.030)			1.016 (0.955,1.079)			1.017 (0.985,1.050)			1.008 (0.987,1.029)	
Male		1.061 (0.779,1.444)			0.663 (0.269,1.631)			0.855 (0.560,1.306)			1.034 (0.794,1.345)	
Black		2.320 (1.312,4.103)			3.022 (0.705,12.952)			2.038 (0.941,4.413)			1.976 (1.167,3.346)	
Other race		1.431 (0.704,2.909)			2.430 (0.574,10.292)			1.512 (0.615,3.714)			1.566 (0.877,2.798)	
Charlson comorbidity index		0.934 (0.845,1.034)			1.029 (0.807,1.312)			0.924 (0.809,1.056)			0.949 (0.873,1.032)	
Age-related macular degeneration		1.100 (0.727,1.664)			2.174 (0.936,5.052)			1.067 (0.626,1.817)			1.103 (0.779,1.562)	
Cataract		1.191 (0.864,1.641)			1.612 (0.650,3.999)			1.405 (0.906,2.177)			1.235 (0.939,1.625)	
Diabetic retinopathy		1.093 (0.468,2.553)						0.828 (0.254,2.704)			1.077 (0.518,2.238)	
Diabetes mellitus		1.099 (0.750,1.611)			0.279 (0.063,1.230)			1.338 (0.834,2.146)			1.027 (0.740,1.426)	
Observations	2,700	2,700		2,700	2,700		2,700	2,700		2,700	2,700	

Notes: BEB: Benign essential blepharospasm; POAG: Primary open angle glaucoma