Does a positive family history of glaucoma foretell severity?

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Abstract

Purpose:
There is a threefold increase in the risk of primary open-angle glaucoma (POAG) in individuals with positive family history.[1] We wished to see if the family history also led to a more severe form of the disease.

Methods:
In an IRB-approved retrospective chart study at a university-affiliated medical center, data was collected from 224 patients diagnosed with glaucoma. Positive family history was defined by first, second, or third degree relatives affected (FHx-pos). Patients with negative family history were referred to as controls. Patients with unknown family history were excluded. Age, gender, race, cup/disk ratio (C/D), visual field defects, intraocular pressure (IOP), central corneal thickness (CCT), and current glaucoma medications were recorded. FHx-pos and control groups were compared using Fisher's Exact and Wilcoxon Rank sum tests for categorical and continuous variables, respectively.

Results:
Among patients with glaucoma, there were 82, 120, and 22 patients with positive, negative, and unknown family history, respectively. The FHx-pos group was 47.6% white, 39% black, and 13.4% Hispanic, while the control group was 40.8% white, 40.8% black, and 18.4% Hispanic; no clinically significant differences were noted. Both groups were similar in age (63.3±14.8 vs. 64.9±11.8 years, p=0.5) and CCT (539 vs. 540 µm, p=0.8). The FHx-pos group was predominantly female (70.7% vs. 45%, p<0.001), had elevated IOPs (16.9±4.0 vs. 15.7±4.2 mm Hg, p=0.040), and were prescribed more glaucoma medications (98.9 vs. 92.5%, p=0.05). The mean C/D for both groups was approximately 0.73 (p=0.86) with the FHx-pos group having slightly more optic cupping (29.6 vs. 26.1% of patients, defined as C/D > 0.9; p=0.6).

Discussion:
The results suggest that glaucoma patients with affected relatives tend to be female. Sex-specific genetic factors or expression may contribute to disease progression, but a full mechanism has yet to be completely delineated. The FHx-pos group also had higher IOP, required more medications, and experienced slightly more optic nerve cupping, all of which indicate a more severe form of the disease.

Conclusion:
The results of this study corroborate the importance of taking a family history of glaucoma. This is especially important for females, for whom aggressive treatment may be necessary. The gender finding merits further study into the possible heritability of predisposing factors in the pathogenesis of POAG in female populations.

Introduction

One of the leading causes of blindness in the world, primary open-angle glaucoma (POAG) is a chronic, multifactorial disease characterized by an insidious onset of progressive vision loss secondary to optic nerve degeneration.[1,2] It is associated with inappropriately high intraocular pressure (IOP), low central corneal thickness (CCT), and a high optic cup to disk ratio (C:D) in affected eyes. It is well known that a positive family history is a significant risk factor for developing POAG. The purpose of this study was to determine, among patients with the disease, whether a positive family history also predisposed to a more severe presentation.

Methods

We carried out a retrospective chart study approved by the Institutional Review Board (IRB) at the University of Texas at Southwestern Medical Center (UTSW). Using EPIC electronic medical records, we collected information from 224 patients undergoing treatment at the James W. Aston Ambulatory Care Center affiliated with UTSW. All of these patients were diagnosed with primary open-angle glaucoma. The age (as of the date of data collection or death), gender, race, cup/disk ratio (C/D), visual field (VF) defects, intraocular pressures (IOP; in mm Hg), central corneal thickness (CCT; in µm), and current glaucoma medications of each patient were recorded. Visual field defects, if present, were categorized as normal, mild, moderate, or severe. The IOPs were calculated as an average of three most recent measurements.

Shown below is a copy of the data form we utilized:

Study date: _____/_____/_____

Patient Information and Demographics
Name (last, first): _____
MR # (last 4): _____
DOB: ____/____/____

Gender: (1/2) *(1=M | 2 = F)*

Race: (0/1/2/3/4/5/6)
(0=white | 1=Black | 2=Hispanic | 3=Asian | 4=East Indian | 5=N/A | 6=other)

Glaucoma information
Glaucoma diagnosis: OD:(0/1/2/3/4) OS:(0/1/2/3/4)
(0=no glaucoma | 1= POAG | 2=LTG/NTG | 3= suspect | 4= other) .

Family history: (0/1/2/3/4)
(0=no | 1= first degree (parents, siblings, offspring) | 2= second degree (grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling) | 3=third degree (first-cousins, great-grandparents or great grandchildren) | 4=unknown)

Date of diagnosis or clinic visit with eye note:
____/_____/_____

Cup/Disc ratio: OD:_____ OS:_____

VF defects: OD: (0/1/2/3) OS: (0/1/2/3)
(0= normal | 1= mild | 2= moderate | 3=severe)

IOP (average of 3): OD:____ OS:____

CCT: OD:____ OS:____

Current glaucoma treatment: (0/1)
(0=no meds | 1=yes | total # of meds_____)

A=Beta blocker: 1=Timolol, 2=Betimol, 3=Betoptic, 4=Betagan, 5=Istalol, 6=Carteolol
B=Agonist: 7=Brimonidine, 8=Iopidine
C=Prostaglandin: 9=Travatan, 10=Xalatan, 11=Lumigan
D=CAI topical: 12=Azopt, 13=Trusopt,
E=CAI oral: 14=Neptazane, 15=Diamox
F=Combo: 16=Cosopt (Dorzolamide/Timolol), 17=Combigan (Brimonidine/Timolol).
18= Simbrinza (Brinzolamide/Brimonidine)
G=Sympathomimetic: 19=Propine
H=Miotics: 20=Pilocarpine, 21=Carbachol

A total of 224 patients were divided into two groups: 82 with positive family history and 120 without. Positive family history was defined as having at least a first, second, or third degree relative diagnosed with glaucoma (FHx-pos). Patients with negative family history were referred to as controls. The remaining 22 patients with an unknown family history were excluded from further statistical analysis. The FHx-pos and control groups were compared using Fisher's Exact and Wilcoxon Rank sum tests for categorical and continuous variables, respectively.

Results and Discussion

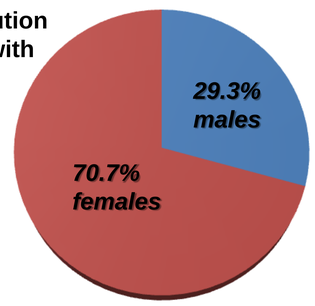
Table 1:

Demographics		FHx-pos	Controls	p-value
Age (years)		63.3 ± 14.8	64.9 ± 11.8	0.532
Gender:	% Males	29.3	55	< 0.001
	% Females	70.7	45	
Race:	% White	47.6	40.8	0.532
	% Black	39	40.8	
	% Hispanic	13.4	18.4	

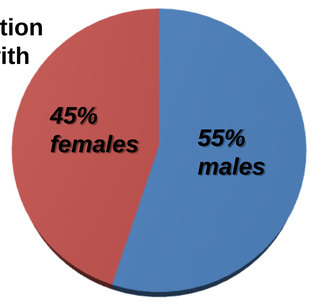
Table 2:

Manifestations		FHx-pos	Controls	p-value
VF defects:	% normal	9	18	0.159
	% mild	28.2	31.5	
	% moderate	24.4	13.5	
	% severe	38.5	37	
Cup/disk (mean)		0.73 ± 0.19	0.73 ± 0.18	0.860
Cup/disk %(≥ 0.9)		29.6	26.1	0.628
Cup/disk %(≥ 0.8)		49.4	48.7	1.000
Cup/disk %(≥ 0.5)		89	87	0.826
Cup/disk %(≥ 0.3)		100	98.3	0.513
CCT (average, µm)		539 ± 67.0	540 ± 39.3	0.800
IOP (average, mm Hg)		16.9 ± 4.0	15.7 ± 4.2	0.040
% taking glaucoma meds		98.8	92.5	0.051

Gender distribution of individuals with positive family history:



Gender distribution of individuals with negative family history:



Results and Discussion (cont.)

For each of the variables in Tables 1 and 2, a p-value less than 0.05 was deemed clinically significant. In other words, differences between the FHx-pos and control groups in those variables were largely attributable to the effect of family history on the clinical severity of POAG. Out of the 224 patients diagnosed with primary open-angle glaucoma, 82, 120, and 22 patients had a positive, negative, and unknown family history, respectively. The racial composition of the FHx-pos group was 47.6% white, 39% black, and 13.4% Hispanic, while that of the control group was 40.8% white, 40.8% black, and 18.4% Hispanic. No clinically significant differences were noted (p=0.532). The average age of the FHx-pos group was 63.3±14.8 years, while that of the control group was 64.9±11.8 years (no significant differences, p=0.532). The average CCT of the FHx-pos group was 539±67.0 µm while that of the control group was 540±39.3 µm (no significant differences, p=0.8). The mean C/D for the FHx-pos group was 0.73±0.19 while that of the control group was 0.73±0.18 (no significant differences, p=0.86). The FHx-pos group experienced slightly more severe optic cupping (29.6% vs. 26.1% of controls, defined as C/D>0.9; p=0.628, not significant).

The FHx-pos group was composed of 70.7% females and 29.3% males, while the control group was 45% female and 55% male. This finding was clinically significant with p<0.001. The FHx-pos group had an average IOP of 16.9±4.0 mm Hg while that of the control group was 15.7±4.2 mm Hg. This finding was clinically significant with p=0.04. Lastly, 98.9% of the FHx-pos group was taking glaucoma medications as of the study date, in contrast to 92.5% of the controls. With p=0.051, this was deemed borderline significant.

Overall, the results strongly suggest that glaucoma patients with affected relatives tend to be female. Sex-specific genetic factors or expression may contribute to the onset and course of the disease, but a full mechanism has yet to be completely delineated. The FHx-pos group also experienced higher IOP, were prescribed more glaucoma medications, and experienced slightly more optic nerve cupping, all of which indicate a more severe form of the disease.

Conclusion

The results of this study corroborate the importance of taking a thorough family history of glaucoma in suspecting individuals. This is especially important for females, for whom aggressive treatment may be necessary. The implication that glaucoma patients with affected relatives were more likely to be female and develop higher IOPs merits further study into the possible heritability of predisposing sex-specific factors in the pathogenesis of POAG.

References

1. Weih LM, Nanjan M, McCarty CA, et al. Prevalence and predictors of open-angle glaucoma: Results from the Visual Impairment Project. Ophthalmology 2001; 108(11):1966-1972

2. Fingert JH. Primary open-angle glaucoma genes. Eyes. 2011; 25, 587-595

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