

Prevalence of Glaucomatous Disease in Young Chinese Adults: A Pilot Study

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Received date: Jan 26, 2014, Accepted date: Mar 27, 2014, Published date: Apr 03, 2014

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Abstract

Purpose: To estimate the prevalence of glaucomatous disease in a pilot study of young adults with Chinese ancestry.

Methods: 164 adults residing in the United States (US) between 20 and 40 years of age inclusively, who self-identified as being born to two ethnically Chinese parents, were prospectively recruited at nine university and medical center campuses in the US without disclosing the study's purpose. All subjects completed a standardized, closed-ended questionnaire detailing their genealogy and ocular history, followed by a comprehensive ophthalmic examination, including measurement of intraocular pressure (IOP), central corneal thickness (CCT), and axial length. Participants suspected of having glaucoma based on family history, optic nerve appearance, or IOP also underwent static automated white on white threshold perimetry. Main outcome measures included the prevalence of glaucomatous appearing optic nerves and visual fields as well as associated clinical parameters, including myopia, tilted optic nerves, and peripapillary atrophy. All comparisons were performed using the Student's T, Mann-Whitney U, Pearson's χ^2 , and Fisher's exact tests.

Results: Nine subjects (5.5%) were observed to have optic nerve appearance and visual field defects suggestive of glaucomatous disease. There was no statistically significant association between this cluster of findings and any other measured clinical parameter.

Conclusions: Young adult individuals of Chinese ancestry may be at substantial risk for glaucomatous disease. Given the cross sectional nature of this study, longitudinal follow-up of participants deemed to be suspicious for glaucoma will be necessary to ascertain whether or not they demonstrate a progressive course consistent with glaucomatous disease.

Keywords: Prevalence; Glaucoma; Chinese

Introduction

Population- and hospital-based studies have shown myopia to be a risk factor for glaucomatous optic neuropathy in many populations throughout the world [1-11], including those of Asian ancestry [12,13]. In urban and suburban Chinese populations specifically, the prevalence of both myopia and glaucomatous disease has increased in successive generations [14-17].

Doshi et al. described a series of sixteen young to middle-aged Chinese males who presented with optic nerve appearance and visual

field loss suggestive of glaucomatous disease and were followed for up to seven years without progression of presumed disease [18]. This report raised the possibility that axial myopia may mimic glaucomatous disease in addition to increasing the risk of open angle glaucoma. Chao et al. subsequently described a series of twenty individuals of Chinese ancestry with the same cluster of clinical findings, but were unable to demonstrate that axial length predicted the degree of visual field loss in individuals in whom one eye demonstrated more advanced optic neuropathy than the other [19]. Given the increasing prevalence of open angle glaucoma in urban Chinese populations as exemplified by the outcomes of the Beijing Eye Study, which also found myopia greater than 6.0 diopters to increase the risk of glaucomatous optic neuropathy [12], there is great interest

in the relationship between myopia and glaucoma in this and other regions of the world.

The purpose of our study was to obtain pilot information regarding the prevalence of the above-mentioned cluster of findings including myopia, tilted optic nerves, peripapillary atrophy (PPA), visual field defects, and suspicion or diagnosis of glaucoma in young individuals with Chinese ancestry residing in the United States.

Materials and Methods

Recruitment commenced after receiving approval from each site's respective institutional review board. Male and female individuals were recruited at university and medical center campuses without disclosing that the purpose of the study was to assess glaucoma prevalence. The inclusion criteria were self-identified Chinese ancestry, defined as being born to two ethnically Chinese parents, and age between 20 and 40 years inclusively. There were no exclusion criteria based upon history of ocular disease.

Participants completed a standardized, closed-ended questionnaire, and underwent screening for glaucomatous disease. The questionnaire included country of birth and the genealogy of the participant's parents (mainland China, Hong Kong, Taiwan, Singapore, or other). Ophthalmic evaluation began with a detailed family, medical, and ocular history, including history of myopia, glaucoma, glaucoma-suspect, ocular hypertension, and previous eye surgery. Comprehensive ophthalmic examination included measurement of visual acuity, manifest refraction, slit-lamp biomicroscopy of the anterior segment, measurement of intraocular pressure (IOP) by Goldmann applanation tonometry, dilated or undilated evaluation of the optic nerve with a 90 diopter handheld lens, measurement of central corneal thickness, and measurement of axial length. The performance of gonioscopy, which was not a requisite test in this study, was left to the discretion of the investigator's judgment regarding whether or not it was medically necessary.

Participants determined to be glaucoma suspects based on family history, optic nerve appearance, or IOP greater than 21 mmHg underwent static automated white on white threshold perimetry using a Humphrey Visual Field 30-2 SITA standard algorithm. A glaucomatous visual field defect was defined as a cluster of three or more non-edge contiguous points in a glaucomatous pattern with a probability of <5% on the pattern deviation plot. Visual field reliability was defined by fixation losses <20%, false positives <33%, and false negatives <33%. Glaucomatous visual field defects were not confirmed with repeat perimetry.

Statistical analyses were performed with a commercially available software package (SPSS for Mac, Version 20.0, SPSS, Chicago, Illinois). Confidence intervals for proportions were calculated using Microsoft Office Excel (Microsoft Corporation, Redmond, Washington). All comparisons were performed using either the Student's T test or the Mann-Whitney U test for parametrically and non-parametrically distributed data, respectively, with the data presented as mean values \pm standard deviation. Correlations between ordinal variables were calculated using Pearson's χ^2 and Fisher's exact tests and provided as percentages (95% confidence interval). All P-values were 2-sided and considered statistically significant when <0.05.

Results

One-hundred-sixty-four participants meeting the study inclusion criteria were enrolled after obtaining informed consent from the nine sites listed in Table 1. The mean age was 28.5 ± 5.3 years, and 59.1% (51.3-66.9) of subjects were female. All subjects self identified as the offspring of two Chinese parents, with 60.4% (52.6-68.2) having two parents from mainland China, 23.2% (16.4-30.0) having two parents from Taiwan, 3.7% (0.5-6.9) having two parents from Hong Kong, 0.6% (-0.9-2.1) having two parents from Singapore, and half of the remainder having one parent from mainland China (5.6%) (Table 2).

Institution	Participants Enrolled
	<i>n/N, %</i>
Stanford U	32/164, 19.5
U of CA, Los Angeles	30/164, 18.3
U of Colorado	30/164, 18.3
U of Iowa	30/164, 18.3
Washington U	26/164, 15.9
MA Eye and Ear Infirmary	9/164, 5.5
Yale U	7/164, 4.3
U of Texas, Houston	5/164, 3.0
U of Southern CA	5/164, 3.0
CA: California; MA: Massachusetts; U: University	

Table 1: Study Sites.

Parameter	Value
	<i>Mean \pm SD, Range</i>
Age yrs	28.5 ± 5.3
	<i>n/N, % (95% CI)</i>
Female	97/164, 59.1 (51.3-66.9)
Place of Birth:	
MC	63/164, 38.4 (30.7-46.1)
USA	62/164, 37.8 (30.1-45.5)
TW	22/164, 13.4 (7.9-18.9)
SP	5/164, 3.0 (0.1-5.9)
Unknown	4/164, 2.4 (-0.2-5.0)
HK	3/164, 1.8 (-0.5-4.1)
IND	2/164, 1.2 (-0.8-3.2)
Malaysia	1/164, 0.6 (-0.9-2.1)
Parental Genealogy:	
<i>Parent 1, Parent 2</i>	
MC, MC	99/164, 60.4 (52.6-68.2)

TW, TW	38/164, 23.2 (16.4-30.0)
Unknown	8/164, 4.9 (1.3-8.5)
HK, HK	6/164, 3.7 (0.5-6.9)
MC, HK	4/164, 2.4 (-0.2-5.0)
MC, SP	2/164, 1.2 (-0.8-3.2)
MC, TW	2/164, 1.2 (-0.8-3.2)
Burma, Burma	1/164, 0.6 (-0.9-2.1)
IND, IND	1/164, 0.6 (-0.9-2.1)
MC, Burma	1/164, 0.6 (-0.9-2.1)
SP, SP	1/164, 0.6 (-0.9-2.1)
CI: Confidence Interval; HK: Hong Kong; IND: Indonesia; MC: Mainland China; SD: Standard Deviation; SP: Singapore; TW: Taiwan; USA: United States of America.	

Table 2: Demographic Characteristics of the Cohort.

Table 3 shows the clinical characteristics of the study subjects, of whom 15.2% (9.4-21.0) had a family history of glaucoma, 1.2% (-0.8-3.2) had a family history of glaucoma-suspect or ocular hypertension, and 76.2% (69.4-83.0) began wearing glasses to correct myopic refractive error prior to 18 years of age. Only 1.2% (-0.8-3.2) of subjects had a history of glaucoma, and 1.2% (-0.8-3.2) had previously been given a diagnosis of ocular hypertension or glaucoma-suspect, but none of these four subjects were among the nine found to have optic nerve appearance and visual field loss suspicious for glaucomatous disease. Three percent (0.1-5.9) of subjects had previously undergone LASIK, of whom one also had a history of a retinal laser procedure. One subject reported prior strabismus surgery without a known history of amblyopia. No participant had previously undergone IOP lowering surgery, and none were receiving IOP lowering medications at the time of the study.

Parameter	Value
	<i>n/N, %(95% CI)</i>
Ocular History	
FH of Glc	25/164, 15.2 (9.4-21.0)
FH of Glc-S or OHTN	2/164, 1.2 (-0.8-3.2)
Myopic Spectacles prior to age 18	125/164, 76.2 (69.4-83.0)
POH of Glc	2/164, 1.2 (-0.8-3.2)
POH of Glc-S or OHTN	2/164, 1.2 (-0.8-3.2)
Prior LASIK	5/164, 3.0 (0.1-5.9)
Ocular Exam	
GON with corresponding VF loss	9/164, 5.5 (1.7-9.3)
Tilted Nerve(s)	109/164, 66.5 (59.0-74.0)
Peripapillary Atrophy	91/164, 55.5 (47.6-63.4)
Myopia	160/164, 97.6 (95.0-100.2)

Myopia > 6.0 Diopters	60/164, 36.6 (28.9-44.3)
	<i>Mean ± SD, Range</i>
VCDR	0.33 ± 0.16, 0.10-0.70
CD Asymmetry	0.04 ± 0.06, 0.0-0.25
IOP	14.8 ± 2.5, 8.5-23.5
CCT	553.8 ± 37.8, 432.5-661.0
SE	-7.3 ± 4.3, -20.1-0.0
Axial length	25.5 ± 1.4, 22.3-28.7
Axial length Asymmetry	0.4 ± 0.5, 0.0-2.9
VA, logMAR	0.002 ± 0.06, -0.12-0.54
CCT: Central Corneal Thickness; CD: Cup/Disk; CI: Confidence Interval; FH: Family History; Glc: Glaucoma; GON: Glaucomatous Optic Neuropathy; Glc-S: Glaucoma-Suspect; IOP: Intraocular Pressure; OHTN: Ocular Hypertension; POH: Past Ocular History; SD: Standard Deviation; SE: Spherical Equivalent; VA: Visual Acuity; VCDR: Vertical Cup to Disc Ratio; VF: Visual Field.	

Table 3: Clinical Characteristics of the Cohort.

Of the 164 subjects who completed the study, nine had optic nerve appearance and visual field loss suspicious for glaucomatous disease (5.5% [1.7-9.3]). Each of these nine individuals had a suspicious optic nerve in both eyes, but manifested glaucomatous visual field loss in only one eye. Five subjects demonstrated arcuate scotomas [55.6% (17.6-93.6)] and four were noted to have nasal steps [44.4% (6.4-82.4)]. None of the visual field defects in these 9 subjects were deemed to be typical of those previously described as characterizing “tilted nerve syndrome” [20]. Sixty-seven percent of subjects (66.5% [59.0-74.0]), however, exhibited some degree of unilateral or bilateral optic nerve tilting. 55.5% (47.6-63.4) demonstrated PPA in one or both eyes, 97.6% (95.0-100.2) were myopic, and 36.6% (28.9-44.3) had greater than 6.0 diopters of myopia. The average vertical cup:disc ratio and cup:disc asymmetry was 0.33 ± 0.16, and 0.04 ± 0.06, respectively. The mean IOP was 14.8 ± 2.5 mmHg. After excluding the five participants who had previously undergone refractive surgery, the mean spherical equivalent (SE) was -7.3 ± 4.3, with an average axial length of 25.5 ± 1.4 mm. The average difference in axial length between the two eyes was 0.4 ± 0.5 mm. Mean logMAR visual acuity was 0.002 ± 0.06.

There was a higher frequency of tilted optic nerves and PPA in subjects with optic nerve appearance and visual field loss suggestive of glaucomatous disease compared to those considered not to be glaucomatous (tilted nerves, 77.8% [45.1-110.5] vs. 65.8% [58.0-73.6], $P=0.72$ Fisher’s Exact Test; PPA, 66.7% [30.4-103.0] vs. 54.8% [46.6-63.0], $P=0.73$ Fisher’s Exact Test); however, these differences were not statistically significant. Another non-statistically significant finding was a higher frequency of myopia greater than 6.0 diopters among participants with optic nerve appearance and visual field loss suggestive of glaucomatous disease versus all other subjects (66.7% [30.4-103.0] vs. 34.8% [27.0-42.6], $P=0.08$). Not surprisingly, subjects demonstrating optic nerve appearance and visual field loss suggestive of glaucomatous disease had a larger mean VCDR compared to subjects without these findings (0.44 ± 0.15 vs. 0.33 ± 0.15, $P=0.03$). There were no significant differences, however, in the mean axial length (26.1 ± 1.0 vs. 25.4 ± 1.4 mm, $P=0.19$) or in the average axial length asymmetry (0.38 ± 0.4 vs. 0.43 ± 0.5 mm, $P=1.00$ Mann-

Whitney U test) between those suspected and not suspected of having glaucomatous disease.

There was a higher frequency of tilted nerves and PPA among participants with myopia greater than 6.0 diopters compared to all others (tilted nerves, 81.7% [73.8-89.6] vs. 57.7% [44.4-71.0], $P=0.002$; PPA, 70.0% [60.7-79.3] vs. 47.1% [33.6-60.6], $P=0.005$).

Univariate binary logistic regression analyses in which the dependent variable was optic nerve appearance and visual field loss suggestive of glaucomatous disease showed no statistically significant predictors of this condition. For the variables of age, gender, myopia greater than 6.0 diopters, axial length, axial length asymmetry, tilted nerves, and PPA, all P -values were > 0.1 , excepting myopia greater than 6.0 diopters for which the P -value was 0.08 with an Odds-Ratio of 3.7.

Discussion

To the best of our knowledge, this is the first prospective, multi-center cross-sectional study to estimate the prevalence of optic nerve appearance and visual field loss suspicious for glaucoma in young adults of Chinese ancestry residing in the United States. Among 164 participants who self-identified as being 100% Chinese, nine (5.5%) had optic nerve appearance and visual field loss suggestive of glaucomatous disease based on a single evaluation. Given the modest size of the survey, it is not surprising that a statistically significant association between glaucoma diagnosis and any measured risk factor for the disease was not found. There was, however, a statistically insignificant 32% higher frequency of myopia greater than 6.0 diopters among the 9 participants with optic nerve appearance and visual field loss suggestive of glaucomatous disease compared to all other subjects (66.7% vs. 34.8%; $P=0.08$). A post hoc power calculation revealed that, given the study sample size, a relationship between high myopia and glaucomatous disease would only be statistically significant when the frequency of this parameter differed by at least 45% between the glaucomatous and non-glaucomatous groups.

Whether these 9 subjects characterized as having glaucoma will show progressive disease characteristic of glaucomatous optic neuropathy rather than a relatively static condition similar to what has been previously described in other young Chinese individuals with myopia [18] remains to be seen. Indeed, approximately half of all untreated subjects in the Collaborative Normal Tension Glaucoma Study showed no progression over 5 years and it is noteworthy that Asian race was found to be a protective variable with regard to progression [21]. Longitudinal follow-up of the nine subjects in our study deemed to be suspicious for glaucomatous disease will be of interest in the coming years.

Although our study differs from previous surveys of ethnic Chinese populations in that we surveyed individuals residing in the United States, our observations seem consistent with those reported from Singapore [12], where a high frequency of myopia greater than 6.0 diopters was noted in individuals determined to have glaucomatous disease. The Singaporean Eye Study (SES) also based the diagnosis of glaucoma on one clinical evaluation of optic nerve appearance and static automated perimetry without evaluating for progression and thus, as with our study, it is possible that some of the individuals found to have high myopia and presumed glaucomatous disease may have had a condition that does not follow a course characteristic of

progressive glaucomatous disease. While our study showed no statistically significant differences in the frequency of tilted optic nerves and PPA in subjects classified as being suspicious for glaucoma compared to those without such findings ($P=0.72$, $P=0.73$, respectively), a higher frequency of tilted optic nerves and PPA was observed among participants with myopia greater than 6.0 diopters relative to all other subjects ($P=0.002$, $P=0.005$, respectively). Such an association between refractive error and optic nerve morphology has also been postulated in the Singaporean Chinese [22,23].

A larger mean VCDR was the only variable significantly associated with glaucomatous visual field loss in our study. Nevertheless, 8 of 9 participants with visual field loss characteristic for glaucomatous disease had either tilted optic nerves or PPA, and it is noteworthy that 73% (65.9-80.1) of all study subjects were also found to have at least one of these two characteristics. A previous study has posited pathophysiologic mechanisms by which oblique insertion of the optic nerve into the globe in myopes may cause damage to ganglion cell axons that is subsequently not progressive in a manner characteristic of glaucomatous optic neuropathy [18]. It is certainly possible that some in our study deemed to have glaucomatous disease will follow a similar course. Given that this was a cross sectional rather than longitudinal study, tests that would commonly be employed to establish a baseline for follow up, including optic disc photography and optical coherence tomography (OCT), were not employed.

The most significant limitation of this prevalence survey is the small number of subjects who were evaluated for glaucomatous disease. The cross sectional nature of the study, as is typical for prevalence surveys, also does not allow confirmation of the diagnosis of a progressive disease such as glaucoma. This study should therefore be considered a pilot for a larger cohort investigation that will undoubtedly provide greater insight into the risk factors associated with glaucomatous appearing optic nerves and visual field loss in young Chinese individuals. One could argue that it would have been beneficial to have obtained a visual field for every participant in the study rather than selectively for those with a family history of glaucoma, suspicious optic nerve appearance, or IOP greater than 21 mmHg. To the extent that some such individuals who did not undergo visual field testing may have ultimately been found to have glaucomatous disease, our study may underestimate the true prevalence of glaucoma in this population. Other factors contributing to such underestimation of glaucomatous disease prevalence include the absence of OCT and blue on yellow perimetry, two tests which would undoubtedly have increased sensitivity to ascertain disease at the expense of decreased specificity. Our findings are thus made more compelling by the fact that these two tests were not employed.

In summary, this prospective, multi-center, cross-sectional survey of 164 young adults of Chinese ancestry studying or working in academic medical centers throughout the United States found 9 (5.5%) to have optic nerve appearance and visual field loss suspicious for glaucoma. While there was no statistically significant association between the finding of glaucomatous disease and any measured clinical parameter, there was a statistically insignificant difference ($P=0.08$) in the proportion of subjects with myopia greater than 6.0 diopters between those with and without a glaucoma diagnosis. This study should serve as a pilot for future work studying the epidemiology of glaucomatous disease in young myopes in an era of exponentially increasing rates of myopia in successive generations of individuals with Chinese ethnicity throughout the world.

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