ORIGINAL ARTICLE

Association Between High Myopia and Progression of Visual Field Loss in Primary Open-angle Glaucoma

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Background/Purpose: Taiwan has a very high prevalence rate of myopia. We retrospectively studied the influence of myopia on the progression of visual field (VF) loss in primary open-angle glaucoma (POAG) patients.

Methods: We studied 515 POAG patients for a minimum follow-up period of 5 years. VF examination was performed with Humphrey perimeter, 30-2 SITA standard program, every 6 months. A point-wise numerical comparison was applied to judge the VF changes. Test points showing more than 1.0 dB of sensitivity loss in mean defect were identified. A location was considered to have progression if it was detected on two consecutive visits. Progression of VF loss was confirmed if three or more test points deteriorated. Multivariate logistic regression was used to evaluate the association between progression of VF loss and various risk factors.

Results: There were 262 cases. Progression of VF loss occurred in 57 eyes (21.8%) during the 5-year follow-up period. Logistic regression revealed that the deterioration was associated with older age, higher mean intraocular pressure, larger vertical cup-to-disc ratio, and greater myopic refraction status. The incidence of VF loss progression was 15.1% in the group of eyes with myopia less than −3 D, 10.5% in the group with −3 D to −6 D, 34.4% in the group with −6 D to −9 D, and 38.9% in the group with myopia greater than −9 D.

Conclusion: POAG patients with myopia greater than −6 D had a greater progression of VF loss. [*J Formos Med Assoc* 2008;107(12):952–957]

Key Words: glaucoma, myopia, visual field

Glaucoma affects more than 66 million people worldwide, and at least 6.8 million individuals have bilateral blindness.[1] Primary open-angle glaucoma (POAG) is the most common type of glaucoma.[2] It is a slow progressive degeneration of retinal ganglion cells and results in a characteristic appearance of the optic disc and concomitant visual field (VF) loss. Without adequate and timely treatment, patients with POAG are threatened with visual disability and possible blindness. A better understanding of the risk factors that contribute to disease progression would be helpful in the management and prevention of further degeneration of retinal ganglion cells.

Glaucomatous VF defects may continue to progress despite good control of intraocular pressure (IOP). Over the past few decades, various studies have identified many risk factors for the incidence and prevalence of glaucoma, but few risk factors that contribute to deterioration of glaucoma

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damage have been reported. These risk factors include increased IOP, diurnal IOP variation,[3,4] disc crescent,[5] and disc hemorrhage.[6,7] There is still a lack of evidence to link other reported risk factors with progression of glaucoma, such as myopia.

Myopia has reached epidemic proportions and is already a serious public health problem in certain parts of the world,[8] including Taiwan.[9] Myopic eyes may be more susceptible to glaucomatous damage at certain levels of IOP for the following reasons. The myopic scleral canal is unusually large, abnormally shaped and tilted,[10] and the myopic lamina cribrosa and peripapillary sclera are unusually thin.[11,12] This may intensify the stress for a given level of IOP.[12] However, the clinical results are not conclusive. Mitchell et al reported increased risk of ocular hypertension in the low myopic group (myopia < −3 D) in the Blue Mountains Eye Study,[13] but they did not find any difference between low and moderate-to-high myopia groups. In the Ocular Hypertension Treatment Study, Kass et al did not show that myopia > −1 D was a significant risk for the onset of glaucomatous damage.[14] In their study of anisometropia, Jonas et al found no considerable difference in neuroretinal rim area and mean VF defect between the eyes, and suggested that for eyes with myopia < −8 D, refractive error did not contribute much to optic nerve head susceptibility to certain IOP levels.[15] However, Chihara and associates made a different observation. They found that moderate-to-severe myopia (> −4 D), but not mild myopia, was a significant risk factor for the progression of VF loss in glaucoma.[16] In the present study, we tried to elucidate the relationship between myopia and the progression of VF loss in POAG patients.

Methods

Patients and examinations

After being approved by the Institutional Review Board for Human Research of the National Taiwan University Hospital, we reviewed the medical records of 515 POAG patients who had been regularly followed-up every 3 months at the glaucoma clinic of National Taiwan University Hospital from January 1995 to December 2005. Minimum follow-up period was 5 years. Ophthalmic examinations included best corrected visual acuity, slit lamp biomicroscopy, evaluation of IOP (Goldmann applanation tonometer), measurement of central corneal thickness (CCT) using ultrasonic pachymetry (Micropach 200P+; Sonomed, Lake Success, NY, USA), and ocular biometry using A-scan ultrasonography (A-1500; Sonomed). Cycloplegic refractive status was determined by an autorefractometer (RK-3000; Topcon, Tokyo, Japan) and stereophotographs were obtained (Topcon TRC-SS2). Spherical equivalent refractive error was calculated as: (sphere + 1/2 cylinder), and expressed in diopters (D) for analysis. VF examination (30-2 SITA standard, Visual Field Analyzer Model 745i; Allergan-Humphrey, San Leandro, CA, USA) was performed on a 6-monthly basis.

The exclusion criteria were: history of ocular trauma or surgery; conditions that may produce VF defects such as corneal opacity, retinopathy, pupil diameter < 3 mm, and non-glaucomatous optic neuropathy; best corrected visual acuity worse than 20/30; and age < 15 or > 75 years. For patients who had POAG in both eyes, the one with milder VF defect was selected for analysis.

Diagnosis of POAG

Stereophotographs were examined. The optic cup was defined on the basis of contour and not of pallor. The border of the optic disc was identical with the inner side of the peripapillary scleral ring. Cup-to-disc (C/D) ratios were computed for vertical and horizontal meridians in each eye. Glaucomatous changes of the optic nerve head included thinning of the inferior or superior neuroretinal rim, and localized or diffuse retinal nerve fiber layer defects. The vertical C/D ratio was used for analysis.

Characteristic glaucomatous VF loss was defined as the following defects not explained by other ocular or neurologic causes: (1) at least three non-edge adjacent test points with a deviation

deeper than 5 dB, and one must be deepened by 10 dB; and (2) at least two non-edge adjacent points with a deviation deeper than 10 dB. The points must be in a cluster in an expected location. The rate of false-positive and false-negative answers had to be ≤ 15%.

The diagnosis of POAG was made by a typical glaucomatous optic neuropathy associated with corresponding VF defects. The patient should have an open and normal anterior chamber drainage angle, and only glaucoma could have explained the optic neuropathy and VF defects. Pre-perimetric glaucoma patients were excluded from this study.

Definition of progression of VF loss

Three VFs were obtained in the first 6 months, and the last two measurements were averaged as the baseline. A point-wise numerical comparison was applied to judge the serial VF examination changes. Test points that showed ≥ 1.0 dB sensitivity loss in mean defect were identified at each follow-up visit. A point was considered to have confirmed progression if it was detected in the same point in two consecutive fields. The criteria for VF progression were confirmed progression in three or more test points.[17] If VF only showed progression the first time, and the next VF result was back to baseline or better than baseline, the first VF result was regarded as no progression and discarded. If the patient's visual acuity had changed more than two lines between VF examinations, the VF results were also abandoned.

Statistical analysis

We used multivariate logistic regression to evaluate the association between progression of VF loss and risk factors. Mean IOP was the average of measurements taken on a 3-monthly basis. Progression of VF loss and IOP (> 21 mmHg or ≤ 21 mmHg) during the follow-up period was the two binary variables in the logistic regression. The other variables were continuous variables. We divided the patients into four groups by their refraction status: (1) myopia ≤ −3 D; (2) myopia > −3 D, but ≤ −6 D; (3) myopia > −6 D, but ≤ −9 D; and (4) myopia > −9 D. We compared the incidence of VF loss progression between groups. The software package SAS version 9.0 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

There were 262 cases, with a mean age of 48.6 ± 14.2 years (range, 16–75); 163 were male and 99 were female. We selected 136 right eyes and 126 left eyes for data analysis. Patients were excluded because of irregular follow-up or VF examination schedule (172 cases), age > 75 years (38 cases), and best corrected visual acuity worse than 20/30 in the better eye (43 cases). The mean follow-up period was 8.7 ± 2.2 years and the patients had 14.8 ± 3.6 VF tests.

Progression of VF loss occurred in 57 eyes (21.8%) in the 5-year follow-up period. As compared with the eyes without VF progression, the eyes with VF progression were from older patients (51.4 ± 12.3 years *vs.* 46.4 ± 14.2 years, $p = 0.034$); had higher mean IOP (16.1 ± 3.7 mmHg *vs.* 15.8 ± 2.8 mmHg, $p = 0.015$); had more eyes with IOP > 21 mmHg (24.6% *vs.* 11.7%, $p = 0.034$); had higher initial vertical C/D ratio (0.83 ± 0.14 *vs.* 0.73 ± 0.16, $p < 0.001$); had greater myopic refraction status (−7.10 ± 4.40 D *vs.* −4.55 ± 4.00 D, $p < 0.001$); and had longer ocular axial length (26.49 ± 1.95 mm *vs.* 25.39 ± 1.83 mm, $p < 0.001$) (Table 1). Their difference in CCT was not remarkable (545.0 ± 29.1 μm *vs.* 549.2 ± 34.6 μm, $p = 0.449$).

We used logistic regression to evaluate the influence of these parameters on progression of VF loss. The variables of logistic regression included age, CCT, mean IOP, C/D ratio, and refraction status. The results revealed that older age, higher mean IOP, larger vertical C/D ratio, and greater myopic refraction status were risk factors for progression of VF loss (Table 2). Thinner CCT was not a significant risk factor for progression of VF loss ($p = 0.924$).

Progression of VF loss between patients with different refraction status is shown in Table 3. Eyes with greater myopic refraction status showed a higher progression rate than those with lower

Table 1. Comparison of risk factors between eyes with and without progression of visual field (VF) loss*

	With VF loss progression	Without VF loss progression	Total	*p*
Eyes	57 (21.8)	205 (78.2)	262 (100)	
Age (yr)	51.4 ± 12.3 (24–74)	46.4 ± 14.2 (16–74)	48.6 ± 14.2 (16–74)	0.034
Central corneal thickness (μm)	545.0 ± 29.1 (488–630)	549.2 ± 34.6 (472–707)	548.3 ± 33.5 (472–707)	0.449
Mean IOP (mmHg)	16.1 ± 3.7 (10–26)	15.8 ± 2.8 (9–26)	15.9 ± 2.9 (9–26)	0.015
Eyes with IOP > 21 mmHg	14 (24.6)	24 (11.7)	38 (14.8)	0.02
Initial VF mean defect (dB)	−5.59 ± 4.33	−5.03 ± 4.50	−5.10 ± 4.41	0.156
Vertical cup-to-disc ratio	0.83 ± 0.14	0.73 ± 0.16	0.75 ± 0.15	< 0.001
Refraction status (D)	−7.1 ± 4.4	−4.55 ± 4.0	−5.1 ± 4.2	< 0.001
Ocular axial length (mm)	26.49 ± 1.95	25.39 ± 1.83	25.63 ± 1.90	< 0.001

**Data presented as n (%) or mean ± standard deviation (range) or mean ± standard deviation. IOP = intraocular pressure.*

status. This phenomenon was more evident when the refraction status was more myopic than −6 D.

Discussion

The present study revealed that IOP and greater myopic refraction status were risk factors for progression of VF loss in POAG patients.

There is no consensus about the best method to detect progression of VF loss. The ideal method for analyzing VF changes should discover progression with a few examinations and be resistant to fluctuation. Methods that yield a high number of progressive cases are often less specific and are influenced by fluctuation. In contrast, those methods that have high specificity often require very long follow-up times. Point-wise linear regression analysis (PLRA) generally has high specificity.[17] The main drawback of this method is that it requires a long time to detect progression. Another issue of PLRA is that there is no accepted criterion on either the number of test locations that show significant decline in sensitivity, or the magnitude of change (db/year) at each location. However, this is also a common problem for other methods.

Whether myopic eyes are more susceptible to glaucomatous damage is still debatable, but increasing evidence supports the suggestion that highly myopic eyes are different in structure from non-myopic or mildly myopic eyes, and may be a risk factor for glaucomatous damage and progression of VF loss in POAG patients.[18,19] Our previous work using confocal laser scanning ophthalmoscopy has revealed that optic disc size is correlated with ocular axial length only in high myopia patients (> −8.0 D), but not in mildly myopic patients (< −3 D).[20] Jonas has also demonstrated a similar finding.[21] Other investigations have focused on the mechanisms that may explain the increased

Table 2. Influence of age, central corneal thickness, mean intraocular pressure, vertical cup-to-disc ratio, and refraction status on progression of visual field loss*

	OR (95% CI)	*p*
Age	1.033 (1.002–1.064)	0.003
Central cornea thickness	0.999 (0.988–1.011)	0.924
Mean intraocular pressure	3.574 (1.393–9.029)	0.019
Cup-to-disc ratio	1.054 (1.023–1.086)	< 0.001
Refraction status	4.686 (2.078–10.568)	< 0.001

**As analyzed by logistic regression. OR = odds ratio; CI = confidence interval.*

Table 3. Incidence of progression of visual field (VF) loss with different myopic refraction status*

Refraction status	With VF loss progression	Without VF loss progression	Total
Myopia			
< −3 D	13 (15.1)	73 (84.9)	86 (100)
> −3 D, but ≤ −6 D	8 (10.5)	68 (89.5)	76 (100)
> −6 D, but ≤ −9 D	22 (34.4)	42 (65.6)	64 (100)
> −9 D	14 (38.9)	22 (61.1)	36 (100)
Total	57 (21.8)	205 (78.2)	262 (100)

**Data presented as n (%).*

susceptibility to glaucoma of highly myopic eyes. In enucleated human eyes, Dichtl et al demonstrated that the lamina cribrosa is significantly thinner in highly myopic eyes.[22] The thinner lamina cribrosa may steepen the translaminar pressure gradient at a given IOP, and contribute to vulnerability to glaucoma progression in myopic eyes.[12] Axial elongation in myopic eyes is associated with scleral remodeling, which causes marked thinning of the sclera, especially at the posterior pole.[23] This scleral remodeling results in reduced glycosaminoglycan and collagen content, and scleral resistance to expansion at a given level of IOP.[24] Furthermore, it is postulated that reduced blood flow in the ocular arteries correlates with neuroretinal rim damage and POAG progression.[25,26] Since blood flow of myopic eyes decreases as myopic refraction status increases, progression of POAG in highly myopic patients may also be caused by decreased optic nerve head perfusion.[27]

We showed that age and initial vertical C/D ratio were also risk factors for progression of VF loss in POAG patients. In general, there is an increase in IOP with age; thus, the prevalence of POAG increases with aging. However, Shiose found a significant decrease in IOP with age in Japanese people,[28] whereas a longitudinal analysis has shown a different result.[29] Optic nerve head perfusion is also reduced in elderly people.[30] However, these findings do not imply increased vulnerability of aged axons to glaucoma damage.[31]

Our results demonstrated that higher mean IOP and greater incidence of IOP > 21 mmHg were both significantly associated with progression of VF loss in POAG patients. It is still a controversial issue as to whether mean IOP or fluctuation in IOP is really important to glaucoma progression. In the *Early Manifest Glaucoma Trial*, Bengtsson et al showed that mean IOP was correlated with risk of progression.[32] Nouri-Mahdavi et al reported in the *Advanced Glaucoma Intervention Study* that IOP fluctuation rather than mean IOP correlated better with progression.[3] Palmberg concluded that in subjects with moderately severe damage, maintaining IOP in the low-to-normal range can give the optic nerve an optimal chance of stabilization. Reducing the IOP by ≥ 35% may be a successful strategy for glaucoma patients with mild disease at diagnosis.[33]

We did not find that CCT was a risk factor for progression of VF loss. The *Ocular Hypertension Treatment Study* reported that the risk of developing POAG was inversely correlated with CCT, when other potential determinants of glaucoma risk were adjusted.[34] Several other studies have provided further evidence to support this finding.[35,36] However, some investigators have not found any association between CCT and optic nerve or progression of VF loss in patients with existing glaucoma,[37,38] and results from the *Early Manifest Glaucoma Trial*[39] and the *Barbados Eye Study*[40] were similar. Jonas et al found that highly myopic cadaver eyes have thinner lamina cribrosa than eyes without high myopia.[11] However, CCT was not found to be correlated with axial length[41] or lamina cribrosa thickness in normal cadaver eyes without glaucoma.[42]

We showed a more rapid progression of VF loss in POAG patients with myopia > −6 D. In these patients, closer follow-up and a lower target IOP may be required to maintain useful vision for the remainder of their lives.

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