Original Article

Five-Year Risk of Progression of Ocular Hypertension to Primary Open Angle Glaucoma. A Population-based Study

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Purpose: To report the progression of ocular hypertension (OHT) to primary open angle glaucoma (POAG) during a 5-year follow up of a population-based sample.
Methods: Twenty-nine patients diagnosed to have OHT and 110 randomly selected normals from a population-based study in 1995 were invited for ocular examination in 2000. All patients underwent a complete ophthalmic examination; including the daytime diurnal variation of intraocular pressure (IOP) and measurement of central corneal thickness (CCT). The "corrected" IOP was used for analysis. Progression to POAG was based on typical optic disc changes with corresponding field defects on automated perimetry.
Results: Twenty-five of the 29 persons with OHT who could be contacted were examined. After correcting for CCT, two persons were reclassified as normal. Four of 23 (17.4%; 95% CI: 1.95 – 32.75) had progressed to POAG. One person amongst the 110 normals progressed to normal tension glaucoma (NTG). The relative risk of progression amongst OHT was 19.1 (95% CI: 2.2 – 163.4). All those who progressed had bilateral OHT. The mean and peak IOP in those who progressed was 25.4 mm Hg and 29.3 mm Hg compared to 23.9 mm Hg and 25.7 mm Hg in those who did not. Those who progressed had more than 8 mm Hg diurnal variation. The diurnal variation was less than 6 mm Hg in those who did not progress. No patient developed blindness due to glaucoma.
Conclusion: The 5-year incidence of POAG amongst OHT in this population was 17.4% (3.5% per year). Bilateral OHT, higher peak IOP and large diurnal variation may be the risk factors for progression.

Key Words: Ocular hypertension, primary open angle glaucoma, progression, population-based, diurnal variation

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Glaucoma is recognised as a major cause of ocular morbidity worldwide.[1] The prevalence and pattern of the disease varies in different regions of the world. It is estimated that 66.8 million people are affected by glaucoma worldwide and 6.7 million are bilaterally blind due to the disease. Extrapolating data from the rest of Asia, an estimated 8 million Indians have glaucoma with a 1:1 ratio of primary open angle glaucoma (POAG) to primary angle closure glaucoma (PACG).[2] Raised intraocular pressure (IOP) is a well-known risk factor for POAG.[3] The reported prevalence of ocular hypertension (OHT) in population-based studies worldwide varies from 1.1 to 13% .[3-12] There are two population based reports from India. The Vellore Eye Study (VES) reported the prevalence to be OHT at 3.0% (95% CI: 2.0 – 4.0%).[13] The Andhra Pradesh Eye Disease study (APEDS) reported this to at 0.32% (95% CI: 0.10%–0.78%).[14]

Population and clinical-based studies report that 0.24 to 2.2% of OHT progresses to POAG per year.[15-22] The collaborative glaucoma study reported that 6.7% patients progressed to glaucoma over 5 years; this progression was closely related to initial IOP.[16] Only 0.8% of those with IOP < 16mmHg, developed glaucoma compared to 3.1% with an initial IOP >20-23 mmHg and 8.1% with IOP > 23 mmHg. The Bedford Study reported 3.5% (95% CI: 0.7-6.3%) progression to POAG among glaucoma suspects over a 5-7 year followup.[17] The Barbados. Eye Study found a 4-year incidence of 9% amongst OHT (>21mmHg) compared to 1.2% in the normal population. A racial difference in progression of OHT to POAG is also reported; 18.1% in the black population compared to 5.4% in the white population with 1-12 year follow-up.[21] The 5-year cumulative probability of developing POAG

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in untreated OHT patients in the ocular hypertension treatment study (OHTS) was 9.5% (95% CI 9.25-9.75) compared to 4.4% (95% CI: 3.05-5.75) in treated OHT patients.[23]

To the best of our knowledge, progression of disease in Indian eyes with ocular hypertension has not been reported in the literature (Medline search). We studied the progression to primary open angle glaucoma in a population-based cohort of persons with ocular hypertension.

Materials and Methods

The results of the Vellore Eye Study (VES) have been published earlier.[13] Briefly, 972 of 1532 randomly selected persons from Vellore town who could be contacted, underwent a complete ophthalmic examination at the Medical College, Department of Ophthalmology in 1995. At the time of the study, ocular hypertension (OHT) was defined as raised IOP (>21mm Hg) associated with an open angle, in absence of optic disc and visual field changes. Primary open angle glaucoma (POAG) was defined as raised IOP (>21 mm Hg) in an open angle with glaucomatous optic disc changes with corresponding field defect.[13] As defined above, 29 persons were diagnosed to have OHT in 1995. Sixteen patients had bilateral OHT and 13 patients had unilateral OHT.

For the follow-up visit we used the same definitions as above with two exceptions; corneal thickness was measured in all patients; IOP above 21 mmHg after correction for corneal thickness was required to diagnose ocular hypertension and POAG. Persons with corrected IOP less than 21 mm Hg and no other changes suggestive of glaucoma were labeled as normal and were removed from final analysis. Normotensive glaucoma was defined as disc and field changes as required for POAG but with a corneal thickness corrected IOP of less than 22 mm Hg on diurnal variation. Pre-perimetric glaucoma was defined as disc changes strongly suggestive of POAG without field defects on conventional automated perimetry, with or without an IOP above 21mm Hg.

In September 2000, all 29 patients previously diagnosed to have ocular hypertension were invited for a review examination. These individuals were approached by a social worker who invited them to undergo a follow-up examination at the hospital. All those who could be contacted were given a specific date for examination. In case of non-response, the social worker once again contacted the individual and a fresh appointment date was arranged.

We also examined 110 normal subjects (with gonioscopically open angles) from the original population. The "normal" subset was selected in a random manner as follows: randomly selected persons who participated in the previous study were assigned hospital numbers in chronological order. From the database we extracted information regarding which population cluster they belonged to and arranged them in chronological order of the date of examination in the hospital. The first 25 previously diagnosed normal persons from each cluster were identified and invited for examination. The next 10 persons were short-listed. If a person from the first list could not be contacted, the next (short-listed) person was contacted. A total of 300 persons were identified and 110 short-listed. These persons too underwent complete ophthalmic examination similar to patients with OHT.

The rate of new POAG in OHT was compared to the rate of new POAG in the normal group to determine the relative risk.

As part of a larger study, the appointments for OHT patients were scheduled along with normals and the rest of the study population. The examination was performed in a masked manner; the examiner was unaware of the results from the initial survey. All persons first underwent visual acuity testing and refraction by one of the two optometrists.

All participants underwent a complete ophthalmologic examination performed by a single qualified ophthalmologist who had worked for at least two years in the glaucoma clinic under the guidance of a glaucoma specialist. The ophthalmologic examination included a slitlamp examination by Haag Streit 900 (HAAG-STREIT AG, Koniz, Switzerland), applanation tonometry (the mean of three consecutive readings) and daytime diurnal pressure measurements at 2-hour intervals from 10 a.m. to 6 p.m.

Gonioscopy was performed on all individuals using a Goldman two-mirror gonioprism under the standard testing conditions as described earlier and the angle was graded.[24,25] Indentation gonioscopy was also performed in all patients.

All patients had their pupils dilated. After dilatation, the lens was examined with the slitlamp; the cataract was graded using the Lens Opacities Classification System III.[26] Indirect ophthalmoscopy was performed; the optic disc was examined stereo biomicroscopically (using a 60 Diopter lens).[13] The examiner looked for any changes suggestive of glaucoma; the vertical cup-to-disc ratio (CDR) was assessed in units of 0.1 by the ophthalmologist.[13] The vertical CDR was measured while viewing the disc with the 60 D lens: the superior and inferior margins of the disc were identified and the height of the vertical slit decreased (and position adjusted) till the slit beam encompassed the vertical diameter of the disc. The measurement was read off the scale on the Haag Streit slitlamp.

Corneal thickness was measured in all individuals using Tomey model AL 1000 (CBD Ophthalmic/ TOMEY, Phoenix, AZ) by one of two observers. A published formula was used to adjust the IOP for deviation from the mean central corneal thickness in normals.[27] The mean corneal thickness in south Indians has been reported at 0.537 mm (± 0.034).[28]

Automated visual fields were performed on all patients using the Humphrey visual field analyzer (Humphrey Instruments Inc., San Leandro, CA)[29] with the Swedish interactive testing algorithm (SITA) strategy. The protocol required a minimum of two fields; any defects were confirmed by a repeat field. Unreliable

fields (> 20% fixation loss, > 33% false positive, > 33% false negatives) [30] were repeated.

Progression of disease was defined in two ways:

1. *Disc and field criteria:* Patients with new disc damage as defined below along with a glaucomatous field defect. Visual field defects were considered glaucomatous if they were consistent with optic disc damage and met at least two of Anderson's criteria.[31] The presence of a visual field defect required confirmation by a repeat field; this was performed within a week of the first field.
2. *Disc criteria alone:* Patients with new disc damage; by this criteria field defects were not required to diagnose progression. These were labeled as "pre-perimetric" glaucoma. The following features were considered evidence of damage to the optic disc: a previously unrecorded (presumed new) finding in the optic disc suggestive of glaucoma (change in the pattern of the neuroretinal rim, notch in the neuro retinal rim, nerve fibre layer defect, disc haemorrhage, or newly recorded asymmetry in cup-to-disc ratio of more than 0.2 between the two eyes). A change in the cup-disc ratio of more than 0.2 was also considered evidence of progression. As disc photographs were not part of the protocol, the above change was based on clinical observation and considered a secondary criterion.

The glaucoma specialist reassessed patients in whom the clinical findings had changed since 1995.

Analysis

The "t" test was used to test the difference in mean and peak IOP as well as diurnal variation between those who progressed and those who did not.

Results

The 29 patients diagnosed to have ocular hypertension in 1995 were invited for a follow up examination and 27 patients could be contacted (one had moved to an unknown address and one had died). Among those contacted, one refused examination and one did not keep the appointment despite repeated requests. Finally, 25 patients were examined. 14 were bilateral OHT and 11 were unilateral OHT. The mean age was 51.3 (± 7.6) years and the male to female ratio was 15:10. Age, gender, refractive error and IOP (1995 examination) were similar in those examined and those who did not respond.

Three hundred normal persons were contacted in order to examine 110 (75 had moved and could not be traced, 23 persons could not be contacted, 10 had expired, one was an invalid and could not come to the hospital, one refused examination and 90 persons did not come for examination despite repeated requests). The mean age of the group, 49.0 (± 8.5) years, was not significantly different from the OHT group. The male-female ratio was 45:65. Two persons were considered to have developed ocular hypertension without visual field defects. One person (0.9%, 95% C.I.: 0.3 – 1.5%) had developed normotensive glaucoma (NTG). Six of the normals had developed visually significant cataracts (best corrected vision less than 6/18).

Two of the 25 persons who responded had a corneal thickness corrected IOP of less than 22mmHg and had no other ocular feature suggestive of glaucoma. Both were bilateral OHT. They were labeled as normal and were removed from further analysis.

Of the remaining 23 patients who responded, 4 (17.4%, 95% CI: 1.95% -32.75%) had progressed to open angle glaucoma (disc and field changes) while 7 (30.4%, 95% CI: 11.6 - 49.2%) had progressed to be classified as "pre-perimetric" glaucoma. Further results are restricted to progression to glaucoma only.

The age of patients who progressed, 44-64 years, was similar to those who did not. The mean IOP (1995) was 24.4 mm Hg in those who progressed to POAG versus 23.3 mm Hg in those who did not (Table 1). The mean diurnal variation in those who progressed was 8.6 mmHg compared to 5.4 mm Hg in those who did not.

Three of four patients had bilateral progression to POAG. All were bilateral OHT. The patient with unilateral progression to POAG had developed disc changes (pre-perimetric glaucoma) in the fellow eye.

There were no cases of blindness due to glaucoma. Clinically, two persons developed visually significant cataracts (best corrected vision (6/18 with LOCS III: NO >3, NC > III).

The rate of new POAG in OHT was compared to the rate of new POAG in the normal group to provide the relative risk. The relative risk of progression of OHT to POAG was 19.1 (95% CI: 2.2 – 163.4).

Discussion

Ocular hypertension is the only known causal risk factor for glaucoma.[3] The Bedford survey,[32] the collaborative glaucoma trial and the Barbados study are population-

Table 1. IOP data for the ocular hypertension group

Variables	Progression	Non-progression
Mean IOP (in 1995) (mm Hg)	24.4 mm Hg	23.3 mm Hg
Mean IOP (present study) (mm Hg)	25.4 mm Hg	23.9 mm Hg
Diurnal variation (present study) (mm Hg)	8.6 mm Hg	5.4 mm Hg
Mean Peak IOP (mm Hg)	29.3 mm Hg	25.7 mm Hg

based studies that reported the progression of ocular hypertension to POAG.[15-17, 21] The Barbados study found progression of 9% in OHT group compared to 1.2% in normal population over four years.[21] The collaborative glaucoma trial reported 7% progression in the OHT group in 5 years compared to 1.5% in the normal population.[16] Our numbers are small but the progression rate was 17%; the confidence interval overlapped the point estimate of other studies.

In the 1995 survey, the mean IOP in the population was 15.7 mm Hg (± 3.4).[13] If we re-classify ocular hypertension using two standard deviations above this population mean as our cut-off (22.5 mm Hg), one person in the progression group had mean IOP of 20.6 mm Hg (peak 22 mm Hg) and would be re-classified as NTG but progression to open angle glaucoma will remain unchanged.

A clinic-based study reported significant racial difference in progression.[20] The progression rate was 18% in blacks versus 5.4% in white population. The Barbados study too found higher rates than those reported in the whites.[21] Our point estimate is similar to the black population, but the confidence limits are very wide.[20,21] Our progression rate also overlaps the point estimate of untreated OHT patients in the OHTS group.[23]

The 110 normals were invited as part of a larger study and not with the aim of determining incidence of POAG. However, one amongst the 110 normals did develop NTG. The number is too small to draw any meaningful conclusion, but the point estimate is similar to the Barbados study [11,20]

Diurnal variations are known to be an independent risk factor for progression of glaucoma.[33,34] The diurnal variation and peak IOP (year 2000) in those who progressed was significantly higher than those who did not. As diurnal variations were not obtained at the time of the initial study, the role of the peak and diurnal IOPs in progression is difficult to comment upon. They seem to be associated with progression.

Most studies have reported an association between baseline IOP and progression to POAG. While the baseline IOP in the current report was higher amongst those who progressed, the difference (P = 0.9) was not impressive. The sample size is small and few patients had higher IOPs (> 30 mm Hg) at initial visit.

Our study has several limitations. A major criticism is the small sample size with the resultant wide confidence intervals. Another major limitation is the lack of photographic documentation of the optic disc. However the use of criteria that required field changes that correlated with the disc changes is likely to be reasonably specific. On the positive side, this is the first population-based study estimating the progression in Indian OHT patients. This study also reiterates the importance of diurnal variation in the diagnosis of POAG.

In conclusion, we report 17% (3.5% per year) progression to POAG amongst OHT with a relative risk of 19. Bilateral OHT appears to be a risk factor for progression. Higher peak IOP and a diurnal variation higher than 8mm Hg are more associated with those who progressed.

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