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ORIGINAL PAPER

Long-term evaluation of ocular hypertension with primary angle closure and primary open angles

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Abstract

Purpose To evaluate the long-term course of primary angle-closure ocular hypertension and primary open-angle ocular hypertension and possible risk factors for progression to glaucoma.

Methods A total of 109 eyes of 109 ocular hypertension (OHT) patients with a minimum follow-up period of 5 years having complete ocular/medical records were evaluated. They were classified into primary angle closure or primary open angle based on gonioscopy at baseline. Baseline and review data of Humphrey field analyser, HFA, and Heidelberg retinal tomography, HRT, were recorded. Guided progression analysis (GPA) and univariate Cox regression were used for time to event analysis in identifying progression to glaucoma.

Results Over a mean follow-up of 12.18 ± 4.8 years, progression to glaucoma was 17.43% (19 eyes), out of whom 5.5% (6 eyes) showed ≥ 3 loci on GPA. Sub-classifying them, progression to primary angle-closure glaucoma was 19.72%, and that of primary open-angle glaucoma was 13.16%. The mean time to progression was 9.34 ± 3.6 years. Significant risk factors included small disc area ($\leq$ 1.99 sq.mm on HRT), requirement of ≥ 2 drugs to maintain target IOP and those engaged in activities yielding a Valsalva effect in daily life. Coronary artery disease (CAD) and systemic use of steroids were associated with increased severity.

Conclusion Overall progression of OHT to glaucoma was 17.43% over a mean of 9 years, with target IOP of $\leq$ 18 mm Hg. Patients with smaller discs, CAD, exercising Valsalva type activities and using ≥ 2 glaucoma medications or systemic steroids should be closely monitored.

Keywords Ocular hypertension · Primary angle closure · Progression · Smaller discs · Number of medications

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Introduction

Ocular hypertension, OHT, is defined as an intraocular pressure, IOP, more than 21 mm Hg on at least 2 occasions, in the absence of optic nerve head (ONH) damage and visual field defects. Population-based studies have reported a prevalence of 1.1–3.5% in individuals over 40 years of age [1, 2]. The ocular hypertension treatment study (OHTS) reported that, at

5 years, the cumulative probability of primary open-angle ocular hypertension (POAHT) patients developing primary open-angle glaucoma (POAG) was 4.4% in eyes treated to reduce IOP by 20 and 9.5% in the observed group [3].

Primary angle closure, PAC, is common, especially in Asian countries, and is known to progress to primary angle-closure glaucoma, PACG, in only some eyes [4, 5]. Though the term 'angle-closure hypertension' was suggested by Kim and Jung in 1997, past studies have considered angles to be open by default when discussing OHT, and little research is available on the long-term prognosis of eyes having primary angle closure with ocular hypertension [6]. This study was therefore designed to comparatively evaluate long-term changes in OHT eyes with primary angle closure, PACHT, and primary open angles, POAHT, by IOP, perimetry and scanning laser ophthalmoscopy.

Materials and methods

The study was conducted between June 2015 and October 2016 as a retrospective cross-sectional cohort study, as there is a long interval between the diagnosis of OHT and development of neuropathy, and there are accurate retrospective means for detecting the onset of the neuropathy by guided progression analysis (GPA) and on Heidelberg retinal tomography (HRT). Consecutive adult patients $\geq$ 40 years with an initial diagnosis of ocular hypertension, based on a thorough evaluation at the Glaucoma Services, including gonioscopy, reliable perimetry, pachymetry and confocal scanning laser ophthalmoscopy were included. Patients, who had >1 visit per year for at least 5 years, were enrolled in the study. The target IOP for all such patients was $\leq$ 18 mmHg and medications were switched/increased over time as necessary, and compliance advised repeatedly at each review by one consultant (RS). Patients with follow-up records <5 years, Snellen visual acuity $<6/18$, other ocular or systemic pathologies likely to cause visual field defects and those not willing to participate were excluded from the study.

Institutional ethical clearance was obtained and the study adhered to the Declaration of Helsinki. A written informed consent was obtained from all subjects. At final review, a detailed ocular and systemic history was elicited, including daily activities that involved a Valsalva effect such as chronic cough, chronic constipation, benign prostatic hyperplasia and breath-holding exercises. All past ocular and systemic medical records were reviewed. A comprehensive examination of both eyes was done for best-corrected visual acuity, applanation tonometry, anterior segment examination and ultrasonic pachymetry (PacScan 300 AP, Sonomed Inc, USA). Gonioscopy was performed by a glaucomatologist to confirm categorization into POAHT and PACHT. A detailed fundus evaluation was done to note cup–disc ratio (CDR), neuroretinal rim and retinal nerve fibre layer defects if present, and to rule out other pathology that could lead to a visual field defect. Anterior segment optical coherence tomography (Casia SS-1000; Tomey, Nagoya, Japan) was done to objectively confirm angle status. Over the course of the review, standard automated static perimetry was performed using 30-2 Swedish interactive thresholding algorithm (SITA) standard/full threshold program of Humphrey field analyser (HFA II, Carl Zeiss Meditec, Germany). GPA was downloaded for all patients from baseline to last review. Mean deviation, MD, pattern standard deviation, PSD, and visual field indices, VFIs, of all available years were noted. Confocal scanning laser ophthalmoscopy using HRT (Heidelberg Retinal Tomography, Heidelberg Engineering, Germany) was performed in a standardized manner by one experienced observer. A poor quality image defined as one with a topographic standard deviation (TSD $>$ 50 μ) was excluded.

On GPA event analysis, a patient with fully shaded triangles at $\geq$ 3 adjacent locations, with $p<5\%$ over 3 consecutive fields, was termed a 'definite progressor'. Patients with one or two such fully shaded triangles on three consecutive fields within Bjerrum's area were termed as 'likely progressors'. The time to occurrence of such an event and the rate of progression, ROP, were noted. HRT 3 (software version 1.5.10.0) stereometric parameters and topographic change analysis (TCA) were studied. Clusters of red pixels on the neuroretinal rim and peripapillary retina within 1 disc diameter of the ONH were identified, and any change recorded, while those over blood vessels and along the contour of peripapillary atrophy were excluded. If red pixel clusters were noted at the last 2 examinations, they were traced back to its first occurrence, and the cluster position, time to appearance and overall change in area were noted. The site of

initiation of the cluster and secondary involvement of adjacent structures was noted. Many clusters showed fluctuating change, and hence, only those which persisted and increased were recorded (Fig. 1). The numerical change in the stereometric parameters from baseline to the last review was studied over time, to exclude inter-visit variability.

The right eye of patients was recruited by default, unless only the left eye showed progression. If both eyes had progressed, the worse eye was included in the study. Categorical variables were summarized as frequency (%), qualitative variables were compared by Chi-square/Fisher's exact test and quantitative variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR) if non-normally distributed. Comparison between the groups was made by *t* test/rank-sum test, one-way ANOVA/Kruskal–Wallis test followed by multiple comparisons using Bonferroni/Dunn test. Repeated measure ANOVA/Friedman test was done to evaluate trends over time and followed by multiple comparisons using Wilcoxon signed rank test (with Bonferroni correction). Univariate Cox regression was applied for time to event analysis and progression to glaucoma. Receiver operator curve analysis was carried out to find the cut-off for HRT global disc area. Stata 12.0 statistical software was used for data analysis, and a p value < 0.05 was considered statistically significant.

Results

In total, 135 consecutive patients with a diagnosis of ocular hypertension were screened and 109 eyes of 109 patients who met all inclusion and exclusion criteria were enrolled in the study. The excluded patients were those who had < 5-year follow-up (8 patients), inadequate medical records (7 patients), other pathologies likely to cause field defects such as dense cataract (4 patients), age-related macular degeneration (3 patients), retinal vascular occlusions (2 patients) and those not willing to participate in the study (2 patients). Seventy-one patients of 109, 65.14%, were PACHT and 38 patients, 34.86%, were POAHT. The mean follow-up was 12.18 ± 4.8 years, range 5–30.5 years. At final review, on HFA-GPA, the overall rate of progression was 17.43% (19 eyes), out of whom 5.5% (6 eyes) showed ≥ 3 loci (definite progressors), and the rest likely progressors. The mean time to progression from OHT to glaucoma was 9.34 ± 3.6 years, range 3.6–14.16 years.

The baseline and final characteristics of ocular hypertensive non-progressors and progressors are

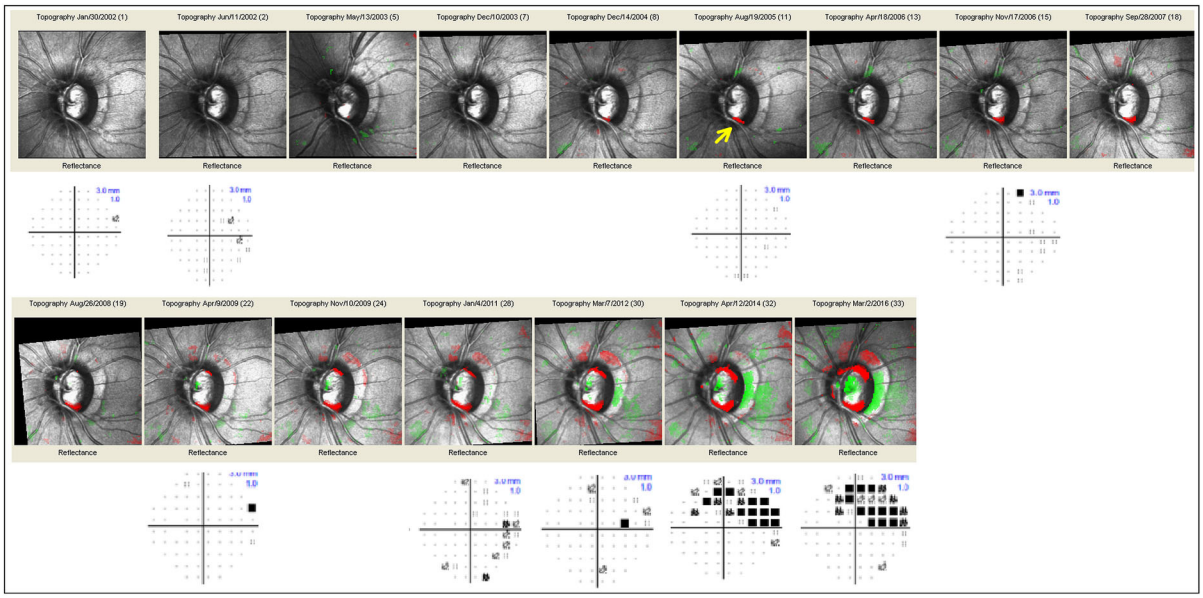

Fig. 1 Heidelberg retinal tomograph (HRT) cluster analysis and corresponding pattern deviation plot images of the respective years of one definite progressor, showing initiation and progression of cluster much earlier than establishment of field defect on perimetry

detailed in Table 1. Age, CCT, baseline HFA and HRT measurements were comparable between both the groups. However, the final VFI was 98.67 ± 2.09 in the former and 93.71 ± 5.35 in the latter group, $p < 0.001$. Similarly, the final PSD also differed significantly between the two groups, with median 1.73 (1.05–8.48) and 3.56 (1.8–8.15), respectively, $p < 0.001$. The median ROP of the non-progressed group was 0 (− 0.5 to 1.6) and that of the progressed group was − 0.2 (− 1.8 to 0.9), $p < 0.001$. All definite progressors had a negative ROP, while 7 of 12 likely progressors, 58.33%, and 20/56, 35.7%, non-progressors had a negative ROP, $p = 0.01$. The progressors had a longer duration of follow-up, 14.78 ± 5.9 years, than non-progressors, 11.71 ± 4.38 years, $p = 0.01$; however, the mean time to progression, 9.34 ± 3.6 years, was well within the total follow-up duration of both groups.

All patients were on topical glaucoma medications. At final review, 18 and 6 patients required 2 and 3 medications, respectively. Nine progressors were on ≥ 2 medications. The percentage of patients using ≥ 2 medications was significantly more in progressors as compared to non-progressors, $p = 0.01$. The 'target' IOP of ≤ 18 mmHg was not achieved over the entire duration of review in 12 patients; however, none of these became definite or likely progressor.

Possible risk factors for progression were evaluated by univariate analysis (Table 2). 'Global disc area' measured by HRT was significantly different between the groups, and smaller discs ≤ 1.99 sq mm were at greater risk of progression, with a hazard ratio of 4.05 (95% CI 1.27–12.96), $p = 0.01$. On Fisher's exact tests, male gender was a risk factor for progression to POAG, while female gender was a risk factor for primary angle-closure disease, $p = 0.015$. A Valsalva effect due to any of, benign prostatic hypertrophy, chronic constipation, chronic cough, breath holding in yoga was found to be significant for conversion of all OHT to glaucoma, $p = 0.005$.

The four subgroups of PACHT, POAHT and their respective progressors PACG, POAG were compared. PACHT patients on ≥ 2 drugs had the highest risk of progression ($p = 0.04$). PACHT progressors had the smallest global disc area as measured on HRT ($p = 0.04$). Valsalva effect was found to be

Table 1 Comparison of clinical characteristics between non-progressors and 'definite + likely' progressors

S. no.	Characteristics	Non-progressors ($n = 90$) Mean (SD)	D + L progressors ($n = 19$) Mean (SD)	p value
Baseline				
1	CCT (microns)	533.81 (81.11)	523.47 (38.56)	0.24
2	Baseline IOP (mm Hg)	25.77 (4.56)	25.31 (3.78)	0.68
3	Baseline PSD* (dB)	1.92 (1.06–8.37)	2.18 (1.03–3.99)	0.29
4	Baseline VFI (%)	97.29 (6.15)	97.68 (2.93)	0.80
5	Baseline vertical CDR* (by HRT)	0.52 (0–0.9)	0.56 (0–0.77)	0.92
6	Baseline linear CDR	0.58 (0.12)	0.56 (0.18)	0.67
7	Global disc area	2.14 (0.43)	2.33 (0.42)	0.08
Final				
1	Age (years)	60.01 (11.19)	64.36 (9.58)	0.11
2	% IOP reduction	32.42 (18.95)	33.41 (16.06)	0.98
3	Final VFI	98.67 (2.09)	93.71 (5.23)	< 0.001
4	Final PSD*	1.73 (1.05–8.48)	3.56 (1.8–8.15)	< 0.001
5	ROP* (% per year)	0 (− 0.5 to 1.6)	− 0.2 (− 1.8 to 0.9)	< 0.001
6	Time to progression (months)	–	112.15 (43.27)	–

Independent *t*-test applied

IOP intraocular pressure, *CCT* central corneal thickness, *PSD* pattern standard deviation, *CDR* cup–disc ratio, *HRT* Heidelberg retinal tomograph, *VFI* visual field index, *ROP* rate of progression, *SD* standard deviation

*Data are expressed in median (range), and Wilcoxon signed rank test is applied

Table 2 Putative risk factor univariate analysis between 'definite + likely' progressors and non-progressors

S. no.	Putative risk factors	Hazard ratio (95% CI)	*p* value
1	Age (3 categories)	1.73 (0.76–3.93)	0.18
2	Sex (female)	0.52 (0.21–1.28)	0.16
3	Family history	0.59 (0.23–1.52)	0.28
4	Diabetes mellitus	1.43 (0.47–4.33)	0.52
5	Hypertension	0.73 (0.24–2.21)	0.58
6	Coronary artery disease	0.88 (0.25–3.07)	0.85
7	Dysthyroid status	1.08 (0.31–3.74)	0.89
8	Hypotension	1.59 (0.46–5.48)	0.45
9	Asthma	1.38 (0.18–10.40)	0.75
10	Valsalva effect[a]	0.66 (0.23–1.84)	0.43
11	CCT (3 categories)	0.99 (0.98–1.00)	0.34
12	Baseline IOP (per mm Hg)	0.97 (0.88–1.08)	0.85
13	Baseline PSD (every 0.5 units)	0.99 (0.71–1.37)	0.95
14	Baseline VFI (every 1 unit)	0.91 (0.70–1.18)	0.50
15	Baseline horizontal CDR (every 0.5 units)	1.35 (0.48–3.77)	0.56
16	Baseline vertical CDR (every 0.5 units)	1.15 (0.45–2.93)	0.76
17	Baseline linear CDR (every 0.5 units)	0.72 (0.27–1.90)	0.52
18	Disc area (3 categories)		
	≤ 1.99	**4.05 (1.27–12.96)**	**0.01**
	2–2.49	1	
	≥ 2.5	2.05 (0.55–7.65)	0.28
19	Final clinical CDR (2 categories)	0.93 (0.04–18.37)	0.96

By univariate analysis

IOP intraocular pressure, *CCT* central corneal thickness, *PSD* pattern standard deviation, *CDR* cup–disc ratio, *HRT* Heidelberg retinal tomograph, *VFI* visual field index, *CI* confidence interval

[a]Valsalva effect includes chronic constipation, chronic cough, benign prostatic hypertrophy and breath-holding exercises in yoga

Eyes with disc area ≤ 1.99 mm^2 are at 4 times more risk of progression

significantly present in both PACHT and their progressors ($p = 0.005$).

On comparing the 6 'definite' and 13 'likely' progressors, coronary artery disease (CAD) was found to be a risk factor for progression, $p = 0.02$. A history of steroid use during the period of review, for dermatological problems, asthma, etc., was present in 4/6, 66.7% of definite progressors, as compared to 1/13, 7.69% of likely progressors, $p = 0.01$. Steroid history was positive in only 3/90, 3.3% of non-progressors. A history of chronic constipation, 3 or fewer bowel movements per week was more common in definite progressors, $p = 0.04$.

On studying HRT stereometric parameters, the mean disc area of subjects was 2.30 ± 0.43 sq.mm. Patients with a global disc area ≤ 1.99 sq.mm had significant risk of progression overall, $p = 0.01$ (Table 3), especially from PACHT to PACG, $p = 0.04$ (Table 4). A receiver operating characteristic (ROC) curve of baseline global disc area, at cut-off ≥ 2.15 sq.mm, showed 66% sensitivity and 63% specificity to detect patients who are less likely to progress to glaucoma (Fig. 2). There was a statistically significant difference between the baseline linear CDR of progressors of PACHT, median 0.54, range 0.15–0.72 and of POAHT, median 0.74, range 0.6–0.8 $p = 0.01$. Paired *t*-test of HRT linear CDR of the progressors showed a mean of 0.56 ± 0.18 and 0.60 ± 0.19 at baseline and last follow-up, respectively ($p = 0.007$), while they were statistically comparable among non-progressors.

Of 109 patients, 90 had at least 4 good HRT images, 2 baseline and 2 follow-ups, which were the bare minimum required for cluster analysis. On HRT TCA, a total of 55 patients had ≥ 1 red cluster with a change in area over time. We considered the cluster with highest area change per patient. A 100% increase in cluster size was seen in 31/90, 34.44% patients. All definite progressors with long-term HRT data (5 patients) showed a cluster increase of at least a 100%, in addition to 4/10 likely progressors and 22/75 non-progressors, $p = 0.07$. HRT TCA progression was detected earlier in most patients, starting at the neuroretinal rim surface or slope, with the adjoining peripapillary retina being involved subsequently. For the definite progressors, the median time for cluster

Table 3 Clinical parameters categorization of 'definite + likely' progressors and non-progressors

No.	Variable	Category	Definite + likely progressors (n = 19)	Non-progressors (n = 90)	p value
1	Age (years)	≤ 49.99	1	14	0.11
		50–59.99	4	34	
		≥ 60	14	42	
2	Baseline IOP (mm Hg)	≤ 25.99	11	51	1
		26–29.99	5	24	
		≥ 30	3	15	
3	CCT (micron)	≤ 499.99	3	12	0.29
		500–549.99	12	42	
		≥ 550	4	36	
4	Final clinical CDR	≤ 0.599	6	27	1
		≥ 0.6	13	63	
5	Follow-up (months)	≤ 60.99	0	6	0.18
		61–119.99	3	29	
		≥ 120	16	55	
6	Disc area (sq.mm)	≤ 1.99	10	19	**0.01**
		2–2.49	4	45	
		≥ 2.5	5	26	

Chi-square/Fisher's exact test applied

IOP intraocular pressure, *CCT* central corneal thickness, *CDR* cup–disc ratio

Eyes with disc area ≤ 1.99 mm^2 are at higher risk of progression

initiation was 59 months of follow-up, range 30–83 months and median time for the cluster size to increase by 100% was 36 months, range 34–42 months, thereon. The median time for peripapillary retinal involvement was 25.5 months, range 0–68 months, after NRR involvement. The position of these clusters on the NRR corresponded with field defects that developed later.

A study of the change in HRT stereometric parameters showed that the global parameters of cup area ($p = 0.005$), rim area ($p < 0.001$), cup–disc area ratio ($p = 0.002$), rim–disc area ratio ($p < 0.001$) and vertical CDR ($p = 0.02$) significantly differed between the definite progressors and the non-progressors over time.

Discussion

Ocular hypertension is relatively common; however, identifying patients who are likely to progress to glaucoma is currently difficult, in eyes with both primary angle closure and open angles. There are very few long-term studies which have looked at OHT with primary angle closure, and none on OHT in primary open angle in Asians. Therefore, this study was carried out to review these in the long term, to determine progression in both categories of ocular hypertensives and to evaluate possible risk factors for progression.

Over a period of 12.18 ± 4.8 years, 17.43% of the 109 patients progressed by GPA event-based analysis [7]. The mean time to progression was 9.34 ± 3.6 years, range 3.6–14.16 years. All patients in this study were on treatment to achieve a 'target' IOP of ≤ 18 mmHg. This was not possible throughout the review in 12 patients, who showed fluctuations of IOP; however, none of these progressed. The OHTS reported a median time to development of POAG of 8.7 years in the treated group [8].

In our study, progression from PACHT to PACG was seen in 14/71 patients, 19.72%. Sihota et al. reviewed PAC eyes without OHT at baseline and reported that one-third are likely to become ocular hypertensives over 5 years and further conversion to PACG of 30.7% [4]. The patients in that study differed significantly from those in this study, where they were

Table 4 Clinical parameters categorization of 'definite + likely' progressors and non-progressors in subgroups of PACHT and POAHT

No.	Variable	Category	PACG (14)	PACHT (57)	*p* value	POAG (5)	POAHT (33)	*p* value
1	Age (years)	≤ 49.99	1	6	0.42	0	8	0.25
		50–59.99	3	22		1	12	
		≥ 60	10	29		4	13	
2	Baseline IOP (mm Hg)	≤ 25.99	7	36	0.47	4	15	0.46
		26–29.99	4	14		1	10	
		≥ 30	3	7		0	8	
3	CCT (micron)	≤ 499.99	3	8	0.26	0	4	0.79
		500–549.99	8	24		4	18	
		≥ 550	3	25		1	11	
4	Final clinical CDR	≤ 0.599	6	20	0.40	0	7	0.33
		≥ 0.6	8	37		5	26	
5	Follow-up (months)	≤ 60.99	0	2	0.26	0	4	1
		61–119.99	2	20		1	9	
		≥ 120	12	35		4	20	
6	Disc area (sq.mm)	≤ 1.99	8	10	**0.004**	2	9	0.84
		2–2.49	2	32		2	13	
		≥ 2.5	4	15		1	11	

Chi-square/Fisher's exact test applied

IOP intraocular pressure, *CCT* central corneal thickness, *CDR* cup–disc ratio, *PACG* primary angle-closure glaucoma, *PACHT* primary angle-closure ocular hypertension, *POAG* primary open-angle glaucoma, *POAHT* primary open-angle ocular hypertension

Primary angle closure eyes with disc area ≤ 1.99 mm^2 are at higher risk of progression

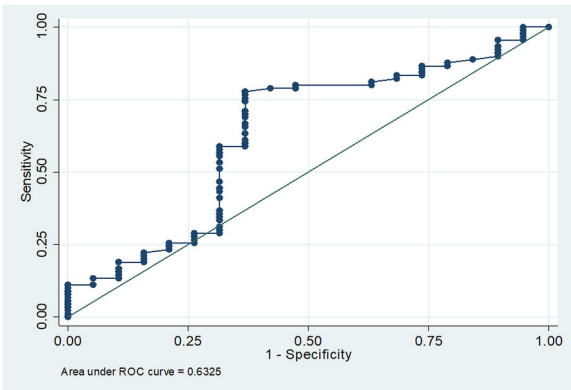

Fig. 2 Receiver operator curve of HRT global disc area. At a cut-off of ≥ 2.15 sq.mm, there was 66% sensitivity and 63% specificity to detect patients who are less likely to progress to glaucoma

part of a spectrum at baseline—physiologically raised IOP to possible preperimetric glaucoma—and therefore, the rate of progression was much lower. Thomas et al. found the 5-year incidence of PACG from PAC to be 28.5% (8/28 eyes), but PACHT was not specifically addressed, nor was IOP [5].

The OHTS reported a probability of progression of OHT to primary open-angle glaucoma as 9.5% in the observed arm and 4.4% in the treated arm over 5 years, and further, 19% of high-risk and 4% of low-risk treated cases at 10 years [3, 9]. At 13 years, it showed a 22% progression in the observed arm and 16% in the treated [8]. Our study showed a much lower progression than theirs in open-angle eyes, 13.16% (5/38 eyes), after more than 10 years of follow-up. This may be because our study had a mean reduction in IOP overall 30% and target IOP of ≤ 18 mm Hg, as against the OHTS where IOP was reduced by ≥ 20% to reach a value of ≤ 24 mm Hg using largely beta blockers. The progression in OHTS was diagnosed by both reproducible visual field and optic disc deterioration by their respective 'reading centres' [3]. Among their overall progressors, roughly 35 and 55% of patients attained the visual field and optic disc end point first, respectively, while 10% attained both concurrently, at 5 years. Using visual field loss alone

as the criteria, 41.7 and 32.6% of the overall progressors to POAG were picked up at 5 years, in the treatment and observation arm, respectively, as against to only 2.63% (1/37 eyes) POAHT and 4.22% (3/71 eyes) PACHT progressed eyes in this study, with none being a definite progressor at 5 years. In 2011, Gordon et al. showed that topical glaucoma medications for OHT reduce the 10-year incidence of POAG by half in all risk categories [9]. Kass et al. had results similar to our work and showed that the median time for development of POAG from OHT was 6 years in the observation arm and 8.7 years in the medicated arm, and further that a 20% reduction in IOP was not ideal and a greater reduction would have further reduced the incidence of POAG [8]. Thomas et al. reported the 5-year incidence of POAG from OHT was 17.4% (4/23 patients), but medications and target IOP were not addressed [10]. Medeiros et al. found that 35% of preperimetric glaucoma progressed to glaucoma over 4 years, with thinner cornea as a major risk factor, as against our results [11].

In our study, the number of patients showing an increase of 100% on TCA was 34.44% as compared to 17.43% who actually progressed to a visual field defect. Fifteen progressors by perimetry had good quality HRT images over their entire review and 8 out of them showed $>$ 100% area size increase. When TCA of definite progressors were reviewed, the red pixels cluster appeared 3–97 months earlier than HFA in 4 progressors and a 100% increase in their size 55, 34 and 6 months earlier than visual field in 3 patients and after visual field defect occurrence in 1 patient. TCA did not show any significant change in one patient who progressed to a visual field defect adjacent to the blind spot. Hence, in subjects whom it occurred, the time to initiation was earlier than perimetry and its position correlated well with field defects seen. Our study also found HRT global parameters of cup area, rim area, cup–disc area ratio, rim–disc area ratio and vertical CDR changed significantly in all definite and PACHT likely progressors, showing good concordance with event-based GPA of progression. Also, on studying the HRT stereoparameters, the linear CDR was found to be a better indicator of progression as compared to horizontal or vertical CDR.

Chauhan et al. showed that 40% of POAG eyes progressed by CSLO only, 4% by perimetry only, 29% by both techniques and 27% by none, over a period of 5.5 years. They concluded that disc changes determined by CSLO occur more frequently than field changes and that field end points are reached first by some, while optic disc end points are reached first by others, both being relatively independent [12]. Also, the time duration between HRT and automated perimetry in detecting progression varies widely. Functional changes may occur without structural changes, i.e. by ischaemia and IOP independent ganglion cell dysfunction or with structural changes, i.e. lamina bowing, astrocyte loss [13]. Moderate to good agreement has been shown by Vizzeri et al. in establishing glaucomatous progression by Moorfields regression analysis, topographic change analysis and trend analysis methods of assessing progression in HRT [14].

On analysing putative risk factors in this study, smaller discs with a global area of $\leq$ 1.99 sq.mm were found to be at greater risk of progression, especially for PACHT to PACG. PACHT eyes also had a significantly smaller baseline linear CDR by CSLO than those of POAG from POAHT. Sihota et al. reported that PACG eyes have smaller discs, smaller cup/disc ratio, smaller cup and larger rim area in comparison with eyes with POAG having a similar visual field loss [15]. To the best of our knowledge, optic disc area has not been shown to be a risk factor for progression from OHT to glaucoma earlier. On the contrary, Hayamizu et al. reported that large disc areas have a higher incidence of progressive visual field defects in normal tension glaucoma [16].

Our study looked at risk factors reported by OHTS and also found male sex, and those with a coronary artery disease were likely to progress. However, in our study, baseline IOP, baseline cup-to-disc ratio and baseline PSD were not found to be significant risk factors; but final VFI, PSD and ROP denoted progression. CCT was not significant, probably because most Indians have a thinner CCT than Caucasians, around 520–530 microns. Thomas et al. found that bilateral OHT, large diurnal variation and higher peak IOP may be the risk factors for progression [10]. Salvetat et al. evaluated baseline clinical, morphological and functional factors in predicting the conversion of OHT to POAG and found that older age, HFA glaucoma Hemifield test 'outside normal limits', scanning laser polarimetry (SLP) greater 'inter-eye asymmetry', CSLO lower rim volume and greater CDR are significant predictors [17]. They also added that baseline IOP, CCT and ibopamine provocative tests

were insignificant. Other described risk factors for glaucomatous progression include family history of glaucoma and myopia [18].

In our study, 16.66% of OHT eyes required ≥ 2 medications, while significantly, 47.36% of progressors required the same. None of our patients were on more than 3 topical medications. In OHTS, one or more medications were used to reach an IOP ≤ 24 mm Hg, and at 5 years, 39.7% of the medication group patients were on ≥ 2 topical medications, while 9.3% were on ≥ 3 [3]. The need for increasing number of topical medications to control a rising IOP in ocular hypertensives has not been evaluated earlier and probably reflects a progressive increase in trabecular dysfunction and higher IOPs, which could lead to glaucomatous optic neuropathy.

Activities of daily living and common ailments in the elderly were evaluated in our study. Chronic constipation, chronic cough, benign prostatic hypertrophy, breath-holding/forceful breathing exercises in yoga were found to be significantly related to progression overall, and especially so for primary angle-closure disease. Gupta V showed that constipation leads to a Valsalva manoeuvre which may raise the IOP [19]. Activities such as straining during chronic constipation and micturition in the presence of benign prostatic hypertrophy may involve Valsalva manoeuvres that increase intrathoracic pressure, decrease venous return and stimulate the peripheral sympathetic system. This has been shown to cause acute elevations of IOP or intermittent angle-closure episodes in predisposed eyes which could be detrimental to the optic nerve [20].

In this study, most of the definite progressors had well-controlled intraocular pressures for years and then showed an episode of increased IOP that was difficult to control, leading to perimetric progression, following the use of steroids as dermatological creams or inhalers. The use of steroids was not as frequent in either 'likely' progressors or non-progressors. The use of systemic steroids for various illnesses and their proclivity to progression suggests that they should be used cautiously in OHT patients, as they may be steroid responders, and this could tip the balance in a compromised optic nerve [21].

The trend-based VFI plot and event-based GPA of the HFA are complimentary to each other in evaluation of OHT patients [22]. In our study, VFI–ROP was not used to assess progression, because, being a global parameter, it could miss early, focal scotomas, which event-based evaluation would detect. The median ROP % per year in the POAHT progressing to POAG group was -0.5 and of PACHT progressing to PACG group was -0.2, both significantly differing from non-progressors whose median value was zero. Giraud et al. showed that VFI trend analysis and GPA event analysis corresponded in 97% of OHT patients [22]. Hence, a negative VFI rate could be a biomarker of progression in ocular hypertensives. PROG-F study 1 showed that VFI–ROP was -0.19% per year in eyes with ocular hypertension [23]. PROG-F3 study further added that VFI–ROP % per year for stable OHT and progressors were -0.026 and -0.407, respectively [24]. Rao et al. evaluated the diagnostic accuracy of trend-based analysis (VFI) considering GPA as standard and showed moderate agreement between the two methods in detection of progression. They considered a ROP of -1% per year with a p-value of < 0.05 as significant [25]. But, Llera et al. have shown that event analysis detects progression earlier and with greater sensitivity than VFI analysis in glaucoma patients [26].

While assessing the GPA of patients who progressed in this study, it was observed that a few suspicious loci on pattern deviation plot were fluctuating in the initial years and these later became permanent and spread to form scotomas. Careful and more frequent observation of such fluctuating loci in OHT patients is required and could necessitate starting/adding topical glaucoma medications to avoid a future field defect.

The limitations of our study include a relatively small cohort and very few definite progressors on HFA for good statistical evaluation. The need for regular follow-up over at least 5 years could have introduced a bias, with patients living near the hospital or from better socioeconomic strata being seen. There were also fewer POAHT patients as compared to PACHT.

In conclusion, setting a 'target' IOP of ≤ 18 mmHg in patients with OHT significantly reduces progression to glaucoma. Patients having a small disc area, requiring ≥ 2 drugs to maintain 'target' IOP and those engaged in activities giving rise to a Valsalva effect in daily life were more likely to progress and should be reviewed more frequently. Coronary artery disease and usage of systemic steroids were associated with more severe progression.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Human and animal rights The procedures performed in this report involving human subject were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed consent Informed consent was obtained from all the participants of this study.

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