Risk Factors for Development of Glaucoma

a report by
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In recent years, our knowledge of risk factors relating to open-angle glaucoma (OAG) has improved substantially. A number of studies have evaluated the cross-sectional association betwen risk factors and OAG, whereas only a few have investigated the risk factors for glaucoma development.[1] Prospective data provide better evidence on which to base inferences on causation because of ascertainment of temporality, which is one of the major causative criteria and has always been an inherent problem in studying a disease with low incidence.[2] The first requirement in assessing glaucoma onset is to study a cohort of individuals or patients over a period of time that is long enough to allow the development of the disease. The second requirement is an adequate definition of progressive change for the development of new cases of OAG. The third requirement is the collection of all of the possible clinical and non-clinical information from each study participant at baseline and, whenever possible, at different times during the follow-up, until the end of the investigation. These three requirements allow all the factors that were noted before the occurrence of the end-point to be weighed, thus elucidating and emphasising the potential relationship between each single risk or protective factor and the studied outcome.

In OAG, the following study designs, which meet all three requirements, are most often used: longitudinal population-based studies (PBS), randomised controlled clinical trials (RCTs) and cohort studies. Few major differences exist between these three study designs. PBS are usually designed to assess the incidence of OAG in a sample of the population of a well-defined geographical area, and are generally based on two examinations taken at least four years apart. This design usually takes into account the factors that were collected at the first examination and the factors that could be retrieved during the follow-up time before the second examination. This allows precise information to be collected only at baseline, as the indirectly acquired follow-up data cannot be matched precisely with the time of occurrence of progression. RCTs are designed to evaluate the efficacy of treatments, using an untreated group or a standard-treated group as control. Information is collected at baseline and at all the observation time-points until the end of the study. This design allows a very precise temporal relationship to be assessed (as the information is collected before the occurrence of the outcome), but is always restricted to a clinically very well-defined population – those with ocular hypertension (OHT), pseudoexfoliation (PEX), etc. This limits the potential for the results to be generalised, which differs from the PBS. Moreover, the intervention interferes with the results. Cohort studies tend to have the same pros and cons as RCTs, differing only in that single hypothetical factors are the targets of the investigation, and the results may provide information concerning only those individuals affected by the studied condition.

An important issue to be outlined is the different relative importance in terms of 'causality' that should be attributed to the various factors. Indeed, there are factors that may precede the progression – such as disc haemorrhage or high cup-to-disc (C/D) ratio – that are often strongly associated with the outcome. These cannot be interpreted as 'causal factors' of the progression, but simply as predictive factors that can be clinically observed. Furthermore, there are other factors, such as high intraocular pressure (IOP), for which a more relevant causal effect has been established. This review will therefore focus only on those longitudinal studies in which OAG onset was documented by the clinical detection of visual field (VF) and/or optic disc progressive changes. The data will be summarised and discussed in the context of each study design.

From Normal to Open-angle Glaucoma

Progression from healthy status to OAG is assessed by PBS. The incidence of diseases and their risk factors are the major findings. Risk factors for the development of OAG have been investigated in the Barbados Incidence Study of Eye Diseases (BISED),[3] which studied a sample of the Afro-Caribbean population, in the Visual Impairment Project (VIP),[4] which studied a sample of the urban Australian population, and in the Rotterdam Eye Study (RES),[5,6] which studied a sample of the Rotterdam population. The most relevant risk factors found consistently in the three studies were older age and high IOP (see *Table 1*). In fact, the relative risks (RR) for every year beyond a certain age in the BISED and RES were almost the same (1.04 and 1.06, respectively), despite the fact that the follow-up time in these two studies was different (nine years in the BISED versus 6.5 years in the RES). In the VIP, a trend towards an increase in the RR for each older decade has been observed, with an RR up to 12.2 (95% confidence interval (CI) 1.5–103) for the 70–79 years age group compared with the 40–49 years age group. It seems plausible that some of the differences may be explained by the different ancestries of the studied populations. As far as IOP is concerned, the three studies found almost the same RRs for each higher mmHg (1.12 in the BISED, 1.14 in the RES and 1.10 in the VIP). These results are consistent with the findings of several cross-sectional studies.[1]

Other factors that have been found in the BISED are a family history of OAG, a thin central corneal thickness (CCT) and a low ocular systolic, diastolic and mean perfusion pressure (systemic blood pressure – IOP). The RES has reported for the first time an association between the use of systemic calcium channel blockers for the treatment of systemic hypertension and the development of OAG. The VIP has reported PEX and a high C/D ratio of the optic disc as major risk factors and, for the first time, the use of systemic a-blockers. Interestingly, the VIP did not confirm a family history of OAG as a risk factor for OAG, and diabetes was not a risk factor in any of the three studies. The report concerning the assessment of risk factors for OAG in PBS is currently incomplete, as the RES has not yet published any detailed analysis similar to that provided by the BISED and the VIP. Moreover, it should be outlined that some factors have been covered in one study but not in the others, which would make a comparison between the results of the three surveys inaccurate.

From Ocular Hypertension to Open-angle Glaucoma

Patients affected by OHT are usually identified on the basis of IOP (>21mmHg on repeated measurements), VF and optic disc – which should, by definition, be normal. The prevalence of OHT in those older than 40 years in the US population may vary between 4 and 7%, and a number of the OHT individuals will eventually develop OAG. For these reasons OHT has been studied extensively in order to evaluate whether it is possible to prevent or delay the development of OAG and to assess its natural history and the risk factors associated with the development of OAG. Two large trials have been completed in recent years – the Ocular Hypertension Treatment Study (OHTS)[7] and the European Glaucoma Prevention Study (EGPS).[8] Both the OHTS and the EGPS provided relevant information concerning both the baseline factors that were associated with the development of OAG (baseline predictive factors)[9–11] and the factors that were noted during the follow-up of the study and were associated with the outcome inter-current factors.[12,13]

Baseline risk factors found in the OHTS, EGPS and in the trial performed in Malmoe[14] are reported in *Table 2*. Interestingly, the vast majority of the baseline risk factors were consistently reported in both OHTS and EGPS – older age, thinner CCT, higher C/D ratio of the optic disc and higher pattern standard deviation (PSD) values. Higher baseline IOP was a major risk factor in the OHTS, but not in the EGPS (hazard ratio (HR) 1.07, 95% CI 0.94–1.22). However, in a secondary analysis in which those factors that may be involved in the determination of OAG damage were excluded (vertical C/D ratio, PSD and vertical C/D ratio asymmetry), baseline IOP resulted in significant risk factors (HR 1.18, 95% CI 1.06–1.31), in agreement with the OHTS findings.[15] Diabetes was found to be protective in the OHTS and not associated with OAG in the EGPS. The OHTS results of Heidelberg retinal tomography (HRT)[16] – particularly an abnormal HRT classification and an abnormal result of the Moorfields Regression Analysis (MRA) performed at baseline or before the development of OAG – were strongly associated with the outcome. These results have been reported for the first time, and are consistent with the observation that a suspect disc or a disc with a larger C/D ratio were risk factors for OAG. Vertical C/D ratio asymmetry has been found to be a relevant risk factor in the EGPS, but was not evaluated in the OHTS.

The Malmoe study confirmed age, baseline IOP and a suspect disc appearance as risk factors for the development of OAG. The inter-current factors are reported in *Table 3*. These factors were recorded during the duration of the follow-up, before the development of OAG. In the OHTS and in the EGPS they were analysed as 'time-dependent' factors by taking into account the time at which the factor was noted. The major risk factor for the development of OAG was a higher mean IOP during follow-up, or a lesser IOP decrease from baseline (achieved by means of medical treatment). This was the result of the primary efficacy analysis of the OHTS and of the secondary *post hoc* analyses of the EGPS and Malmoe Study.[17] The risk related to higher IOP may then be estimated to be around 0.1–0.15 higher for each higher mmHg measured during a follow-up ranging between five and 8.5 years. As far as IOP fluctuation is concerned, the EGPS did not find any significant association between long-term IOP fluctuation and the development of OAG, and the Malmoe study did not find any statistical association between the mean daily range of IOP and the development of OAG. In this study, three daily IOP measurements were taken from 8.00am up to 3.30pm every three months for an average follow-up of 8.5 years.

Table 1: Risk Factors for Open-angle Glaucoma

Incidence	BISED 9 years	RES 6.5 years	VIP 5 years
Age (per older year)	1.04 (1.02–1.05)	1.06 (1.02–1.09)	–
Age at baseline 50–59	–	–	NS
Age at baseline 60–69	–	–	8.4 (1.1–66.6)
Age at baseline 70–79	–	–	12.2 (1.5–103)
Age at baseline ≥80	–	–	NS
OAG family history	2.4 (1.3–4.6)	–	NS
IOP (per mmHg)	1.12 (1.08–1.16)	1.14 (1.08–1.21)	1.10 (1.04–1.20)
CCT (per 40mm thinner)	1.41 (1.01–1.96)	–	–
Ocular MPP (<40mmHg)	2.6 (1.4–4.6)	–	–
SBP (per 10mmHg)	0.91 (0.84–1.0)	–	–
Diabetes	NS	NS	NS
Ca channel antagonists	–	1.9 (1.1–3.3)	–
a-blocker	–	–	4.8 (2.0–63.3)
C/D ratio >0.7	–	–	11.0 (4.6–26.8)
PEX	–	–	11.2 (2.0–63.3)

BISED = Barbados Incidence Study of Eye Diseases; RES = Rotterdam Eye Study; VIP = Visual Impairment Project; OAG = open-angle glaucoma; IOP = intraocular pressure; CCT = central cornea thickness; MPP = mean ocular perfusion pressure; SBP = systolic blood presssure; Ca = calcium; C/D = cup-to-disc; PEX = pseudoexfoliation syndrome.
(Relative risk with 95% confidence intervals) for development of OAG in population-based longitudinal studies.

Table 2: Baseline Risk Factors for Open-angle Glaucoma

Follow-up	OHTS 5 years	EGPS 5 years	Malmoe 8.5 years
Age (per decade)	1.22 (1.01–1.49)	1.32 (1.04–1.69)	–
Age (per year)	–	–	1.05 (1.03–1.09)
OAG family history	NS	–	NS
Baseline IOP (per mmHg)	1.10 (1.04–1.17)	NS	1.14 (1.01–1.29)
CCT (per 40mm thinner)	1.71 (1.40–2.09)	1.32 (1.05–1.67)	–
Vertical C/D ratio (per 0.1 larger)	1.32 (1.19–1.47)	1.34 (1.14–1.58)	–
Horizontal C/D ratio (per 0.1 larger)	1.27 (1.14–1.40)	–	–
Vertical C/D ratio asymmetry (per 0.1 larger)	–	1.46 (1.11–1.93)	–
Suspect disc appearance	–	–	2.90 (1.34–6.30)
PSD (per 0.2dB greater)	1.27 (1.06–1.52)	1.66 (1.15–2.38)	–
Diabetes	0.37 (0.15–0.90)	NS	NS
Ca channel blockers	NS	NS	–
PEX	–	NS	NS
HRT classification, outside normal limits versus within normal limits*	2.54 (1.31–4.90)	–	–
HRT MRA, outside normal limits versus within normal limits – overall*	2.39 (1.02–5.62)	–	–

OHTS = Ocular Hypertension Treatment Study; EGPS = European Glaucoma Prevention Study; OAG = open-angle glaucoma; IOP = intraocular pressure; CCT = central cornea thickness; C/D = cup-to-disc; PSD = pattern standard deviation; dB = decibel; Ca = calcium; PEX = pseudo-exfoliation syndrome; HRT = Heidelberg retinal tomograph; MRA = Moorfields Regression Analysis.
**Secondary analysis performed on a subset of the original OHTS population (438 participants) (hazard ratios with 95% confidence intervals) for development of open-angle glaucoma in randomised clinical trials on ocular hypertensive populations.*

The observation of optic disc haemorrhages during the follow-up was a relevant risk factor reported in both the OHTS and the EGPS. The HR reported in the OHTS (3.7) was larger than that reported in the EGPS (1.97). It should be noted that the median follow-up was 96.3 months in the OHTS and 59 months in the EGPS, which may explain the difference in HR between the two studies: the probability of developing a disc haemorrhage may be greater during a longer follow-up, and the longer follow-up allows

Table 3: Inter-current Risk Factors for Open-angle Glaucoma

Follow-up	OHTS 5 years	EGPS 5 years	Malmoe 8.5 years
Mean IOP decrease from baseline (20% or 5mmHg)	0.40 (0.27–0.59)	–	–
Mean IOP decrease from baseline (per mmHg)	–	0.89 (0.80–0.98)	–
Mean IOP during follow-up (per mmHg higher)	–	1.12 (1.03–1.22)	1.21 (1.09–1.38)
AUC of IOP during follow-up (per mmHg higher per year)	–	1.09 (1.06–1.12)	–
IOP fluctuation during follow-up (SD of mean IOP)	–	NS	–
Diurnal IOP fluctuation during follow-up	–	–	NS
Disc haemorrhage (any)	3.70 (2.10–6.60)	1.97 (1.21–3.22)	–
Systemic diuretics	–	2.41 (1.12–2.68)	–

OHTS = Ocular Hypertension Treatment Study; EGPS = European Glaucoma Prevention Study; IOP = intraocular pressure; AUC = area under the curve; SD = standard deviation. (hazard ratios with 95% confidence intervals) for development of open-angle glaucoma in randomised clinical trials on ocular hypertensive populations.

Table 4: Ocular Hypertension Treatment Study – European Glaucoma Prevention Study

	HR (95% CIs)
Age (per decade)	1.26 (1.06–1.50)
Baseline IOP (per mmHg)	1.09 (1.03–1.17)
CCT (per 40mm thinner)	2.04 (1.70–2.45)
Vertical C/D ratio (per 0.1 larger)	1.19 (1.09–1.31)
Pattern standard deviation (per 0.2dB greater)	1.13 (1.04–1.24)

HR = hazard ratio; CIs = confidence interval; IOP = intra-ocular pressure; CCT = central corneal thickness; C/D = cup to disc; dB = decibel.

for time between the observation of a disc haemorrhage and the observation of a disc or VF change (13 months on average in the OHTS). An interesting finding of the EGPS was the association between the use of systemic diuretics to treat systemic hypertension during the follow-up and the development of OAG. Although not confirming the findings of the RES about the association between the use of calcium channel blockers and OAG, the findings of the EGPS and of the RES may support the hypothesis that systemic antihypertensive treatment eventually contributes to the development of OAG.

Risk Estimate for Open-angle Glaucoma

OHT is the leading risk factor for the development of primary OAG (PAOG) and is the only factor that can be modified by current treatment. It is estimated that approximately 4–7% of the US population over the age of 40 years has ocular hypertension without detectable glaucomatous damage using standard clinical tests. Therefore, as many as 10 million Americans are at risk of developing glaucoma because they have OHT. The OHTS data suggest that the treatment of all ocular hypertensive individuals is neither "medically indicated nor economically justified because of the high prevalence of the condition; the low conversion rate to POAG; and the cost, inconvenience and possible adverse effects of treatment".[18] Economic analyses from OHTS suggested that ocular hypotensive treatment is cost-effective in the subgroup of ocular hypertensive individuals with an IOP >24mmHg and an annual risk of POAG >2%.[19]

Unfortunately, it is difficult for clinicians to determine the annual risk of POAG for an individual ocular hypertensive. Prediction models and, in particular, risk calculators can provide this information. On the basis of the OHTS results a number of risk calculators have been developed in order to estimate the individual risk of developing glaucoma among OHT patients.[20,21] The most recent risk calculator has been developed by merging the OHTS and EGPS data sets.[18] First, the EGPS data were used as an independent data set to validate the OHTS predictive model. This validation study showed that the predictive factors for developing POAG were remarkably similar in the two studies. The data from the two studies were then combined to produce a new risk model (see *Table 4*), which was then developed into an online risk calculator that clinicians can use to assess the risk of the development of POAG for an individual OHT patient. This pooled analysis not only yielded greater stability of the HRs and narrower confidence limits for prediction, but also improved the possibility of generalising the results and allowed for subgroup analysis, which was not possible with the sample size of either study alone.

A risk calculator provides only an estimate of an individual's risk of developing glaucoma; it cannot provide guidance to support the physician's decision of whether to treat or monitor the patient. This final decision is dependent on the physician's judgement. ■

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