An Epidemiological Study Of Risk Factors Associated With Progression From Ocular Hypertension To Primary Open Angle Glaucoma

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ABSTRACT

Background: As a multifactorial disease glaucoma may be associated with pressure-dependent and -independent factors. Ocular hypertension (OHT) may develop into primary open angle glaucoma (POAG) for many patients. We compared groups with OHT and POAG for pressure-dependent and -independent risk factors. A high prevalence of any factor(s) could indicate a contribution to progression from OHT to POAG.

Method: A sample of patients with POAG (n=438) and with OHT (n=301) were selected from those attending a tertiary referral private glaucoma practice, and data were collected regarding age and intraocular pressure at the time of diagnosis, gender, family history of glaucoma, systemic hypertension, diabetes, Raynaud's phenomenon, migraine and myopia.

Results: After multivariate analysis, older age at time of diagnosis ($P<0.001$), myopia (odds ratio (O.R)=1.5, 95% confidence interval (C.I)1.0-2.2; $P=0.05$), a family history of glaucoma (O.R=1.6, 95% C.I 1.1-2.3; $P=0.01$) and a high intraocular pressure ($P=0.002$) were associated with POAG. No other significant differences were found between the two groups.

Conclusion: Patients who have OHT may be at higher risk of developing POAG if they also have myopia, a family history of glaucoma or are of older age.

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NOTE ON THE AUTHOR'S CONTRIBUTION

The Author was solely responsible for the data collection, analysis and writing of this treatise. Opinions from Dr Ivan Goldberg and Dr Stuart Graham were sought regarding its content and accuracy, which were incorporated into the final work. Advice from Associate Professor Robert Cumming was also sought regarding the epidemiological considerations involved in this study.

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LIST OF SPECIAL NAMES OR ABBREVIATIONS

AAP	Achromatic Automated Perimetry
GON	Glaucomatous Optic Neuropathy
HFA	Humphrey Field Analyzer
IOP	Intraocular Pressure
NTG	Normal Tension Glaucoma
OHT	Ocular Hypertension
POAG	Primary Open Angle Glaucoma

INTRODUCTION

Primary open angle glaucoma (POAG) is a chronic condition affecting the eye in which the intraocular pressure (IOP) is elevated above levels considered compatible with its health, in the presence of an open angle, a reduced facility of outflow and glaucomatous optic neuropathy (GON).[1] The aetiology POAG has been a debated issue which has continued up to the present day.[2] In 1855, after the development of ophthalmoscopy, Weber described the glaucomatous optic disc, highlighting a 'pressure excavation' effect and adding further debate to the pathogenesis of the disease.[3] In 1879, Smith introduced the concept of vascular factors being at least partly responsible for disc cupping and not purely a result of mechanical compression.[3]

These two views regarding causation in POAG are still the topic of research today. Glaucomatous optic neuropathy (GON) may result from a variable combination of factors.[4,5,6] These have been described as pressure-dependent factors such as those contributing to trabecular meshwork damage and thus impaired aqueous outflow (e.g mutation in the GLC1A (TIGR) gene) and pressure-independent ones which may result in ischaemia of the optic disc (e.g microvascular damage or vasospasm).[7,8,9,10,11] Figure 1 shows the possible mechanisms.

Raised intraocular pressure (IOP) is associated with GON.[12,13] While the probability of glaucomatous damage increases with higher IOP, for long periods an optic disc may tolerate elevated IOP. This is called "ocular hypertension" (OHT)(raised IOP with no detectable GON).[14] Conversely, GON may occur with IOP within the usual range: "normal tension glaucoma" (NTG)(GON without raised IOP).[14,15] These discrepancies may be accounted for by pressure-independent factors.

Age has been shown to be related to the likelihood of developing GON.[16,17,18] This may be the result of atrophy of otherwise supportive collagenous structures in the lamina cribrosa and as such may contribute to the development of GON as a pressure-independent or –dependent factor.[19] Conditions resulting in microvascular damage such as systemic hypertension and diabetes mellitus have been found to be more common amongst individuals with POAG.[5,17,20,21,22,23,24,25] Microvascular damage leading to optic nerve head ischaemia may itself result in retinal ganglion cell loss.[19] Additionally, ischaemia may make the lamina cribrosa vulnerable to mechanical compressive forces leading to axon bundle damage and GON.[26] Vasospastic conditions such as migraine and Raynaud's phenomenon are more common amongst those with normal pressure glaucoma.[27,28,29,30] It is possible that vasospasm is a systemic disorder, affecting various vascular beds.[8,10,30,31,32] Vasospasm in the vicinity of the optic nerve and lamina cribrosa may contribute to GON independent of IOP, or may render the optic disc more vulnerable to IOP-induced damage.[8,33]

The contribution of genetic factors to GON is complex and not yet explained.[4] While a family history of glaucoma is more common in patients with POAG than in the general population,[17,24,34,35,36] it may be more strongly associated with OHT than with POAG.[11] This suggests a pressure-dependent factor, through trabecular meshwork dysfunction. A positive family history of glaucoma may be associated with earlier GON among OHT patients[4,37,38] and a more rapid progression of GON.[4,8] This suggests both genetic pressure-independent and –dependent factors.

Myopia appears to be a risk factor for GON.[17,24,39] This may relate to the larger size of the myopic optic disc, with reduced physical support to retinal ganglion cell axons and astroglial elements, predisposing to GON.[39]

It may be that subjects develop OHT, but then the presence of pressure-independent risk factors is what makes them prone to progressing to POAG from the development of GON. Many studies have examined pressure-independent factors, which could contribute to GON (Appendix 1). The majority have concurred regardless of the study design. However, only a few have analysed numerous risk factors in a multivariate fashion. Fewer still have compared OHT to POAG in this way.

In the study described in this paper, we compared groups with OHT and POAG. In clinical practice patients with OHT are observed for signs that they might be developing GON and thus progressing to POAG. The objective of the paper was to assess whether risk factors for GON (i.e IOP, microvascular damage, vasospasm, positive family history, refractive error, age) may be associated with the progression of OHT to POAG from the subsequent development of GON.

METHOD

All available files of new patients who had attended an urban glaucoma clinic during the past six years with POAG or OHT were reviewed (n=1043). Only those patients who had all variables documented were included in the final sample (n=739). Patients were not excluded based on the presence of any variables (e.g age, sex, referral source, risk factor). Patients had been diagnosed by one of two glaucoma specialists prior to this study and included the following criteria: patients with POAG had an IOP 21 mmHg or greater at diagnosis, no angle closure, no primary cause for raised IOP, a cup/disc ratio of 0.7 or greater and/or a glaucomatous abnormality on achromatic automated perimetry (AAP). Patients with OHT had an IOP 21 mmHg or greater at diagnosis, no angle closure, no primary cause for raised IOP, a cup/disc ratio of less than

0.7 and no glaucomatous abnormality on AAP. Every patient had their diagnosis well established with two or more consecutive visual field tests and intraocular pressure readings. An abnormality on AAP was based on the Humphrey Field Analyzer pattern deviation plot, which measures how likely a test point is to be normal for age (i.e P<5%, indicates a less than 5% probability that a point is normal for age). The pattern was considered abnormal if it was of a typical glaucomatous pattern and in a cluster of 3 or more abnormal points of P < 5%, or 2 or more points of P < 1%, in a field with 5 or more points of P < 5%. The points could not cross the horizontal axis.

At their initial visit, all patients answered a questionnaire which inquired about potential risk factors for POAG. These included systemic hypertension (elevated blood pressure necessitating treatment with medication), diabetes (elevated blood sugar warranting treatment either by diet, oral medication or insulin), migraine (episodic unilateral headaches with or without vomiting or photophobia, which interrupt every day life), Raynaud's phenomenon (persistently cold or painful/numb hands or feet) and family history among first degree relatives. Patients also had their refractive error and IOP measured. A patient with a refractive error of spherical equivalent ≥ -1 D was considered to have myopia. IOP at diagnosis was grouped into five risk levels based on the potential risk an eye might have of developing GON with this IOP. The reference group for raised IOP was between 21 mmHg and 23 mmHg. We then used two low risk IOP groupings (24 to 26 mmHg and 27 to 29 mmHg) and two high risk IOP groups (30 to 31 mmHg and ≥ 32 mmHg).

Statistical Analysis System 6.12 (SAS Institute Inc, Cary, NC) was used for statistical analysis including Student t-test, chi-square and Mantel-Haenszel test statistic for univariate analyses and multiple logistic regressions for multivariate analyses. In

logistic regressions, age and IOP at diagnosis were used as ordinal categorical variables and sex, systemic hypertension, diabetes, myopia, Raynaud's phenomenon and family history of glaucoma were used as dichotomous variables. Adjustment was made for the route by which patients were referred to the glaucoma clinic: general practitioner (and other non-ophthalmic medical practitioner), optometrist and ophthalmologist. Odds ratios and 95% confidence intervals were calculated.

RESULTS

There were 438 subjects with POAG and 301 with OHT. Of those with OHT, 189 (64%) were female compared with 243 (56%) females with POAG. The difference between these proportions just reached statistical significance (P=0.05). The numbers and percentages of subjects in the OHT and POAG samples are summarised in Table 1.

Mean age at diagnosis was 51 years (SD=12.6) with OHT and 59 years (SD=13.0) with POAG. This difference was statistically significant ($P < 0.001$). As a univariate risk factor, age was significantly associated with POAG (Mantel-Haenszel $X^2_1=58.91$; $P<0.001$). This association was strengthened in multivariate analysis (Table 2.).

After univariate analysis of risk factors, systemic hypertension appeared to be more prevalent among POAG patients than OHT patients (O.R= 1.5, 95% C.I: 1.1-2.2, P=0.02) (Table 2). However, after multivariate (logistic regression) analysis, adjusting for age and confounders there were no significant between-group differences for systemic hypertension, diabetes mellitus, Raynaud's phenomenon or migraine. However, there was a significantly higher prevalence for myopia (O.R=1.5, 95% C.I: 1.0-2.2, P=0.05) and family history of glaucoma (O.R=1.6, 95% C.I: 1.1-2.3, P=0.01) among POAG subjects (Table 2.).

As a univariate risk factor, IOP appeared significantly associated with POAG (Mantel-Haenszel X^2_1=14.99; P<0.001) (Table 2.). However in multivariate analysis, IOP no longer had as clear an association.

DISCUSSION

Many studies have examined pressure-independent factors, which could contribute to GON.[33] Our study highlights the age difference between populations with OHT and POAG.[16] Subjects who were 50 years or older were significantly more likely to have POAG. This in itself may be a pressure-independent factor, in that age-related degenerative changes to the lamina cribrosa may lead to ganglion cell axon ischaemia or to loss of structural support.[19] Furthermore, with advancing age comes the increased risk of other causative factors for GON e.g systemic hypertension, diabetes, elevated serum lipids. There is also increased time for these factors to damage blood vessels and retinal ganglion cells. Lastly our results could be evidence of a pressure-dependent mechanism, whereby prolonged exposure to raised IOP could lead to GON.

In our study, there were more male subjects among those with POAG than those with OHT. This has been demonstrated in previous studies.[34,40] Males with OHT may be more likely to develop POAG, however the prevalence of males may indicate a difference in referrals between OHT and POAG groups for the two sexes in our sample.

Although more subjects in the POAG group had systemic hypertension, this difference was reduced with multivariate analysis; [41] our results did not suggest systemic hypertension to be a separate pressure-independent factor.[42] Previous research has shown a possible link between systemic hypertension and raised IOP.[40,43,44] This is consistent

with our finding of similar prevalence of this risk factor in OHT and POAG patients. Perhaps systemic hypertension can be a pressure-dependent variable.

After adjustment for confounders [45,46,47,48] no association was found for diabetes, Raynaud's phenomenon or migraine. This has been seen in other studies,[12,49,50,51] although the small numbers in the diabetes groups (14 in the OHT group and 24 in the POAG group) may have reduced the power of the study to detect an association. A family history of glaucoma among first degree relatives was frequent in both OHT and POAG groups (41% and 47% respectively) and was also found to be more prevalent in POAG patients after multivariate analysis. Those patients with OHT and a family history of glaucoma may be more likely to develop POAG. While the proportion of those with a family history was higher in our study than other reports of 10%,[52] McNaught et al. suggest that the true rate may be as high as 30% due to patients' lack of knowledge about glaucoma in their family.[53]

We found myopia to be more prevalent amongst POAG subjects after multivariate analysis. Myopia may play a role in the progression of OHT to POAG. This agrees with other studies.[39] Reasons are not known, but the larger cup size seen in myopia may weaken the optic nerve head and make it more susceptible to mechanical damage. To date this has not been confirmed.[39]

IOP at diagnosis was considered a confounding variable for the association between pressure-independent variables and the development of GON.[13] After univariate analysis there was a statistically significant linear trend between IOP group and POAG (Mantel-Haenszel X^2_1=14.99; P<0.001). The data suggest this might be a threshold effect, with increased risk of POAG only with IOP ≥ 30mmHg. However, after multivariate analysis this trend was diminished (Table 2).). This supports the concept that for an OHT patient, IOP is a causal and dose-related risk factor for POAG, and also that the

development of POAG is a multifactorial process. Alternatively, it may be that another pressure-dependent variable such as perfusion pressure (blood pressure minus IOP) is a stronger risk factor for the development of POAG than IOP at diagnosis. This relationship has been examined in other larger studies such as The Barbados Eye Study,[54] however it was not measured in this study.

Our study relied on self-reporting of conditions as noted in medical records, with its inherent inaccuracies. However, there is no reason to suspect that these inaccuracies would be different between groups and this limitation should only contribute to non-differential misclassification (which makes it more difficult to detect differences between groups). Thus it was possible that subjects had any of the risk factors, but if they weren't aware of their presence, then they would be misclassified as absent.

Systemic hypertension was coded as either present or absent. Our data does not take into account whether hypertension was treated or untreated. We could not separate the risk from the disease compared with its treatment. The length of time the patient had systemic hypertension was also not recorded. Diabetes too was coded as present or absent. Type and treatment were not noted. Neither was level of control. Migraine was coded dichotomously with the possibility of confusion between true migraine and severe headache. This misclassification was likely to be equal between POAG and OHT patients. Raynaud's phenomenon was recorded as present or absent and took into account those with true painful chilblains and those with cold hands or feet. Myopia was defined as a spherical equivalent $\geq$ -1 D. The grades of myopia were not differentiated. Myopia was recorded on refractive error and not differentiated into axial or refractive groups. Future studies may use axial length as a variable to be analysed.

Our study was a case-control study with a poorly defined study base. This was not the most ideal study design, however it should be able to provide hypothesis generation

for future work. Whilst having a large sample, it could have been improved had it been a population-based case-control or cohort study. The location of the study was a private practice specialising in glaucoma, which may have resulted in an increase of certain proportions of risk factors such as family history. However, these increases are likely to be similar for both groups. Whilst clinicians were not blinded to outcome status when recoding exposures, they were unaware of the study at the time of collecting the data.

Recall bias was not likely to have occurred between the groups with regard to family history and other risk factors. Participants would need to have an appreciation of the difference between OHT and POAG. As both conditions involve measuring IOP and repeatedly checking visual fields, the experiences each person has would be similar. It would therefore be easy to confuse the two conditions. Participants with POAG would be no more likely to incorrectly recall risk factors than OHT participants.

Referral bias could have potentially occurred in this study, however it was felt that it would most likely result in a bias towards the null. Subjects with POAG might be referred regardless of the presence of risk factors. However those with both OHT and a risk factor might be more likely to be referred than those with OHT alone.

CONCLUSION

We have no reliable method of determining precisely who will develop GON. Yet such knowledge would improve our ability to initiate and/or accelerate treatment significantly. Our study suggests that patients who have OHT may be at higher risk of developing POAG if they have myopia, a family history of glaucoma, a higher intraocular pressure (≥ 30mmHg) or are of older age (≥ 50 years). These groups, in particular should be monitored carefully. Those with OHT and migraine or Raynaud's phenomenon may not be at higher risk.

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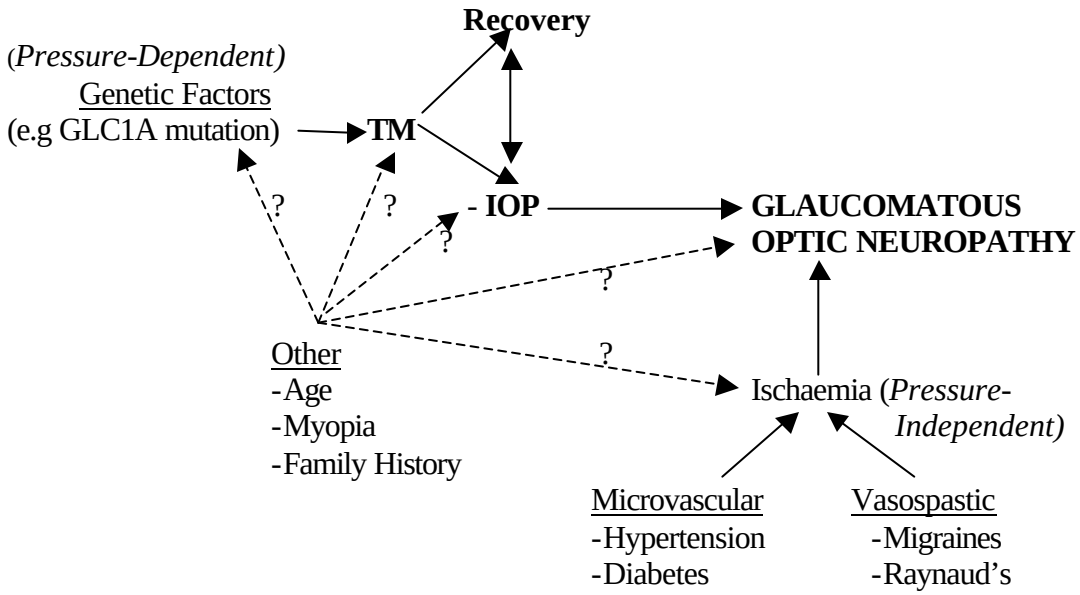

Figure 1. Diagram showing the possible pathways to glaucomatous disc damage (Modified with permission from Dr R.Ritch[11])

Table 1. Characteristics of study subjects in the Ocular Hypertension (OHT) and Primary Open Angle Glaucoma (POAG) groups

	OHT (n=301)		POAG (n=438)	
	No.	(Percentage)	No.	(Percentage)
Sex:				
Female	189	(64%)	243	(56%)
Male	112	(36%)	195	(44%)
Age at diagnosis:				
< 39	53	(18%)	32	(7%)
40-49	85	(28%)	77	(18%)
50-59	85	(28%)	107	(24%)
60-69	58	(19%)	127	(29%)
70-79	18	(6%)	80	(18%)
≥ 80	2	(1%)	15	(3%)
Systemic Hypertension	63	(21%)	126	(29%)
Diabetes	14	(5%)	24	(5%)
Raynaud's Phenomenon	58	(19%)	107	(24%)
Migraine	56	(19%)	77	(18%)
Myopia	94	(31%)	162	(37%)
Family History of Glaucoma	124	(41%)	207	(47%)
IOP at diagnosis:				
21-23 mmHg	114	(38%)	160	(37%)
24-26 mmHg	115	(38%)	120	(27%)
27-29 mmHg	49	(16%)	65	(15%)
30-31 mmHg	8	(3%)	38	(9%)
≥ 32 mmHg	15	(5%)	55	(13%)
Referral Source:				
General Practitioner	109	(36%)	115	(26%)
Optometrist	145	(48%)	100	(23%)
Ophthalmologist	47	(16%)	223	(51%)

Table 2. Univariate and multivariate odds ratios of the likelihood that a patient with one of the risk factors for glaucomatous optic neuropathy has glaucoma versus ocular hypertension

Risk Factor	Univariate Odds Ratio (95% C.I)		Multivariate Odds Ratio(95% C.I)	
Sex:				
Female	1.0		1.0	
Male	1.4	(1.0-1.8)*	1.9	(1.3-2.7)**
Age at diagnosis:				
< 40	1.0		1.0	
40-49	1.5	(0.9-2.6)	1.8	(1.0-3.4)
50-59	2.1	(1.2-3.5)**	3.3	(1.8-6.2)**
60-69	3.6	(2.1-6.2)**	6.6	(3.5-12.8)**
70-79	7.4	(3.8-14.4)**	18.0	(8.4-42.1)**
≥ 80	12.4	(2.7-57.9)**	34.8	(6.8-186.4)**
	(MH: X^2_1=58.91; P<0.001)***			
Systemic Hypertension	1.5	(1.1-2.2)*	0.9	(0.6-1.4)
Diabetes	1.2	(0.6-2.3)	0.8	(0.4-1.8)
Raynaud's Phenomenon	1.4	(0.9-1.9)	1.0	(0.6-1.5)
Migraine	0.9	(0.6-1.4)	1.0	(0.6-1.6)
Myopia	1.3	(0.9-1.8)	1.5	(1.0-2.2)*
Family History of Glaucoma	1.3	(1.0-1.7)	1.6	(1.1-2.3)**
IOP at diagnosis:				
21-23 mmHg	1.0		1.0	
24-26 mmHg	0.8	(0.5-1.1)	0.6	(0.4-0.9)*
27-29 mmHg	1.0	(0.6-1.5)	0.8	(0.4-1.2)
30-31 mmHg	3.6	(1.6-7.9)**	2.8	(1.1-7.1)*
≥ 32mmHg	2.7	(1.5-5.1)**	1.5	(0.8-3.2)
	(MH: X^2_1=14.99; P<0.001)***			

* P<0.05, ** P<0.01, *** MH=Mantel-Haenszel test for trend. Multivariate adjusted odds ratios adjusted for all other variables listed including referral source.

Appendix 1. Table describing previous epidemiological research which has been performed analysing risk factors for raised IOP, OHT and POAG.

Ref.	Authors	Study Type	Sample Size	Study Factor	Outcome Factor	Confounders	Results
2	Morgan R.W Drance S.M (1975)	Case-Control (Well-defined study base)	POAG 91 Control 91 OHT ?	Transfusions Diabetes Migraine Hypertension Smoking Family Hist.	POAG OHT	Sex Age Residence	POAG: Transfusion OR=3.3(P<0.1) Fam. Hist. OR=7.5(P<0.005) OHT: Fam. Hist. OR=3.3(P<0.1)
4	Uhm K-B Shin D.H (1992)	Case-Control (Poorly-defined study base)	POAG 361 OHT 178 Control 927	Family Hist.	POAG OHT	Sex Age Race	POAG: Fam. Hist. OR=3.15(P<0.0001) OHT: Fam. Hist. OR=7.56(P<0.0001) Fam. Hist was significantly more associated with OHT than POAG OR=2.40(P<0.0001)
5	Orgül S Flammer J (1995)	Case-Control (Poorly-defined study base)	NTG 23 Control 23	Headache	IOP	Effect Modifier: NTG	Among NTG patients: Headache associated with lower IOP (P<0.0004) Among Control patients: Headache not associated with IOP
8	Gasser P Flammer J (1991)	Case-Control (Poorly-defined study base)	NTG 30 POAG 30 Control 30	Mean capillary blood cell velocity	NTG POAG	Effect Modifier: Cold Provocation	POAG patients had same capillary dynamics as controls. NTG patients had significantly lower mean capillary blood cell velocity than controls (P<0.05), especially after cold provocation (P<0.0005).
9	Gasser P Flammer J Gauthauser U et. al. (1990)	Non-randomised Controlled Trial	Vasospasm patients 16 Control 10	Cold water exposure. Nifedipine ingestion	Visual field mean sensitivity	Nil	Cold Exposure: 12/16 cases showed worsening of visual field compared with 4/10 controls. Nifedipine ingestion: 15/16 cases showed improvement in visual fields compared with 4/10 controls

Ref.	Authors	Study Type	Sample Size	Study Factor	Outcome Factor	Confounders	Results
10	Gasser P Flammer J (1990)	Non-randomised Controlled Trial	Vasospasm patients 48 Control 14	Nifedipine ingestion; short and long term	Visual field mean defect	Nil	After short term treatment visual fields improved in both (P<0.0001) and in controls (P<0.017). After long term treatment visual fields improved at 2 months (P=0.02), 6 months (P=0.017) and 12 months (P=0.09) [no mention of differences between cases and controls]
12	Quigley H.A Enger C et al. (1994)	Cohort study	647	Family Hist. Nerve Fibre Layer appearance	Goldman's Visual Fields	Age Sex Race Hypertension Diabetes Smoking Alcohol	NFL defect: Multivariate Analysis -Mild RR=2.96* -Moderate RR=4.06* -Severe RR=4.40* IOP RR=1.52* Cup/disc ratio RR=1.10* (*P<0.05)
13	Sommer A Tielsch J.M Katz J et al. (1991)	Cross Sectional Analysis	5308	IOP	POAG	Effect Modifier: Race	IOP was significantly associated with POAG for both black and white race (P<0.0001)
17	Georgopoulos G Andreanos D Liokis N et al. (1997)	Cohort Study	345	Age Family Hist. IOP Myopia Hypertension Diabetes Exfoliation	POAG	Nil	POAG: Multivariate Analysis Family Hist. (P<0.001) Age ≥ 60 yrs (P=0.013) Axial Myopia (P=0.029) Hypertension (P=0.041)
18	Uhm K-B Shin D.H (1992)	Case-Control (Poorly-defined study base)	POAG 361 OHT 178 Controls 927	Age Hypertension Diabetes Family Hist. Race	POAG OHT	Sex	POAG: Multivariate Analysis Compared with controls, Family Hist. 3.46 (P<0.001). Compared with OHT, no independent associations

Ref.	Authors	Study Type	Sample Size	Study Factor	Outcome Factor	Confounders	Results
20	Mitchell P Smith W Chey et al. (1997)	Cross Sectional Analysis	3654	Diabetes	POAG OHT	Age Sex	OHT: Diabetes OR=1.86 (1.09-3.20) POAG: Diabetes OR=2.12 (1.18-3.79)
21	Leighton D.A Phillips C.I (1972)	Case-Control (Poorly-defined study base)	POAG 11 NTG 11 Control 11	Systemic Hypertension	POAG NTG	Nil	Compared with controls: POAG patients had significantly higher systolic (P<0.05) and diastolic (P<0.01) blood pressure
22	Zeiter J.H Shin D.H Baek N.H (1991)	Retrospective Cohort Study	Cases: (Diabetic Glaucoma patients) Controls: (Non-diabetic Glaucoma patients)	Diabetes	Visual field defects in the inferior field	Nil	Diabetic glaucoma patients were more likely to have visual field defects in the inferior field (P<0.0001)
23	Mcleod S.D West S.K Quigley H.A et al. (1990)	Cohort Study	572	Blood Pressure Age	IOP	Initial IOP	Changes in IOP were positively associated with systolic blood pressure (P<0.05) and inversely with age (P<0.05)
24	Wilson M.R Hertzmark E Walker A.M et al. (1987)	Case-Control (Poorly-defined study base)	POAG 83 Suspects 121 Controls 237	Family Hist. Race Hypertension Smoking	POAG POAG suspects	Age Sex Reason for referral Myopia Diabetes	POAG: Multivariate Analysis Race OR=6.8 (2.8-16) Hypertension OR=5.8 (2.2-15) Smoking OR=2.9 (1.3-6.6) Suspects: Family Hist. OR=3.2 (1.2-8.6) Race OR=1.9 (1.0-3.7)

Ref.	Authors	Study Type	Sample Size	Study Factor	Outcome Factor	Confounders	Results
25	Klein B.E.K Klein R Mess S.E (1997)	Cohort Study	1298	Age IOP Cataract Sx Insulin Use	Self-reported glaucoma among diabetics	Hypertension BMI, HbA_{1C} Cardiac Dis. Proteinuria Refractive error, Retinopathy	If <30 yrs: Multivariate Analysis Age OR=1.77 (P<0.0001) If >30 yrs; Age OR=1.37 (P<0.05) IOP OR=1.25 (P<0.0001) Insulin use OR=2.66 (P<0.005) Cataract OR=2.39 (P=0.06)
27	Wang JJ Mitchell P Smith W (1997)	Cross Sectional Analysis	3654	Migraine	POAG	Sex Family Hist. Diabetes Hypertension Pseudoexfol. Effect Modifier: Age	POAG: Multivariate Analysis Migraine OR=1.65 (0.88-3.08) EM: 60's OR=0.53 (0.07-4.26) 70's OR=2.74 (1.14-5.58) 80's OR=0.98 (0.26-3.66)
28	Phelps CD Corbett JJ (1985)	Case-Control (Poorly-defined study base)	NTG 54 POAG 182 OHT 126 Control 493	Migraine Headache	NTG	Effect Modifier: Age	Compared with Controls, migraine is associated with NTG (P=0.02). Those with NTG and were aged 70+ were more associated with headache (P=0.04) than other age groups.
29	Drance SM Douglas GR Wijsman K et al. (1988)	Case-Control (Poorly-defined study base)	Control 38 Migraine 13 NTG 29 Migraine+ NTG 17	Mean capillary blood flow after cold or heat exposure	Migraine NTG	Nil	Migraine: Blood flow after heating is less than other groups (P=0.02) NTG: Flow lower at baseline (P=0.013) and after cold exposure (P<0.0001)
30	Guthauser U Flammer J Mahler F (1988)	Cohort Study	23	Capillaro-scopic cooling test	Perimetry	Nil	Patients with vasospasm were associated with worsening visual field (P<0.025)
32	Chai E Goldberg I Chia A et al. (1999)	Non-randomised Controlled Trial	Intervention 75 Control 31	Hand Vibration test (vasospasm test)	Visual Field Mean Defect	Age Medication	In arcuate zone of visual field the hand vibration test was associated with a worsening of mean defect (P=0.005)

Ref.	Authors	Study Type	Sample Size	Study Factor	Outcome Factor	Confounders	Results
34	Leske MC Connell AMS Wu S-Y et al. (1995)	Cross Sectional Analysis	4709	Age Sex BMI Cataract IOP>21 Family Hist.	POAG	Treatment Education Occupation Race	POAG: Multivariate Analysis Age OR=1.07 (1.05-1.08) Male Sex OR=1.66 (1.24-2.24) BMI:High OR=0.38 (0.23-0.62) Med.OR=0.72 (0.52-0.99) Cataract OR=1.52 (1.08-2.13) IOP>21mmHg OR=11.34(8.51-15) Family Hist. OR=2.43 (1.43-4.15)
35	Rosenthal AR Perkins ES (1985)	Case-Control (Well-defined study base)	Patients with family history of POAG 268 Control 5919	Family Hist.	IOP POAG	Age Sex	Family History: IOP>21mmHg =3.8% of sample 10 yr follow up 9% develop POAG
36	Tielsch JM Katz J Sommer A et al. (1994)	Cross Sectional Analysis	5308	Family Hist.	POAG	Age Race	POAG: Siblings OR=3.69 (2.10-6.48) Parents OR=2.17 (1.07-4.41) Children OR=1.12 (0.21-4.86) Any 1st deg. relative OR=2.85(1.82-4.46)
38	Konareva-Kostianeva M (1998)	Case-Control (Poorly-defined study base)	Patients with family history of POAG 67 Control 138	Age	Family Hist.	Sex Refractive Error Hypertension Diabetes	Those with Family History of POAG were younger at disease onset (~8yrs)(P<0.001)
39	Mitchell P Hourihan F Sandbach J et al. (1999)	Cross Sectional Analysis	3654	Myopia	POAG OHT	Diabetes Hypertension Family Hist. Migraine Inhaled Steroids Pseudoexfol.	POAG: Multivariate Analysis Low myopia OR=2.3 (1.3-4.1) High myopia OR=3.3 (1.7-6.4) OHT: Low myopia OR=1.8 (1.2-2.9) High myopia OR=0.9 (0.4-2.0)

Ref.	Authors	Study Type	Sample Size	Study Factor	Outcome Factor	Confounders	Results
40	Leske M.C Warheit-Roberts Wu S-Y (1996)	Case-Control (Poorly-defined study base)	POAG 122 OHT 108 Control 190	Age Sex Fam. Hist. Hypertension	OHT POAG	Smoking Alcohol Diabetes	Compared Multivariate Analysis with Controls: POAG: Age OR=1.03(1.00-1.05)* MalesOR=1.69(1.03-2.79)* Fam.Hist.OR=3.08(1.70-5.58)* OHT:Fam.Hist.OR=2.38(1.3-4.5)** HT OR=2.36(1.42-3.92)* Compared with OHT: POAG: Males OR=2.08(1.18-3.57)* (*P<0.05, **P<0.01)
42	Reynolds DC (1977)	Case-Control (Poorly-defined study base)	POAG 87 Controls 87	Hypertension treated with medication Diabetes ↑B.P	POAG	Nil	Hypertension treated with medication OR=2.3(P<0.05) Diabetes OR=4.7 (P<0.01) ↑B.P O.R=1.7 (P>0.05)
43	Klein BE Klein R (1981)	Cross Sectional Analysis	508	Hypertension	IOP	Age Haematocrit ESR Pulse Cholesterol	Significant correlation between systolic BP and IOP seen in both sexes and black/white patients. White/Male R=0.17 White/Female R=0.24 Black/Male R=0.22 Black/Female R=0.25
44	Kahn HA Milton RC (1980)	Cross Sectional Analysis	2433	Diabetes Hypertension Pulse Alcohol	IOP	Nil	Significant associations were found between hypertension (z=4.52) and diabetes (z=4.56) and IOP
50	Usui T Iwata K Shiakashi M et al. (1991)	Case-Control (Poorly-defined study base)	NTG 77 POAG 73 Control 75	Migraine	POAG NTG	Nil	There was no association between the prevalence of migraine and NTG or POAG when compared with controls (P>0.05)
51	Klein BEK Klein R Meuer SM (1993)	Cross Sectional Analysis	4926	Migraine	POAG	Age Sex Drinking Smoking	No association found between migraine and POAG (P=0.96)