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Risk factors for incident open-angle glaucoma in outpatient eye care

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Populärvetenskaplig sammanfattning (Popular science summary)

Bakgrund

Det finns en brist på kontrollerade studier om rollen av olika riskfaktorer hos glaukompatienter som upptäcks i klinisk verksamhet. Syftet med den här studien var att undersöka effekten av potentiella riskfaktorer för öppenvinkelglaukom hos en population i åldern 55–84 år.

Metod

Materialet till studien insamlades mellan åren 1988–2003 och inkluderade patienter från Tierp och Älvkarleby kommuner i Uppsala län. I samband med öppenvårdsbesök i Tierp mättes trycket i främre ögonkammaren. En noggrann ögonundersökning utfördes och sjukhistoria, rönkningsvanor och ärftlighet för ögonsjukdomar noterades. Register över vårdtillfällen vid akademiska sjukhuset och ögonmottagningen i Tierp användes för att täcka in alla patienter från området som sökte för ögonproblem. Riskfaktorer för sjukdom, uttryckta som oddskvoter, justerades för kön enligt Mantel–Haenszel. Logistisk regressionsanalys användes för att utvärdera effekten av flera störfaktorer. En synfältsdefekt krävdes för glaukomdiagnos.

Resultat

Öppenvinkelglaukom påträffades hos 107 deltagare. Sextio (56%) av dessa hade kapsulärt glaukom och 47 (44%) kroniskt enkelt glaukom. Sex patienter hade normaltrycksglaukom. Ett ögontryck på 30 mmHg eller högre medförde mer än 80 gånger ökad risk för sjukdom i jämförelse med ett tryck under 22 mmHg. Proportionen av kapsulärt glaukom ökade exponentiellt med stigande ögontryck. Ålder var starkt associerat med öppenvinkelglaukom. Män hade en fördubblad risk jämfört med kvinnor. Ärftlighet för öppenvinkelglaukom gav en nära trefaldig riskökning. Proteinutfällningar i ögat, så kallad pseudoexfoliation, medförde en icke signifikant riskökning på nära 80%.

Slutsatser

Ett förhöjt ögontryck, tilltagande ålder, manligt kön och ärftlighet för öppenvinkelglaukom ökade risken för sjukdom. Få patienter hade normaltrycksglaukom.

Abstract

Purpose:

To study risk factors for open-angle glaucoma (OAG) in new cases aged 55–84 years detected in clinical practice.

Methods

The study was conducted following the model of a *nested case-control study*. It was conducted between the years of 1988 and 2003 at the Eye Department in Tierp and included patients from the two northern municipalities in Uppsala county. In conjunction with open care visits at the Eye Department, a detailed eye examination including automated perimetry (Competer 350) and gonioscopy was undertaken. Intraocular pressure (IOP) was registered as the mean of the first two pressure readings at presentation. Registers of open care visits at Uppsala University Hospital and the Eye Department in Tierp was used to detect all patients seeking ophthalmic care between the years 1988–1995. A total of 544 patients were included in the study. Risk factors for OAG, expressed as odds ratios, were adjusted for gender according to Mantel-Haenszel. Multiple logistical regression analysis was also preformed, using OAG as the dependant variable.

Results

Open-angle glaucoma was found in 107 subjects. Sixty (56 %) had capsular glaucoma and 47 (44 %) had chronic simple glaucoma. Six of the OAG patients were classified as normal tension glaucoma. Increased IOP was strongly associated with OAG. Subjects with an IOP ≥ 30 mmHg experienced an 83 times increased risk compared with patients with IOP < 22 mmHg. The proportion of capsular glaucoma increased exponentially with increasing IOP. Other risk factors associated with OAG were older age, male gender and a positive family history. Every additional year of age was associated with an 7% increased risk. A family history of OAG increased the risk nearly 3-fold. In the multivariate model, pseudoexfoliation was not associated with OAG.

Conclusion

Open-angle glaucoma patients detected in clinical practice have largely the same risk factors as those found in population screening studies. Increased IOP, pseudoexfoliation, increased age, male gender and a positive family history were the most important risk factors identified. Normal-tension glaucoma seem to be less frequent and capsular glaucoma more frequent in ophthalmic outpatients.

Background

Open-angle glaucoma in the ICD-10-SE

The Swedish version of the World Health Organizations classification of diseases, the ICD-10-SE, separates open-angle glaucoma (OAG) into four different categories ¹. Chronic simple glaucoma is OAG without pseudoexfoliation, while capsular glaucoma is characterized by the presence of pseudoexfoliation in the anterior eye segment. The third type of OAG is normal-tension glaucoma, with or without pseudoexfoliation, characterized by intraocular pressure (IOP) within the normal range. The fourth category is pigmentary glaucoma, which is related to pigmentary dispersion syndrome. No cases of pigmentary glaucoma were included in this study.

Pathophysiology of open-angle glaucoma

Open-angle glaucoma (OAG) is recognized as an optic neuropathy, resulting in structural damage at the location of the optic nerve head as well as functional loss in the visual field. At least one eye must be affected both structurally and functionally to fit the diagnosis. Damage must also be sufficiently indicative of substantial retinal ganglion cell death. As OAG progresses, the excavation of the optic nerve head is deepened and widened, indicating both deformation of connective tissue as well axonal degeneration and the death of retinal ganglion cells. Structural damage can also be recognized by reduction of the axonal layer surrounding the optic disc ².

The cause of the structural damage in OAG is not completely understood, but it is induced by harmful effects at the location of the optic nerve head. Retinal ganglion cell axons are likely damaged and axonal transports consequently inhibited. For their survival, retinal ganglion cells are dependent on axonal neurotrophic signals from brain target cells and from other retinal cells. From the absence of incoming neurotrophic signals, apoptosis is triggered in the retinal ganglion cells. The initial apoptosis of retinal ganglion cells is considered to induce a toxic environment of glutamate and free radicals. This toxic environment may contribute to further damage of additional retinal ganglion cells ².

The main harmful effect at the location of the optic nerve head is caused by increased IOP ³. In clinical practice, IOP reduction remains the only treatment strategy of OAG. Evidence suggest however, that there may be other contributing factors to the pathogenesis of OAG. Furthermore, we cannot exclude that there may be several separate and independent pathogenesis of OAG. Chronic simple glaucoma may have a different pathogenesis from normal-tension glaucoma.

There is further evidence that OAG, and normal-tension glaucoma in particular, is somehow linked with ocular and systemic vascular abnormalities. Compared to controls, OAG patients have been found to have lower retrobulbar blood velocity, lower ocular pulse amplitude, higher retinal venous saturation and altered retinal and choroidal flow, compared to controls. In some studies, they also suffer at a higher rate from vascular conditions such as systolic hypotension, migraine and peripheral vasospasm ⁴.

The role of IOP in the pathogenesis of OAG may be understood in relation to its surrounding pressures. The pressure generated over the optic nerve head and the lamina cribrosa can be considered as the mean difference between the IOP and the low-pressure environment of the subarachnoid space. This mean pressure differential is referred to as the translaminar pressure gradient. An imbalance in the translaminar pressure gradient may be contributing to the damage of retinal ganglion cell axons crossing the lamina cribrosa, as seen in OAG. Translaminar pressure gradient imbalance may also affect neural function, blood flow and lamina cribrosa morphology. The thickness of the lamina cribrosa is also considered to be contributing to the translaminar pressure gradient ⁵.

Intracranial pressure is likely to have an important influence on translaminar pressure gradient, acting as a counter pressure to IOP from the contrary side of the subarachnoid space. The combination of a normal IOP and a low intracranial pressure may generate a similarly harmful translaminar pressure gradient on retinal ganglion cells as the combination of a high IOP and a normal intracranial pressure.

There is conflicting evidence in support of the role of intracranial pressure and translaminar pressure gradient in OAG pathophysiology. Retrospective studies of patients who had lumbar punctures, revealed that OAG patients (both chronic simple glaucoma and normal-tension glaucoma) had 3-4 mmHg lower intracranial pressure compared to both control subjects and to patients with intraocular hypertension ^{6 7}. The amount of glaucomatous damage was also found to correlate with translaminar pressure gradient. Furthermore, animal experiments have shown that chronically reduced cerebrospinal fluid in monkeys correlate with glaucoma-like, structural damage of the optic nerve head ⁵.

However, in a more recent prospective case-control study, normal-tension glaucoma patients were demonstrated to have normal intracranial pressure and translaminar pressure gradient compared to controls, in every tested body position ⁸. This study also used lumbar punctures to measure intracranial pressure. The study was set out to test the hypothesis that normal-tensions glaucoma patients may have low intracranial pressure, conceivably causing an increased translaminar pressure gradient in combination with their normal IOP. But the hypothesis proved not to be supported by the evidence. A plausible source of error to keep in mind in these studies is that momentary intracranial pressure measurements by lumbar puncture may not be reflective of long-term pressure variations.

OAG patients with increased IOP typically suffer from abnormally high outflow resistance from the inner wall region of the trabecular meshwork outflow pathways ⁹. Evidence suggest that increased outflow resistance in OAG may be the result of a characteristic transformation of cells of the juxtacanalicular connective tissue, taking on a phenotype like contractile myofibroblasts. A loss of lining cells in the trabecular meshwork and accumulation of extracellular molecules blocking outflow may also contribute to the increased IOP in some OAG patients ¹⁰.

Since most patients with intraocular hypertension will not develop OAG, there may be other biomechanical features of the eye that determine how stress in the anterior segment of the eye translate to the retinal axons of the optic nerve head. Large eye size (axial myopia), large disc size and thin central cornea, all seem to be contributing an increase of translated stress to the optic nerve head ².

The genetics of open-angle glaucoma

Glaucoma has long been thought to be a familiar disorder. First-degree relatives are ten times more likely to develop OAG, compared to controls. Twin studies have also shown a significant but modest heritability for OAG ¹¹. Heritable glaucoma that follow a Mendelian autosomal pattern, is more likely to be early onset. Compared to the more common adult onset forms, juvenile OAG is also more likely to be linked to single gene mutations. However, these monogenetically caused forms are rare. Less than 5% of OAG cases can be linked to any of the single gene mutations that are known to be associated with glaucoma. Adult onset OAG is more commonly associated with a complex combination of genetic and environmental factors that collectively produce a general susceptibility to OAG ¹².

Since OAG typically seem to be multicausal, parsing out the various contributing genetic factors does present a challenge. Genome-wide association studies (GWAS) can be used in order to find alleles that are statistically more common among OAG patients compared to controls. Looking at genetic risk factors for normal-tension glaucoma in a Japanese population, a recent GWAS found an association (odds ratio 2.8) with a genetic marker located within an intron of the gene *SBRD1*¹³. The role of this gene in the pathogenesis of OAG or normal-tensions glaucoma is unknown.

The same GWAS identified another genetic marker within the *ELOVL5* gene. The protein encoded by this gene is involved in the synthesis of long-chain polyunsaturated fatty acids. It is speculated that a certain allele of the *ELOVL5* gene may induce an increase in the synthesis of long-chain polyunsaturated fatty acids, promoting harm to retinal ganglion cells.

Another GWAS used cohorts from Iceland, Sweden, United Kingdom, Australia and China¹⁴. A region of two genes was identified with an apparent association with glaucoma. These genes were caveolin 1 (*CAV1*) and caveolin 2 (*CAV2*). The magnitude of the association varied between cohorts, being especially pronounced in the cohort from Iceland (odds ratio 1.36) whilst less notable in pooled analysis and not detected at all in the cohort from United Kingdom¹².

The first single gene to be linked with OAG was *Myocilin*¹⁵. Primarily, it has been associated with juvenile OAG. Between 3-4% of OAG patients and 8-36% of juvenile OAG patients have been found to carry a *Myocilin* gene mutation. Most of these polymorphisms being very rare in controls. The mutation also seems to be more common among patients with a family history of glaucoma. Little is known about the function of the protein that the *myocilin* gene encodes. It is produced by many cell types of the eye and secreted into the aqueous humor, for unknown functions. The mechanism of *myocilin* gene mutation in the pathogenesis of OAG has been speculated to be toxic accumulation within trabecular meshwork cells, due to poor secretion because of abnormalities of the protein. Harm to trabecular meshwork cells may lead to dysfunction and cell death, and furthermore to increased outflow resistance of aqueous humor and increased IOP¹².

Optineurin is another single gene which mutation is associated with OAG. This gene mutation is especially associated with normal-tension glaucoma. Population studies suggest that *optineurin* mutations may be causal of up to 1.5% of normal-tensions glaucoma cases, largely dependent on what populations are observed¹². In most populations, *optineurin* mutations are not associated with increased IOP. Evidence suggest that normal *optineurin* expression may have a neuro-protective effect. The path mechanism of *optineurin* gene mutation may therefore be an absence of neuro-protection, perhaps facilitating harmful effects on retinal ganglion cells¹².

Another single gene that has been associated with glaucoma is *TBK1*. This is a gene that encodes a kinase regulating the NF- κ B signaling pathway. It is not the mutation of TBK1 that is associated with glaucoma but rather the copy number variations of the gene. Duplication of the TBK1 gene and of the neighboring genes seem to be linked with OAC, especially normal-tension glaucoma cases ¹².

Genome wide association studies have also led to the discovery of a genetic factors associated with capsular glaucoma. Multiple single-nucleotide polymorphisms in the first exon of the gene *LOXL1* have shown to be associated with both exfoliation syndrome and capsular glaucoma ¹⁶. Subjects who were homozygous for the high-risk haplotype were shown to be more than a hundred times more likely to suffer from exfoliation syndrome, compared to those homozygous for the low risk haplotype. The protein encoded by LOXL1 functions as catalyst in the synthesis of elastin fibers, which constitute a major part of pseudoexfoliation lesions.

Increased intraocular pressure and open-angle glaucoma

The earliest known risk factor for OAG is increased IOP. This has been the strongest and most consistent association found in follow-up studies. A seven-fold relative risk increase for patients with IOP ≥ 20 mmHg was found in a Swedish population-based study ¹⁷. The risk increase has also been shown to be progressive. In the Barbados Eye study, every 1 mmHg of IOP increase was demonstrated to correspond with a 12% relative risk increase ¹⁸. Another interesting find in the Swedish study was that the risk increase associated with a combination of increased IOP and exfoliations was greater than the risk increase associated with any one of these two factors alone ¹⁷.

It has been proposed that the increased IOP associated with OAG may be a secondary effect rather than a driving cause of OAG ^{19 20}. It was argued that IOP may increase due to vascular events of the papilla area that cause outflow resistance to rise. However, these arguments have largely fallen out of favor since the publication of convincing evidence from large scale randomized trials demonstrating successful prevention and delay of glaucoma onset in subjects with ocular hypertension ²¹. There have also been similar large randomized trials demonstrating successful treatment of early manifest glaucoma with hypotensive drugs ²².

Although increased IOP is a clear risk factor for OAG, many individuals with increased IOP never develop glaucoma and some develop glaucoma despite normal IOP. Normal-tension glaucoma patients may be at risk of being overlooked by clinicians. Population screening studies have been identifying normal-tension glaucoma patients at four times higher rates compared to self-selected patients in outpatient care.

Although these undiagnosed normal-tension glaucoma patients showed less severe clinical signs and symptoms compared to other glaucoma patients, many still suffered from considerable glaucomatous damage. In order to identify these patients in an earlier stage there would have to be a screening program in practice ²³.

Pseudoexfoliation and open angle glaucoma

Pseudoexfoliation is commonly found in glaucoma patients. These are protein deposits, observed in slit lamp examinations as granular white accumulations in the anterior segment of the eye. Pseudoexfoliation has been consistently demonstrated to be a considerable risk factor for glaucoma²⁴.

In Nordic populations, pseudoexfoliation is found in most known OAG patients in open care ²⁵. In the Tierp population study, pseudoexfoliation was found in 60% of OAG patients. It is less common, however to find pseudoexfoliation in glaucoma that were identified through non-selected population studies ^{26 27}.

Pseudoexfoliation is considered to contribute to glaucoma by blocking trabecular outflow of aqueous humor from the anterior chamber and thereby increasing outflow resistance and IOP. Pseudoexfoliation are most commonly observed in the eye but they have also been discovered in other organs such as the heart, blood vessels, skin and kidneys. They are therefore considered to be manifestations of a systemic syndrome, referred to as pseudoexfoliation syndrome ²⁴.

Other known risk factors of open-angle glaucoma

Every large population study that has attempted to evaluate the effect of *aging* on the incidence of open angle glaucoma, has found it to be a consistent and progressively impactful risk factor. In a population-based study from Iceland, there was an annual risk increase of 10% in persons 50 years of age or greater ^{28 29 30}. It is less evident whether *sex* is a risk factor for glaucoma. However, the Tierp population study did find a higher prevalence among men than among women ²⁶.

In the Los Angeles Latino Eye Study, *myopia* was found to be a risk factor both at baseline and compared to subjects with the same IOP³¹. In a Swedish population study, myopia was again found to be an important risk factor, especially at lower IOP levels³².

Various properties of the cornea have been associated with a higher risk of OAG. The Los Angeles Latino Eye Study demonstrated that central corneal thickness had a negative correlation with OAG prevalence³¹. Low cornea hysteresis is a predictor of a faster rate of visual field loss compared to those with a higher corneal hysteresis³³.

There is evidence of an association between systemic hypertension and increased IOP, but the association to glaucoma is only speculative at this point³⁴. Meta-analysis has shown an association between diabetes and risk for glaucoma as well as slightly increased IOP³⁵.

It was first suggested by Drance in 1970, that *optic disc haemorrhages* were an important marker for glaucomatous damage³⁶. Populations-based and longitudinal studies have since then demonstrated that disc haemorrhages are strongly associated with open-angle glaucoma and especially normal-tension glaucoma. Disc haemorrhages are now considered a significant clinical sign of glaucoma and a predictor of glaucomatous progression. Several theories of the underlying pathogenesis have been proposed, including mechanical rupture as well as vascular dysregulation³⁷.

Purpose

The purpose of this study is to further examine the different risk factors for OAG in a population of ages ranging from 55-84 years. Special attention is paid to increased IOP and pseudoexfoliation as risk factors for OAG. The study includes self-selected patients from outpatient care, and it is based on automatic perimetry.

There is a lack of controlled population-based studies of the role of various risk factors in glaucoma patients that are discovered in clinical practice. Available studies are generally based on surveys of non-selected populations. But there is evidence to suggest that glaucoma patients that are identified in non-selected population-based studies have a characteristically distinct profile compare to known glaucoma patients that are treated in open care clinical practice²³.

Method

Study design

The study has the characteristics of a case-control study in a cohort, a *nested case-control study*³⁸. It was conducted between the years of 1988-2003 and included patients from Tierp and Älvkarleby municipalities in Uppsala county, in ages ranging from 55-84 years. Examinations were conducted at the eye clinic in Tierp.

Basic examinations

The IOPs registered were the two first IOP readings without pressure reducing treatment. The time lapse between measurements was at least three hours. A mean value was calculated and rounded up in accordance with the first measurement in order to avoid non-integer values. The highest measured IOP on either eye was chosen to represent the subject.

Study population

In order to achieve an equal distribution of patients with IOPs averaging around 22 mmHg, the recruitment was guided by IOP measurements. The first years, mainly patients with IOPs ≥ 18 mmHg were offered to participate. The last year, subjects with IOPs < 18 mmHg were offered to participate.

To be eligible for the cohort, there were several criteria to be met:

First visit to ophthalmologic open care in Uppsala county between the years of 1988-1995

Examination by ophthalmologist in Tierp between the years of 1988-2003

Patient was registered in Tierp or Älvkarleby municipalities

Aged between 55-84 years at the first visit in Tierp

IOP measurement criteria met (initially exceeding 18 mmHg, later succeeding 18 mmHg)

No signs of narrow-angle glaucoma or secondary glaucoma

No intraocular surgeries

Since the study is based on incidental illness, patients in regular ophthalmologic care could not be included. These are for example diabetes patients that have been regularly checked for retinopathy using fundus photography within the last three years. Singles visits however did not merit exclusion.

Data collection

Registers of open care visits at Uppsala university hospital and the Tierp eye clinic was used in order to cover patients seeking ophthalmic care between the years 1988-1995. Unfortunately, these registries don't cover patients from Älvkarleby municipality who sought eye care at Uppsala university hospital. To avoid selection bias, these patients were excluded from the study, if they had visited the Eye clinic in Tierp.

The study is based on automated perimetry (Competer 350). Patients that were not in need of visits at the Eye clinic were offered repeated cost-free examinations. The other patients were dealt with according to the routines at the eye clinic.

For diagnosis of OAG, a reproducible visual field defect needed to be detected with one of the screening programs of the Competer. Patients with end-stage disease, that prohibited visual fields examination, were also classified as having OAG.

In this study, normal-tension glaucoma was defined as a variant of OAG in cases where not more than one IOP reading above 21 mmHg, and no readings above 24 mmHg, had ever been recorded.

In conjunction with the open care visits in Tierp, a detailed ophthalmological examination was performed and medical history, smoking habits and heredity for ophthalmological illness was noted. The information gathered was supplemented with additional health details collected from the registries.

The eye under study

For every subject, a first eye was selected. If both eyes were affected, the most severely affected eye represented the individual. In subjects with no visual field defect, the eye with the highest IOP was chosen. If a first eye could not be selected using any of these criteria, a coin flip was used to finally separate the eyes.

Statistical analysis

In the statistical analysis, each subject is represented by the first eye. Risk factors for OAG, expressed as odds ratios, were adjusted for sex according to Mantel-Haenszel. Multiple logistical regression analysis was also performed, using OAG as the dependant variable. In both the stratified model and the multiple logistical regression analysis, the risk factor of IOP was divided into separate consecutive intervals.

Results

Composition of the cohort

The cohort included 583 eligible persons. Of these, 20 subjects were excluded according to registry problems and 3 did not comply with the testing of visual fields in neither eye. One patient was not invited and 15 declined participation. Thus, 544 people remained in the study cohort, whose characteristics is presented in *Table 1*. The non-participation rate was low (2.8%, 16 out of 563 persons).

Table 1. Characteristics of participants in the Tierp case-control study, by age and gender.

	No. of people (n = 544)		
Age	Females (%)	Males (%)	All (%)
55–64 years	63 (20)	40 (18)	103 (19)
65–74 years	157 (49)	100 (45)	257 (47)
75–84 years	102 (32)	82 (37)	184 (34)
55–84 years	322 (100)	222 (100)	544 (100)

Mean age: 71,8 years (standard deviation: 7,3)

Prevalence of open-angle glaucoma and pseudoexfoliation in the cohort

Open-angle glaucoma was found in 107 of subjects. Sixty had capsular glaucoma (56%) and 47 (44%) chronic simple glaucoma. Six patients had normal-tension glaucoma (6% of all OAG). None of these had increased IOP at any later visit. Open-angle glaucoma in both eyes was found in 55 persons and in one eye in 52 persons. Pseudoexfoliation were found in 157 persons. Conditions were diagnosed either in conjunction with the basic examination or in the following two years. Four persons with pseudoexfoliation on one eye received the diagnosis of chronic simple glaucoma on the other eye. One person had chronic simple glaucoma in the first eye and capsular glaucoma in the other eye.

Intraocular pressure as a risk factor in the stratified analyses

Increased IOP was strongly associated with open-angle glaucoma in the stratified analyses. For every consecutive interval of increased IOP, there was an associated increase in the proportion of glaucoma. This is demonstrated in both *Table 2* and *Figure 1*.

Table 2. Distribution of 107 cases of incident open-angle glaucoma by mean intraocular pressure in the Tierp case-control study.

No. of people (n = 544)					
IOP (mmHg) *	No.	OAG (%)		No OAG (%)	
<22	288	9	(3.1)	279	(96.9)
23–29	180	39	(21.7)	141	(78.3)
≥30	76	59	(77.6)	17	(22.4)

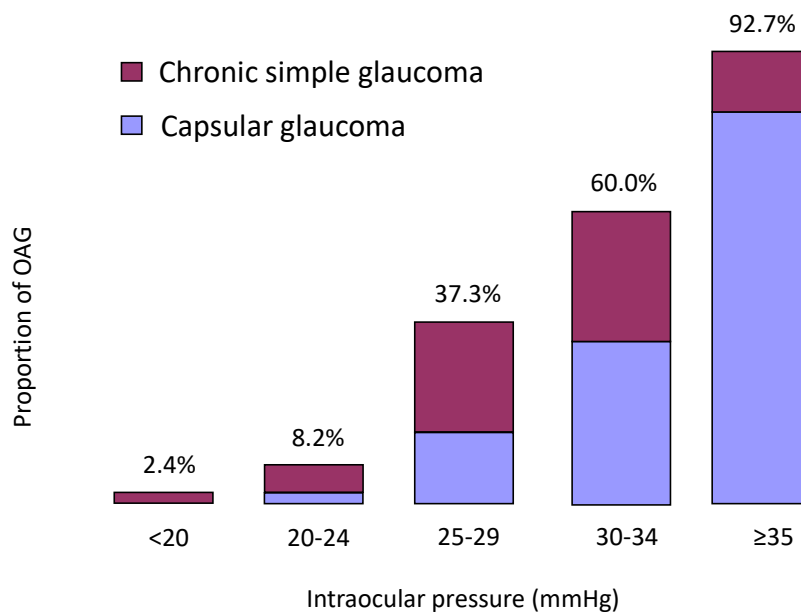
IOP = intraocular pressure

* The highest mean pressure in either eye

The highest proportion of OAG (92,7%) was found among subjects with the highest IOP (≥ 35 mmHg). In this same segment of subjects with the highest IOP, the maximum odds ratio (of 519) was also found. Looking at the proportion of capsular glaucoma versus chronic simple glaucoma, the capsular form grew in proportion in association with increased IOP. This is demonstrated in *Figure 1*. Looking at a broader segment, subjects with an IOP ≥ 22 mmHg were at an almost twenty-fold risk increase compared to those with an IOP < 22 mmHg (see *Table 3*).

Due to a low number of subjects in the lowest IOP interval, adjusting for sex and age in this interval was inappropriate.

Figure 1. Proportion of open-angle glaucoma by mean intraocular pressure and type of glaucoma



Other risk factors found in the stratified analyses

Advanced age was found to be associated with OAG. Subjects ≥ 70 years of age had an odds ratio of 2.1. Males were demonstrated to be at a higher risk of OAG (OR 1.6) compared to females. Those with a family history of OAG were also at an increased risk (OR 2.85). Subjects with pseudoexfoliation on either eye were at more than a six-fold risk increase compared to those without (OR 6.24). Due to a low number of subjects, optic disc haemorrhage data was not adjusted for age or sex. An optic disc haemorrhage on either eye was associated with a ten-fold unadjusted increased risk. Cataract on either eye was moderately associated with OAG (OR 1.57).

Treated systemic hypertension and diabetes had a protecting effect on the risk for having OAG. However, there were relatively few subjects exposed to diabetes. None of the other investigated variables in *Table 3* were significant associated with OAG.

Table 3. Associations between potential risk factors and incident open-angle glaucoma, adjusted for gender in the Tierp case-control study.

Characteristics		No. of cases		
		(<i>n</i> = 107)	OR	(95% CI)
Age ≥70 years	No	29	1.00	
	Yes	78	2.11	(1.32–3.37)
Male gender *	No	53	1.00	
	Yes	54	1.60	(1.04–2.45)
Family history, open-angle glaucoma	No	83	1.00	
	Yes	24	2.85	(1.62–5.00)
Mean IOP ≥22 mmHg, either eye	No	9	1.00	
	Yes	98	19.83	(9.69–40.57)
Pseudoexfoliation, either eye	No	43	1.00	
	Yes	64	6.24	(3.91–9.95)
Optic disc haemorrhage, either eye †	No	92	1.00	
	Yes	15	10.02	3.70 – 29.71
Myopia, ether eye	No	85	1.00	
	Yes	22	1.14	(0.67 – 1.94)
Cataract, either eye	No	38	1.00	
	Yes	69	1.57	(1.01–2.46)
Current smoker	No	94	1.00	
	Yes	13	0.79	(0.41–1.52)
Diabetes mellitus	No	97	1.00	
	Yes	10	0.40	(0.20–0.79)
Hypertension, treated	No	73	1.00	
	Yes	34	0.63	(0.40–0.99)
Ischaemic heart disease	No	76	1.00	
	Yes	31	1.44	(0.88–2.34)

* Adjusted for age; † Unadjusted; OR = odds ratio; CI = confidence interval; IOP = intraocular pressure

Findings in the logistic regression model

The ultimate multivariable logistic regression model is shown in Table 4. Increased IOP was identified as an important risk factor, concurrent with the findings in the stratified analyses. An IOP between 22–29 mmHg in either eye was associated with an eight-fold increased risk of having OAG, while subjects with an IOP ≥ 30 mmHg experienced an 83 times increased risk compared with subjects with IOP < 22 mmHg.

In the regression model, age was accounted for as a continuous variable. Every additional year of age was associated with an increased risk of 7%. Concurrent with the results of the stratified analyses, males were at a higher risk in the regression model as well (OR 2.01). Also concurrent with the stratified analyses, family history of OAG was associated with a higher risk (OR 2.86). However, when adjusting for the variables in *Table 4*, pseudoexfoliation was not significantly associated with OAG. Furthermore, diabetes and systemic hypertension had no longer a protecting effect (data not shown). Optic disc haemorrhages were not included in the regression model due to an imbalance in the distribution of data.

Table 4. Logistic regression model assessing the influence of risk factors for incident open-angle glaucoma in the Tierp case-control study.

Covariate		No. of cases	OR	(95% CI)
Older age, per year		107	1.07	(1.03–1.12)
Male gender	No	53	1.00	
	Yes	54	2.01	(1.12–3.61)
Family history of OAG	No	83	1.00	
	Yes	24	2.86	(1.32–6.21)
Mean IOP, mmHg				
	<22, both eyes	9	1.00	
	22–29, either eye	39	8.08	(3.73–17.5)
	≥30, either eye	59	83.2	(32.7–212)
Pseudoexfoliation, either eye	No	43	1.00	
	Yes	64	1.77	(0.95–3.31)

OR = odds ratio; CI = confidence interval; OAG = open-angle glaucoma; IOP = intraocular pressure.

Discussion

This study was conducted in response to the lack of controlled population-based studies on the role of different risk factors for OAG in patients seeking medical attention for eye problems in clinical practice. Such studies are needed, since evidence suggest that patients identified in non-selected population-based studies have a characteristically different profile of risk factors ²³.

The setup of the present study is like a previous study conducted by Pohjanpelto and Palva in Finland ³⁹. However, in contrast to our study, which is based on the demonstration of visual field defects, they investigated the occurrence of optic nerve damage in new cases of ocular hypertension. A close connection between increased IOP and nerve damage, particularly in patients with pseudoexfoliation, was found. In addition, the Finish study lacked a control group of subjects with pressures within the normal range.

In this case-control study, nested in a cohort including 544 ophthalmic out-patients 55–84 years of age from Tierp and Älvkarleby municipalities in Uppsala county, OAG was found to be strongly correlated with *increased intraocular pressure*. This held true in chronic simple glaucoma but was more pronounced in capsular glaucoma. The odds ratio increased exponentially for every level of increased IOP. This finding is concurrent with previous studies ¹⁷. In follow-up of the Barbados Eye Study, every 1 mmHg increase of IOP was associated with a 12% increased risk of OAG ¹⁸.

Pseudoexfoliation is a well-known risk factor for the development of OAG ⁴⁰. In the present study, pseudoexfoliation was significantly associated with OAG in the stratified analyses. However, the effect decreased in the multivariate model, adjusting for the impact of increased IOP. This finding agrees with the result of a previous follow-up study in Tierp, where the effect of pseudoexfoliation was found to be mediated by increased IOP ¹⁷.

Our findings of a positive *family history* as an important risk factor for OAG agrees with previous studies ¹¹. However, our study demonstrated a more modest association (OR 2.86) compared to the ten-fold increased risk found in the study referred to. *Optic disc haemorrhages* have previously been indicated as an important marker of OAG ³⁷. Our findings from the stratified analysis further demonstrate the strong association between haemorrhages and OAG.

The association between *older age* and OAG, that was already well known from several large population studies, was confirmed in our present study^{28 29 30}. The association between *male gender* and OAG, that was found in a previous study of a population in Tierp, was also confirmed in our study²⁶.

The finding that *diabetes* had a protecting effect for the risk of having OAG in the stratified analyses is conflicting. Previous studies have indicated that diabetes is a possible risk factor for the disease³⁵. However, it should be kept in mind that there were few cases exposed to diabetes in the study. Moreover, the effect of diabetes disappeared in the multivariate model. *Treated hypertension* was also found to have a protecting effect in the stratified analyses but not in the multivariate model.

Previous comparison of glaucoma patients found through non-selected population screening versus studies on self-selected outpatients have indicated a difference in the proportion of capsular glaucoma out of all OAG. In a previous study from the south of Sweden, the capsular form was found to be more prevalent in self-selected patients (44%) compared to those found through population screenings (16%)²³. The finding in our study agrees with the result of this study. Capsular glaucoma accounted for 56% of all OAG in the present study.

Normal-tension glaucoma was diagnosed in only 6 out of 107 cases of OAG (6%) in our study. This finding agrees with the result of the study by Grødem, Heijl, & Bengtsson²³. They found that normal-tension glaucoma accounted for 14% of the self-selected patients compared with 53% of the patients identified in mass screening. Normal-tension glaucoma typically represents a majority of all OAG found in screening studies. In the Swedish study in Dalby, 7 out of 15 previously undiagnosed cases had an IOP ≥ 21 mmHg²⁷. Pseudoexfoliation was found in only one glaucoma patient.

A strength of the present study is that it represents a population-based cohort from a defined geographic area. Another strength is the supplementation of subject's through registries of outpatients visits at the University hospital and the Eye department in Tierp in order to make the study complete. There was a high participation rate, making the cohort more likely to be representative of this type of patient. All subjects were also examined by the same ophthalmologist, reducing the risk of different assessments of examination findings.

One weakness of this study is that patients from private clinics are not included. This may cause selection bias, because patients with more advanced glaucoma may have been remitted to the University hospital as urgent cases and thereby included in the study, while patients with pressures within the normal range were not. Another weakness is the limited size of the cohort. Finally, smoking habits could have been better measured using a continual variable like package years instead of a simple categorical variable.

It may be interesting to follow up the associations between OAG, diabetes, treated hypertension and smoking in outpatient care populations. It may also be interesting to study the role of optic disc haemorrhages in OAG and in their association with pseudoexfoliation.

Conclusion

Open-angle glaucoma patients discovered in clinical practice seem to have largely the same risk factors as those discovered in population screening studies. Increased IOP, pseudoexfoliation, older age and a positive family history are the most important risk factors in both categories. Normal-tension glaucoma is a rare finding in eye health care and pseudoexfoliation a common finding.

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